ARIC Manuscript Proposal #4717

SC Reviewed: 08/12/25 **Status: _____** **Priority: 2**

1.a. Full Title: Plasma Pentadecanoic Acid is Related to Cardiovascular Health

b. Abbreviated Title (Length 46 characters): Pentadecanoic acid and cardiovascular outcomes

2. Writing Group: Brian T. Steffen, Daniel Duprez, MD, David R. Jacobs, Jr, PhD, So-Yun Yi, PhD, MPH, Xia Zhou MS, Lyn M. Steffen PhD. We welcome any further nominations.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.

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3. Timeline: Analysis and manuscript draft have been completed
The following proposal is being submitted for the inclusion of a replication sample

4. Rationale

Pentadecanoic acid (PDA) is an odd-chain saturated fatty acid (SFA, C15:0) that has been used as a proxy of dairy fat intake [1-3], and it is currently being marketed as a supplement that boosts heart health and increases longevity [4]. This runs counter to the traditional doctrine that saturated fats are risk factors for cardiovascular disease (CVD) due to their influence on blood cholesterol [5, 6]. And yet, PDA has been inversely associated with heart failure [7] and CVD [8-10] in observational studies, consistent with potential cardiovascular benefits.

In agreement with observational studies, experimental evidence suggests that PDA affects proteins involved in cardiovascular health. Specifically, PDA has been shown to inhibit mammalian target of rapamycin (mTOR) [11] while activating peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and 5' adenosine monophosphate-activated protein kinase (AMPK) [11-14]. These proteins have been differentially implicated in blood pressure (BP) regulation, vascular tone, and hypertension [15-18] as well as cardiac structure and function [19-22]. And yet, it is unclear whether these experimental findings translate to humans. No study has tested whether circulating PDA levels may be related to lower BP, risk of developing hypertension, or related measures of systolic or diastolic cardiac function.

Considering the above observational and experimental evidence as well as the claims of health benefits of PDA, further examination of this fatty acid and cardiovascular outcomes was warranted. So far, we have shown that plasma PDA is associated with lower systolic BP (SBP), diastolic BP (DBP), and risk of incident hypertension in over 3,200 participants of the Coronary Artery Risk Development in Young Adults (CARDIA) study. To demonstrate the robustness of these findings, we are proposing to conduct a replication analysis in the Atherosclerosis Risk in Communities Study for these outcomes.

5. Main Hypothesis/Study Questions:

Plasma PDA will be inversely associated with systolic and diastolic blood pressure as well as incident hypertension as found in the CARDIA sample.

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).

Design: cross-sectional and prospective analyses will be performed. Fatty acids were measured in plasma samples at ARIC Visit 1 in participants at the Minneapolis field center. Cross-sectional associations will be tested with SBP and DBP at Visit 1, and prospective associations of PDA with 10-year risks of incident hypertension and coronary heart disease will also be tested, in-line with the CARDIA analysis.

Inclusion/Exclusion: We will exclude participants who do not have fatty acid or covariate data.

Exposure: Plasma PDA at Visit 1 (N=3,935).

Outcomes: SBP and DBP at Visit 1 as well as 10-year risks of incident hypertension and coronary heart disease. Hypertension will be defined as SBP≥140, DBP≥90, or initiation of antihypertensive medications, which will capture individuals with higher cardiovascular risk, to wit: the 140/90 definition has greater specificity and fewer false positives compared to the 130/80 definition as well as a higher positive predictive value for events. Coronary heart disease will be defined as fatal or non-fatal MI, percutaneous coronary intervention, coronary artery bypass graft surgery, or angina.

Statistical Analysis: Regression analyses will be conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC). Plasma PDA was examined as a continuous variable (per SD) as well as in quartiles to detect potential non-linear associations. Multiple linear regression analysis will evaluate the associations between plasma PDA and each of the outcome variables with adjustments for age, sex, race, education, field center, smoking status, physical activity, alcohol consumption status, waist circumference, prevalent diabetes, and self-reported use of BP medications. Cox regression estimated hazard ratios between plasma PDA and risk of incident hypertension over a median 10-year follow-up with adjustment for age, sex, race, education, field center, smoking status, physical activity, alcohol consumption status, waist circumference, and prevalent diabetes. Schoenfeld residuals will test the proportional hazards assumption. Participants will be excluded if they showed hypertension or took blood pressure-lowering medication at the baseline exam. Statistical significance was assessed using analysis of variance for continuous outcomes and chi-square tests for categorical outcomes.

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

b. If Yes, is the author aware that the file ICTDER03 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 __x__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes __x__ 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: ___x___ 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)?

No investigators have proposed a hypothesis-driven analysis of PDA with these outcomes.

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

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.cscc.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.

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