ARIC Manuscript Proposal # 1293

PC Reviewed: _10/09_/07   **Status:** __A__   **Priority:** _2__
SC Reviewed: _____   **Status:** _____   **Priority:** ____

1.a. Full Title: Dairy intake and changes in blood pressure: the ARIC study

  b. Abbreviated Title (Length 26 characters): Dairy and blood pressure

2.   Writing Group:
      Writing group members: Alvaro Alonso, Lyn M. Steffen, Aaron Folsom, others

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

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3.   Timeline:
      Data analysis: 3 months (Alonso)
      First draft of the paper: 6 months
      Co-author review/revision: 3-6 months

4.   Rationale:
High blood pressure (BP) remains one of the major public health problems in the US, because of both a high prevalence (27% of the US adult population according to 1999-2000 NHANES)[1] and its effect on cardiovascular disease risk. Diet, among other lifestyles, affects the risk of developing high BP. In fact, following an appropriate dietary

pattern is a key element in the prevention of this disorder. Current AHA guidelines for the primary prevention of high BP recommend a reduction in alcohol and sodium intake, an increase in potassium intake, and adhering to a DASH-type dietary pattern.[2] This diet, named after the Dietary Approaches to Stop Hypertension trial, is characterized by a high intake of fruits, vegetables, and low-fat dairy, and low intake of total and saturated fat.[3] However, there is scarce evidence supporting the independent effect of dairy on the risk of developing high BP. Three prospective studies have found lower risk of developing high BP among individuals with higher intake of dairy.[4-6] Among 3157 participants in the CARDIA study, aged 18-30 at baseline, higher intake of dairy was associated to lower risk of developing elevated BP (defined as BP of at least 130/85 or use of antihypertensive medication) after 10 years of follow-up, particularly among overweight individuals.[4] A similar inverse association between milk and dairy desserts, and risk of elevated BP was observed in the same population after 5 years of additional follow-up.[7] However, neither article reported specific results for low-fat dairy. In a small longitudinal study, in the context of the Framingham Children's Study, daily intake of 2 or more serving of dairy was associated to lower increases in BP over time among children.[5] Finally, in the SUN study, a prospective cohort in Spain that followed 5880 adults for an average of 2 years, low-fat but not whole-fat dairy was associated to a decreased risk of self-reported medical-diagnosed hypertension.[6] Overall, these results suggest a beneficial effect of dairy on BP, but it is not clear yet whether this association would be different for low-fat and whole-fat dairy, and which are the underlying biological mechanisms. Also, none of the previous studies have assessed the association between dairy intake and changes in BP considered as a continuous variable.

Several mechanisms have been proposed to explain the inverse association between dairy intake and BP. Calcium present in milk could reduce levels of BP, though a meta-analysis of randomized trials does not support an important role of dietary calcium on prevention of high BP.[8] However, dietary calcium interacts with saturated fats in the intestine, creating soaps that reduce calcium absorption. This phenomenon could explain why, if calcium is the responsible for the potential benefit of dairy, low-fat but not whole-fat dairy reduce BP or why an association between dairy and BP was only observed among individuals with low saturated fat intake in the NHLBI Family Heart Study.[9] Other nutrients abundant in dairy, such as magnesium or potassium, have been associated to lower risk of hypertension.[10] Finally, dairy products contain vasoactive peptides with angiotensin-converting enzyme inhibitory properties, elements that could reduce BP levels.[11]

The ARIC study is an excellent setting to study the association between dairy intake and changes in BP, given the breadth of information on confounding variables, the diverse study population and the potential for conducting future studies that address gene-diet interactions. Interestingly, these future studies could shed new light in the physiological mechanisms underlying this association. In addition, this study could be extended to study the association between dairy intake and metabolic syndrome components, link suggested from studies conducted in other populations.[4, 12]

5. **Main Hypothesis/Study Questions**:

The main objective of this study is to assess the association between dairy intake and the changes in BP over time among individuals free of high BP at the beginning of the ARIC follow-up. Specifically, we will address potential differences between low-fat and whole-fat dairy. We hypothesize that low-fat dairy exerts a beneficial action on BP levels, while whole-fat dairy intake would not cause changes in BP. As a secondary objective we plan to estimate potential effect modification by saturated fat intake[9] and body mass index.[4]

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).

We will conduct a longitudinal analysis studying the association between dairy intake at baseline and change in BP over time. Data from visits 1 to 4 will be used.

Exclusion criteria

Initially, we will exclude those individuals with missing dietary information or extreme energy intakes (less than 500 and 700 kcals for women and men, respectively, and greater than 3500 and 4500 kcals for women and men, respectively), and those with history of cardiovascular disease, diabetes, cancer or hypertension at baseline. Hypertension will be defined as systolic BP ≥140mmHg or diastolic BP ≥90 mmHg or both or use of antihypertensive medication. Also, participants without any BP measurement in visits 2 to 4 will be excluded.

Exposure assessment

The main exposure variable will be intake of dairy foods (total, low-fat, and whole fat). We will use dietary information both from the baseline visit and visit 3 through two different approaches. First, the main exposure will be diet obtained at baseline. In this approach, visit 3 dietary information will not be considered. Second, we will use diet at baseline as predictor for BP measured at visit 2 and 3 and we will use the average of dietary intake at baseline and at visit 3 to predict BP measured at visit 4.

Outcome variable

The main outcome variables will be levels of systolic and diastolic BP obtained in the examinations 1 through 4 in the ARIC participants. For the analyses, we will use the average of the second and third BP measurements obtained in each visit.

Statistical analysis

We will use general mixed linear models (PROC MIXED in SAS) to estimate separately differences in systolic and diastolic BP according to quintiles of total, low-fat and whole-fat dairy. All foods and nutrients will be adjusted by energy using the residuals method.[13] The models will include potential confounding variables for the association between dairy and BP: age, sex, socioeconomic status, race, smoking, body mass index, waist-to-hip ratio, physical activity, family history of high BP, total energy intake, and intake of alcohol, sodium, fruits and vegetables. In an additional analysis we will adjust for other nutrients that could be part of the causal pathway between dairy intake and BP, such as calcium, potassium and magnesium. Interactions between dairy and potential effect

modifiers will be explored using stratified analysis and tested with the likelihood ratio test.

Limitations

The proposed analysis presents several limitations:

- Measurement error in the exposure
  Diet assessment is one of the most challenging topics in nutritional epidemiology. We will use data from a reproducibility study conducted on ARIC patients to address this type of information bias.

- Measurement error in the outcome
  The outcome of interest, BP, will be just an approximation to the true value of BP. Because this error is independent of the exposure, the misclassification will be non-differential.

- Unmeasured and residual confounding
  Being ARIC an observational study, it is not possible to rule out the existence of unmeasured confounding. However, the available information includes the most important risk factors for high BP and cardiovascular disease. It is very unlikely the existence of an unmeasured confounder that could jeopardize the validity of our results.
  A different issue is the existence of residual confounding. As with the exposure and the outcome, measurements of control variables are not perfect. Then, using variables with some error means we will not be able to remove confounding completely from our estimations.

- Misspecification of statistical models
  Because we will be using linear models, departures from normality or lack of linear associations between the independent and dependent variables, would reduce the validity of our results. We will perform diagnostic tests, and conduct proper transformations, to ensure the appropriateness of the statistical models.

All these limitations are common to many epidemiologic studies and will be taking into account when interpreting and reporting results.

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 ICTDER02 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 _X_ No
   (This file ICTDER02 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 ICTDER02 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/search.php

    __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)?
#1208 Dietary intake is related to risk of developing elevated or high blood pressure in middle-aged adults: the ARIC study (First author: Lyn M. Steffen).

> This paper looks at the association between different foods and the risk of incident hypertension. Our proposal is different in several aspects: we will look at BP as a continuous variable (which will increase the statistical power), we will pay particular attention to differences between low-fat and whole-fat dairy; and, finally, we will assess effect modification between dairy intake and other variables (dietary and non-dietary), suggested by the literature.

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 at http://www.cscc.unc.edu/aric/forms/

12. 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.

<div align="center">References</div>

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2.   Appel LJ, Brands MW, Daniels SR, Karanja N, Elmer PJ, Sacks FM. Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. *Hypertension* 2006;47:296-308.

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13.   Willett WC, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* 1986;124:17-27.