ARIC Manuscript Proposal #3742

PC Reviewed: 11/16/20   **Status: _____**   **Priority: 2**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.
   a. Full Title:
   Plant based diet types and risk of hospitalization with respiratory infection: results from the Atherosclerosis Risk in Communities (ARIC) Study

   b. Abbreviated Title (Length 26 characters):
   Plant based diets and respiratory infections

2.   Writing Group:
   Writing group members: Karla Kendrick, Hyunju Kim, Casey Rebholz, Lyn Steffen, Elizabeth Selvin, Stephen Juraschek

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

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3.   Timeline:
   Data analysis will begin once this proposal is approved and data is released with the goal of a manuscript draft by Spring 2021.

4.   Rationale:

   Plant-based diets have been associated with a host of health benefits. Diets low in or without animal products are associated with lower risks of obesity, diabetes, cardiovascular disease, and cancer.[1] However, the association of plant-based diets on the risk of developing an infection is less clear. Some of the health benefits of plant-based diets are thought to be due to modulation of inflammatory pathways and immune responses.[2,3] Several key micronutrients, such as vitamins A, C, and E, found in plant foods are essential for proper immune function, and deficiencies can lead to decreased activity of several immune cells such as macrocytic phagocytosis.[3,4] Therefore, it is possible that diets high in plant sources of food may contribute to lower infection risk.

   Studies that have examined the association of diet types and key micronutrients with certain infections suggest that plant-based diets might be associated with more favorable infectious outcomes. Plant-based diets derived using principal component analysis were associated with a lower risk of sepsis in a cohort of Black and White adults in the United States over age 45.[5] In this study, however, the association of plant-based diets and decreased risk of sepsis was not significant after adjusting for sociodemographic, lifestyle and clinical factors. In another study, low intake of fruits and vegetables was associated with a higher risk of hospitalization for influenza.[6] In the Nurses' Health Study, higher intake of oleic acid, found in vegetable oils, was associated with a lower risk of community-acquired pneumonia.[7] Adoption of a Mediterranean diet, high in vegetable, fruit, and nut intake, was associated with a lower rate of upper respiratory tract infections and inflammatory complications in Spanish children whose families enrolled in a nutritional education program.[8] In Korea, kimchi consumption was associated with lower prevalence of rhinitis.[9] Furthermore, vegetarian diets were associated with a lower rate of urinary tract infection in Taiwanese Buddhists.[10]

   Given the results of these studies, we hypothesize that plant-based diets are associated with a lower risk of hospitalization with common infections, such as pneumonia and influenza. Plant-based diets have been classified into healthy and unhealthy based on the quality of plant foods and their associations with adverse health outcomes like obesity, type 2 diabetes, cardiovascular disease, and cancer.[11] Unhealthy plant-based diets, high in refined grains, juice, sugar sweetened beverages, sweets and desserts, and potatoes have been associated with worsened outcomes like type 2 diabetes mellitus[11] and coronary artery disease.[1] This differential effect of plant-based diet type likely extends to other health outcomes. As such, our objective is to determine the associations of healthy and unhealthy plant-based diet types on the risk hospitalization with common respiratory infections.

5.   Main Hypothesis/Study Questions:
1. Are plant-based diets associated with risk of hospitalization with ICD codes consistent with infectious causes?
     a. Higher consumption of plant-based foods overall will be inversely associated with risk of hospitalization with infectious causes.
     b. Higher consumption of plant-based foods overall will be inversely associated with risk of hospitalization with pneumonia and influenza.
2. Does the risk of hospitalization with pneumonia and influenza differ based on type of plant-based diet?

  a. Higher consumption of healthy plant-based foods will be inversely associated with risk of hospitalization with pneumonia and influenza.

  b. Higher consumption of unhealthy plant-based foods will be positively associated risk of hospitalization with influenza and pneumonia.

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).

Data
This study will use data from participants in ARIC who completed dietary assessments at Exam 3.

Exposures
Exposures are diet types as determined by the Willett food frequency questionnaire completed at visit 3. These dietary assessments will be used to create indices of plant-based diet types, overall plant based diet (oPDI) healthy plant based diet (hPDI), and unhealthy plant based diet (uPDI), as described in previous work.[13,14] Briefly, we will classify all food items in the FFQ to 17 food groups. These food groups will be further divided into healthy plant foods (fruits, vegetables, whole grains, nuts and legumes, coffee and tea), unhealthy plant foods (refined grains, fruit juices, sugar-sweetened beverages, potatoes, sweets), and animal foods (animal fats, eggs, dairy products, meats, and miscellaneous animal foods). For the oPDI, all plant foods (healthy and unhealthy plant foods) will be positively scored. For the hPDI, only healthy plant foods will be positively scored. For the uPDI, only unhealthy plant foods will be positively scored. All plant-based diet indices will negatively score animal foods.

Outcomes
The primary outcome is hospitalization with pneumonia or influenza. All infectious cause of hospitalizations will also be explored. Hospitalization data will be obtained through patient self-report during annual telephone interviews and through ARIC community surveillance of hospital discharges. Diagnostic codes from hospital discharges will be used to extract hospitalizations for infections, and specifically pneumonia and influenza. Codes of interest include those for pneumonia and influenza (ICD-10: J09-J18; ICD 9: 480-488), and those related to acute non-respiratory infections, such as cellulitis, urinary tract infections, pyelonephritis, meningitis, infectious colitis, bacteremia and other viral, bacterial and protozoal infections (ICD-10: A00-B99, G00-07, L00-008, N10, N30, N39.0, R78.81; ICD-9: 001-139, 320-324, 590, 595, 680-686, 790.7). Any codes within these ranges will be used as the outcome of interest, given possible variation in physician selection of billing diagnoses.

Statistical Analysis
FFQs will be used to score participants for overall plant-based diet, healthy plant-based diet, and unhealthy plant-based diet. Food items within each group mentioned above will be summed by number of servings per day. Consumption of food items will be adjusted for caloric intake, given possible variation in the number of servings of food items in high or low caloric diets. Scores will be divided into quintiles for analysis. The follow up period for the outcomes of interest will

start after visit 3. Participants without dietary data will be excluded. In accordance with previous ARIC studies, participants with improbable dietary intakes ($<$500 or $>$3500 kcal for women and $<$700 or $>$4500 kcal for men) will also be excluded.[13,15]. We will exclude participants without complete covariate information.

Baseline characteristics of participants, and vitamin and mineral intake of participants will be described by quintiles of plant-based diets (PDI, hPDI, uPDI), and compared with chi square tests or ANOVA, as appropriate. Cox regression will be used to calculate hazard ratios and 95% confidence intervals for the risk of hospitalization, then specifically for pneumonia or influenza based on diet types. Covariates will include race-center, age, gender, education level, income level, alcohol intake, tobacco use, body mass index, and history of chronic respiratory disease (asthma, COPD), as determined by self-reported medical history.

Limitations

FFQ responses might be subject to misclassification. Hospitalization records might be incomplete or incorrectly coded. There are likely confounders, such as socioeconomic and lifestyle factors, that cannot be accounted for.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes   __x__ 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 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 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: http://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html

   ___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)?

- Diet Pattern and Respiratory Morbidity in the Atherosclerosis Risk in Communities Study
  - Lead author: Emily Brigham
- Dietary fiber, lung function, and chronic obstructive pulmonary disease in the atherosclerosis risk in communities study
  - Lead author: Haidong Kan
- Plant-Based Diets Are Associated With a Lower Risk of Incident Cardiovascular Disease, Cardiovascular Disease Mortality, and All-Cause Mortality in a General Population of Middle-Aged Adults.
  - Lead author: Hyunju Kim

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes ___x_ 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://sites.cscc.unc.edu/aric/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 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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