ARIC Publication Admin Use Only: ARIC Manuscript Proposal # 4326

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1.a. Full Title: Association of Prematurity and Low Birth Weight with Periodontal Disease and Tooth Loss in Adulthood: The ARIC study.

b. Abbreviated Title (Length 26 characters): Low Birth Weight and Tooth Loss

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

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3. Timeline:We aim to submit the manuscript within the next 3-6 months.

4. Rationale: Pre-term birth, defined as delivery before the completion of 37 weeks of gestation, poses a significant public health concern worldwide (1). An estimated 15 million babies are born prematurely annually, experiencing both immediate and long-term health implications (2). Among these implications is the contribution to low birth weight, defined as a birth weight of less than 2500 grams (5.5 pounds) (3).

A range of health issues are associated with premature birth. Importantly, pre-term infants often experience decreased bone health later in life (4), with events that can permanently impact bone growth and mineralization, affecting peak bone mass attainment and increasing osteoporosis risk as they grow. Associated factors include disrupted mineral transfer, limited nutrition, reduced mechanical stimulation (5), and prematurity-related conditions and treatments (6) as well as disrupted autonomic nervous regulation (7). In addition to these bone health concerns, children born prematurely are at a heightened risk of requiring hospitalization due to femur fractures. In fact, compared to full-term births, preterm infants face a 1.27-fold increased risk of hospitalization specifically for femur fractures (8).

Low birth weight, closely associated with prematurity, has also been linked with a hyper-responsive innate immune system, which aligns with increased inflammation and endothelial activation. This correlation may provide insights into the link between low birth weight, various components of the metabolic syndrome, and ischemic heart disease (9). Furthermore, prematurity and low birth weight have been tied to secondary hypertension (10).
Periodontitis, an inflammatory disease and bone disorder, manifests as the progressive deterioration of the structures that support the teeth, primarily the alveolar bone. (11). It significantly impacts the US population, affecting over 42.2% of individuals aged 30 and above, and 59.8% of those over 65 years (12, 13). The World Health Organization recognizes periodontitis as the primary cause of tooth loss among adults (14). The development of periodontitis is influenced by environmental, microbial, and host factors, all of which contribute to the progression and severity of the disease. Many systemic conditions, such as diabetes mellitus, cardiovascular disease (CVD), osteoporosis and metabolic syndrome, have been associated with periodontitis, further emphasizing its relevance beyond oral health (11, 15).

Interestingly, periodontal disease has been tied to increased levels of systemic C-reactive protein, N-terminal pro-B-type natriuretic peptide (NT-proBNP), troponin, and heart failure incidence (16). This association underscores the importance of understanding the factors related to tooth loss, given the established connection between periodontal disease and increased CVD risk (17).

Despite these associations, data about the relationship between prematurity and low birth weight with periodontal disease, and tooth loss are limited, particularly in large cohorts. Therefore, it is imperative to further explore these relationships for improved risk stratification and preventive strategies. We hypothesize that individuals with a history of prematurity and low birth weight have an elevated sympathetic tone leading to increased risk of bone fracture incidence and increased incidence of periodontal disease and subsequent tooth loss.

5. Main Hypothesis/Study Questions:

1. Primary Aim: Our primary objective is to explore the relationship between pre-term birth and low birth weight and the increased prevalence of periodontal disease and tooth loss later in life within a community-based cohort after controlling for conventional risk factors such as aging, systolic blood pressure, inflammation, and clinical CVD.

2. Secondary Aim: We also aim to explore the relationship between prematurity and low birth weight and the risk of bone fracture.

6. Design and analysis

a) **study design**
b) **inclusion/exclusion**
c) **outcome and other variables of interest with specific reference to the time of their collection**
d) **summary of data analysis**
e) **Any anticipated methodologic limitations or challenges if present**

Study Design

We will examine the independent association between prematurity and low birth weight with periodontal disease and tooth loss. The baseline for this analysis will be ARIC visit 4 (1996–1998). At visit 4, participants were asked about their birth weight in pounds and ounces. They were also asked if they were a premature baby, i.e., born, a month or more, earlier than the expected date. Periodontal status was also measured during the same visit. We will also examine the independent association between prematurity and low birth weight with risk of bone fracture that was collected annually after Visit 4 (1996-1998).

Inclusion

Participants who attended ARIC visit 4 and have:

1. Undergone a comprehensive full-mouth clinical periodontal examination.
2. Documented birth weight records, either in terms of their exact birth weight or categorized into specific birth weight ranges.

3. Confirmed information regarding their birth term, specifically whether they were born prematurely or at full term.

Exclusion

1. Participants who lack comprehensive documentation of their periodontal status, making it impossible to accurately assess their oral health condition.
2. Participants who do not have definitive records of their birth weight, either in exact figures or as classified into specified weight categories.
3. Participants who lack verifiable information regarding their birth term, specifically whether they were born prematurely or at term.
4. Participants with missing data on key covariates such as body mass index (BMI), diabetes, smoking status and other traditional cardiovascular risk factors that may impact periodontal disease.
5. Incident fracture-hospitalization before Visit 4 (1996-1998).

Exposure

The main exposures of interest will be prematurity and low birth weight.
Prematurity was evaluated by asking the participants if they were born a month or more early. Birth weight was evaluated by asking the participants about their birth weight in pounds and ounces. Recalled exact birth weight was converted to kilograms. Those who could not provide their exact birth weight were asked to categorize their birth weight as low, medium, or high. Low birth weight (LBW) was defined as <2.5 kg, medium birth weight (MBW) as 2.5 to 4 kg, and HBW as ≥4 kg. Both qualitative and quantitative birth weight variables will be combined in one single variable to be used in the analysis.

Outcome

The primary outcome is periodontal health. Full-mouth periodontal examinations were conducted by trained examiners calibrated against a standard examiner. Examiners measured probing depth, gingival recession, and bleeding on probing at 6 sites per tooth. Attachment loss was calculated from probing depth and gingival recession. Through these measurements (attachment loss, probing depth, and bleeding on probing), the Periodontal Profile Class (PPC) was created in ARIC as previously validated (18) . The PPC categories were then collapsed into 3 categories for analyses: 1) healthy; 2) any periodontal disease; and 3) edentulism.
The secondary outcome is risk of fracture.
Incident fracture hospitalization was any hospitalization that occurred after the fourth visit (1996-1998) and before the end of ARIC follow-up for hospitalization (12/31/2011), and had an International Classification of Diseases, 9th revision (ICD-9) discharge code of 733.1, 733.19, 733.93–733.98, or 800–829. Hip fracture had an ICD-9 discharge code of 820.00–821.39. Hospitalizations were identified through two primary sources: patient self-report during annual telephone contact and active surveillance of hospital discharges in the communities in which the participants were recruited (19).

Covariates

Covariates that will be included in the models are: age, sex, race/center, BMI (in kg/m2), hypertension (defined as systolic blood pressure (BP) ≥140 mm Hg and diastolic BP ≥90 mm Hg or the use of antihypertensive medications, log-triglycerides, low-density lipoprotein cholesterol

(LDL-C), diabetes mellitus (defined as fasting plasma glucose ≥126 mg/dl, or self-reported physician diagnosis of diabetes or use of diabetes medications), smoking status (in pack-years), ethanol use, physical activity, education, insurance, use of lipid-lowering medication, beta-blockers, heart rate variability (HRV) measures, and menopausal status and HRT use (for women). Antidepressant medication, albumin, thiazide diuretic, loop diuretic, thiazolidinedione, bisphosphonate, proton pump inhibitor and glucocorticoid use will also be considered.

Main analysis

Percents or means (SD) will be presented across participant characteristics at visit 4 based on whether the participant had a history of prematurity.

P-values for group-differences based on prematurity and low birth weight (defined as weight <5.5 pounds) statuses will be obtained via chi-square for categorical variables or F-tests from analysis of variance for continuous variables.

We will first assess the association between both prematurity and low birth weight with the prevalence of each periodontal disease and edentulism compared to those of healthy participants using bivariate analyses.

We will then use logistic regression to show the association between the exposure variables of interest (prematurity and low birth weight) with each of periodontal disease and edentulism. Predictors which are significantly associated with each of periodontal disease and edentulism will be retained in the model if they have a significant effect on the coefficient of the independent variable of interest or will be forced into the model if known to have an important effect on either the independent or dependent variables. Interactions between these factors will also be assessed.

We will construct separate logistic regression models using each exposure variable prematurity and low birth weight to estimate odds ratios (95% confidence intervals) for each outcome (periodontal disease and edentulism) using the following models:

-Model 1: Adjusted by Prematurity / Low Birth Weight, age, sex, and race/center
-Model 2: Model 1 + Traditional Cardiovascular Risk Factors (i.e., smoking status + BMI+ systolic blood pressure + treatment for hypertension + diabetes + total cholesterol + HDL-C+ statin use+ ethanol use + physical activity + HRV measures)
-Model 3: Model 2 + education + income + insurance

Cox proportional hazards models will be used to estimate the hazards ratio (95% confidence intervals) for the association of prematurity and low birth weight with risk of hospitalized fractures (either all fractures or just hip fractures) by prematurity status and low birth weight.

To adjust for potential confounders, we will use models with increasing degrees of adjustments.

- Model 1: Adjusted by Prematurity / Low Birth Weight, age, sex, and race/center

- Model 2: Model 1 + Traditional Cardiovascular Risk Factors (i.e., smoking status + BMI + systolic blood pressure + treatment for hypertension + diabetes + statin use + total and HDL-C +

ethanol use + physical activity + HRV measures) + osteoporosis+ bisphosphonate use, proton pump inhibitor use, glucocorticoid use, albuminuria levels + postmenopausal status and hormone replacement therapy (in women) + thiazide diuretics+ estimated glomerular filtration rate + antidepressants

- Model 3: Model 2 + education + income + insurance

All analyses will be conducted using STATA version 18.

Limitations

- There is the likelihood for some residual confounding by other risk factors not included in these models.
- Changes in periodontal status could not be considered, as periodontal examinations were conducted only at ARIC v4.
- Self-reported birth weight and birth weight categories were collected without verification of their accuracy.
- No assessment of bone mineral density was present, as ARIC participants did not undergo routine dual energy X-ray absorptiometry scanning.

f) Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed. ☒ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, and Proteomics/Somalogic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ☐ Yes ☒ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ☐ Yes ☐ No
(The file ICTDER is distributed to ARIC PIs annually, 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 current derived consent file ICTDER05 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: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website→Publications→Proposal Search]

☒ 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)?

1- Takiar R, Lutsey PL, Zhao D, Guallar E, Schneider AL, Grams ME, Appel LJ, Selvin E, Michos ED. The associations of 25-hydroxyvitamin D levels, vitamin D binding protein gene polymorphisms, and race with risk of incident fracture-related hospitalization: Twenty-year follow-up in a bi-ethnic cohort (the ARIC Study). Bone. 2015 Sep;78:94-101. doi: 10.1016/j.bone.2015.04.029. Epub 2015 Apr 25. PMID: 25920689; PMCID: PMC4466148.

2- Pellanda LC, Duncan BB, Vigo A, Rose K, Folsom AR, Erlinger TP; ARIC Investigators. Low birth weight and markers of inflammation and endothelial activation in adulthood: the ARIC study. Int J Cardiol. 2009 May 29;134(3):371-7. doi: 10.1016/j.ijcard.2008.02.024. Epub 2008 Jun 27. PMID: 18585798; PMCID: PMC4682734.

3- Molinsky RL, Yuzefpolskaya M, Norby FL, Yu B, Shah AM, Pankow JS, Ndumele CE, Lutsey PL, Papapanou PN, Beck JD, Colombo PC, Demmer RT. Periodontal Status, C-Reactive Protein, NT-proBNP, and Incident Heart Failure: The ARIC Study. JACC Heart Fail. 2022 Oct;10(10):731-741. doi: 10.1016/j.jchf.2022.05.008. Epub 2022 Jul 6. PMID: 36175058; PMCID: PMC9976480.

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* __)**

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

*ancillary studies are listed by number https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website→Ancillary Studies→Approved Ancillary Studies]

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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC WebsiteàPublicationsàPublication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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