

ARIC Manuscript Proposal #2495

PC Reviewed: 2/10/11

Status: A

Priority: 2

SC Reviewed: _____

Status: _____

Priority: _____

1.a. Full Title:

“Association of habitual milk intake with cognitive decline from mid-life to late-life in the ARIC Neurocognitive Study.”

b. Abbreviated Title (Length characters): Milk intake and cognitive decline

2. Writing Group:

Natalia Petruski-Ivleva, Anna Kucharska-Newton, David Couper, David Knopman, Lyn Steffen, A. Richey Sharrett, Gerardo Heiss, others welcome.

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

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3. Timeline: Analysis to be completed immediately. First draft completed by August 2015.

4. Rationale:

Cognitive impairment covers a large spectrum of clinical manifestations, from mild cognitive impairment (MCI) to dementia. The prevalence of dementia is estimated at 3.9% globally and at 6.4% in the United States (1). The age specific prevalence of dementia in the United States doubles by every five years of age, from 1.5% in persons aged 60-69 years to 40% in those 90-99. It is estimated that 16 million people in the US live with cognitive impairment, incurring substantial healthcare costs (2).

There is at this point no effective pharmaco-therapy to delay the onset or halt the progression of cognitive decline, although elements of the lifestyle are under active investigation as factors that can influence brain plasticity and neurocognitive decline (1). Recent studies suggest that oxidative stress may play an important mechanistic role in linking behavioral and environmental factors to neurocognitive impairment (1,3-5). Oxidative stress results from an imbalance of pro-oxidants and antioxidants that leads to accumulation of reactive oxygen species (ROS). The brain is particularly vulnerable to oxidative damage due to its high metabolic activity and low antioxidant defense (1). Therefore, protection against oxidative stress is considered to be critical for delaying brain aging and preventing neurodegenerative disorders.

Studies of dietary impact on cognition via oxidative stress have been few and inconclusive (6). D-galactose, a metabolic derivative of lactose that can generate ROS in a predictable fashion has been of particular interest. Based on extensive animal studies, a dose of D-galactose equivalent to 1-2 glasses of milk is sufficient has been studied in well-established animal models of aging. When administered subcutaneously for 5-7 weeks in mice D-galactose induces memory deficit, decrease the number of new neurons, and increase oxidative stress (7,8). High milk intake was associated with (higher) mortality in two large prospective studies in a population with low lactose intolerance, and with higher fracture incidence in women (8). Higher milk consumption has also been posited to influence the risk of certain cancers and of cardiovascular disease (9-11).

No human studies have examined the association of milk intake, separately from other dairy products, with cognitive decline from middle age to old age in a large prospective cohort. Consideration of milk intake separately from other dairy products is salient since fermented dairy products like yogurt and cheese have little lactose and do not have the same oxidative properties. The few prospective studies that have examined milk intake separately from other dairy products reported contradictory results, but were heterogeneous in their methodological approaches. Some of the important limitations were small sample size, restriction to one gender group, restriction to White or Asian population, assessment of cognitive status at one point in time, and older populations at baseline (12-14).

Milk intake is a widely prevalent, modifiable factor whose putative association with cognitive decline in adulthood deserves attention because of its high potential impact and public health relevance. The proposed study will measure the association of milk intake with cognitive decline in the Atherosclerosis Risk in Communities (ARIC) cohort. The cognitive assessment conducted in ARIC at three time points over the course of a 22-year follow-up, together with repeated measures of dietary intake provide an exceptional opportunity to estimate cognitive decline from middle age to old age in association with habitual intake of milk in adulthood.

5: Main Hypothesis/Study Questions:

Our goal is to examine the association of habitual milk intake with in the rate of cognitive decline form mid-life to late-life.

Hypothesis: Milk intake is associated in a dose-dependent manner with the rate of cognitive decline.

Conditional on rejecting the null hypothesis for an association between milk intake and cognitive decline, we will examine the association between milk intake and the risk of MCI and dementia.

Hypothesis: Milk intake is associated in a dose-dependent manner with the risk of MCI and dementia.

A further aim is to examine the association between low-lactose dairy products and the rate of cognitive decline form mid-life to late-life.

Hypothesis: The reported intake of low-lactose/fermented dairy products is inversely associated with the rate of cognitive decline.

Conditional on rejecting the null hypothesis for an association between low-lactose dairy intake and cognitive decline, we will examine the association between low-lactose dairy intake and the risk of MCI and dementia.

Hypothesis: Low-lactose dairy intake is inversely associated in a dose-dependent manner with the risk of MCI and dementia.

Based on reported associations between milk intake, oxidative stress and inflammation (8) and the cytokine measurements available on the ARIC cohort we further propose to examine the association between intake of dairy products and the pro-inflammatory molecules IL-1 and IL-6.

Hypothesis: Milk intake is associated in a dose-dependent manner with circulating levels of IL-1 and IL-6.

Exploratory aim: The reported intake of low-lactose/fermented dairy products is not associated with circulating levels of IL-1 and IL-6.

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 methodological limitations or challenges if present).

Study population

The study population will include participants of The Atherosclerosis Risk in Communities Study (ARIC) prospective cohort who completed cognitive status assessments at Visits 2, 4 and 5 as well as a dietary intake by FFQ at Visit 1 and Visit 3. Participants with a history of cancer, myocardial infarction, stroke, or heart failure at the Visit 2 baseline will be excluded.

Individuals at the extremes of caloric intake distribution will also be excluded from the analysis.

Assessment of milk intake

Milk intake will be measured at Visit 1 and Visit 3 as the reported average number of glasses of milk per day. Intake of both low-fat/skim and whole milk will be treated as a combined exposure. Habitual intake will be estimated as the average of Visit 1 and Visit 3 reported intakes.

Low lactose/fermented dairy products (fermented milk, yogurt, and cheese) will be measured as number of serving a day (1 serving = 1 cup of yogurt, or ½ cup of cottage cheese, or 1 slice of cheese). Habitual intake will be estimated as the average of Visit 1 and Visit 3 reported intakes.

Assessment of cognitive decline

Domain-specific and global cognitive decline will be assessed on the basis of performance on the following cognitive tests administered at Visit 2, Visit 4, and Visit 5: Delayed Word Recall, Digit Symbol Substitution, and Word Fluency tests. Ascertainment of cognitive status (including MCI and dementia) at Visit 5 was based on change in cognitive performance measures, neuropsychiatric information, medical/family history, subjective memory, neurologic/physical examination/labs, imaging, and medication use. Probable dementia was also assessed by hospital and death certificate codes.

Statistical analysis

Characteristics of the study population will be presented by groups of milk intake (none, less than 4 glasses per week, 4 or more glasses per week). Average decline in cognitive test scores will be calculated by groups of milk intake (none, less than 4 glasses per week, 4 or more glasses per week). Milk intake will combine skim, low-fat and whole milk into one category. Low lactose dairy products will include intake of yogurt, cottage cheese, and cheese.

Cognitive function will be assessed by three cognitive tests: the Delayed Word Recall Test, the Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale-Revised, and the Word Fluency Test. Comparison across cognitive tests will be done by calculating Z scores for each test standardized to visit 2. A composite global Z score will be calculated by using the average of the Z scores of the three tests, and standardized to visit 2 using global Z mean and global Z standard deviation. Latent growth modeling will be applied to examine change in cognitive performance (global and domain specific). A mixed effects model will be used to evaluate the association of milk intake with cognitive performance. Linear spline terms will be used with a knot at 6 years, corresponding to the time interval from visit 2 to visit 4.

Logistic regression will be used to ascertain the odds of MCI and dementia among different intake groups. Covariates considered will be age, race, sex, ARIC study center, total energy intake, education, cigarette smoking (current, former, never), alcohol consumption (g/week), physical activity (Baecke's physical activity score, leisure-related physical activity), bmi

(kg/m²), pre-existing conditions (stroke, MI, HF, diabetes), total protein intake (quintiles), protein to carbohydrate ratio, and fat intake as omega-3 and omega-6 (quintiles).

Analyses will be stratified by race with assessment of effect measure modification will be explored due to known differences in the frequency of lactose tolerance. The impact of attrition will be addressed using multiple imputation chained equations.

A limitation of the study is the use of a short version of the Willett FFQ to assess habitual intake. This will be addressed by using quintiles of reported intake of protein, carbohydrates, and fat, rather than the absolute estimated amount. Another limitation is the considerable potential residual confounding by other dietary components. To address some of this confounding the model will be adjusted for those dietary factors that are known to have an association with oxidative stress (alcohol, protein, and fat intake), and the use of propensity scores based on a larger number of nutrients.

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 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 ICTDER03 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 ICTDER03 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 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 AIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary 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 at <http://www.csc.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-year from the date of approval, the manuscript proposal will expire.

- 1) Caracciolo B, Xu W, Collins S, Fratiglioni L. Cognitive decline, dietary factors and gut-brain interactions. *Mechanism of aging and development* 2014, 136-137: 59-69.
- 2) Cognitive Impairment: a call for action, now! Centers for Disease Control and Prevention (CDC). February 2011.
- 3) Deschamps V, Barberger-Gateau P, Peuchant E, Orgogozo JM. Nutritional Factors in cerebral aging and dementia: epidemiological argument for a role of oxidative stress. *Neuroepidemiology* 2001, 20: 7-15
- 4) Cimini et al. Cocoa Powder triggers neuroprotective and preventive effects in a human Alzheimer's disease model by modulating BDNF signaling pathway. *J Cell Biochem* 2013, 114 (10): 2209-2220
- 5) Freeman et al. Obesity increases cerebrocortical reactive oxygen species and impairs brain function. *Radic Biol Med* 2013, 56: 226-233.
- 6) Crichton GE, Bryan J., Muphy KJ, Buckley J. Review of dairy consumption and cognitive performance in adults: findings and methodological issues. *Dement Geriatr Cogn Disord* 2010, 30: 352-361
- 7) Cui X, Zuo P, Zhang Q, Li X, Hu Y, Long J, et al. Chronic systemic D-galactose exposure induces memory loss, neurodegeneration, and oxidative damage in mice: protective effects of R-alpha-lipoic acid. *J Neurosci Res* 2006, 83:1584-90.
- 8) Michaelsson et al. Milk intake and risk of mortality and fractures in women and men: cohort studies. *BMJ* 2014; 349
- 9) Soedamah-Muthu SS, Ding EL, Al-Delaimy WK, Hu FB, Engberink MF, Willett WC, et al. Milk and dairy consumption and incidence of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies. *Am J Clin Nutr* 2011;93:158-71.
- 10) Song Y, Chavarro JE, Cao Y, Qiu W, Mucci L, Sesso HD, et al. Whole milk intake is associated with prostate cancer-specific mortality among U.S. male physicians. *J Nutr* 2013;143:189-96.
- 11) Lampe JW. Dairy products and cancer. *J Am Coll Nutr* 2011;30(5 Suppl 1):464S-70S.
- 12) Almeida OP, Norman P, Hankey G, Jamrozic K, Flicker L; Successful mental health aging: results from longitudinal study of older Australian men. *Am J Geriatr Psychiatry* 2006, 14; 27-35.

- 13) Vercambre MN, Boutron-Ruault MC, Ritchie K, Clavel-Chapelon F, Berr C: Longterm association of food and nutrient intakes with cognitive and functional decline: a 13-year follow up study of elderly French women. *Br J Nutr* 2009, 102: 419–427.
- 14) Yamada M, Kasagi F, Sasaki H, Masunari N, Mimori Y, Suzuki G: Association between dementia and midlife risk factors: the radiation effects research foundation adult health study. *J Am Geriatr Soc* 2003, 51: 410–414.