ARIC Manuscript Proposal # 1586

1.a. Full Title: Diet and Hospitalized Gallbladder Disease: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Diet and Gallbladder Disease

2. Writing Group:
   Writing group members: Pamela L. Lutsey, Aaron R. Folsom, Alvaro Alonso, Lyn M. Steffen, Jennifer A. Nettleton, Wayne D. Rosamond

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

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3. Timeline: Literature review – 2 months
   Data analysis – 3 months
   Writing the manuscript – 3 months
   Coauthor review and revisions – 2 months
4. **Rationale:**

Gallbladder disease (GBD) is one of the most common and costly of all digestive diseases\(^1\)–\(^5\). In the U.S., the prevalence of gallstone disease is 10\%-12\%\(^7\), and in 2004 it was associated with an estimated 1.8 million ambulatory care visits\(^2\). Hospital discharge data from 2006 report 335,000 hospitalizations due to cholelithiasis\(^5\). This number, however, is an underestimate of the actual hospital burden because most hospitalizations due to gallstones were for cholecystectomy, of which a high proportion are now performed laparoscopically without overnight hospitalization, and therefore not included in hospitalization statistics\(^3\).

In Western countries approximately 80\% of gallstones have cholesterol as their major component\(^6\), and many of the major risk factors for GBD are influenced by diet (i.e. obesity, diabetes mellitus, hypertrygliceridemia, insulin resistance)\(^7\), \(^8\). Thus, it is reasonable to hypothesize that diet may influence GBD development.

Despite the large public health burden of GBD, and potential biologic plausibility of a link between diet and GBD, relatively little is known about the relation of diet to the development of GBD. Most research in this arena has evaluated intakes of fiber, fat, cholesterol, refined sugars and total energy to GBD\(^8\), \(^9\). Only select food groups have been explored in relation to GBD, and only one study has evaluated the relation of dietary patterns to GBD\(^10\). In general, an inverse association has been observed between GBD risk and intakes of coffee\(^11\)–\(^14\), nuts\(^15\), \(^16\), and alcohol\(^7\), \(^17\). Clearly, additional research on the relation of food intake and dietary patterns to GBD is warranted.

To address key knowledge gaps, we propose to comprehensively evaluate the relation of dietary patterns and food groups to incident hospitalized GBD using data from the ARIC study. Further, we intend to evaluate whether observed relations are mediated by obesity, hyperinsulinemia, or dyslipidemia.

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

We hypothesize that:

1) Consumption of a ‘Prudent’ dietary pattern, dairy, whole grains, fruit, vegetables, fish, coffee, and alcohol will be inversely associated with incident GBD, whereas a positive association will be observed with consumption of a ‘Western’ dietary pattern, meat, refined grains, regular (sugar-sweetened) soda, and diet soda.

2) Relations of these food groups and patterns to incident GBD will be largely explained by metabolic abnormalities which are known to influence GBD development (i.e. obesity, hyperinsulinemia, and dyslipidemia).

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).**
Study Design
The analysis will be prospective. Incident GBD will be identified through hospital discharge diagnosis codes.

Inclusions/Exclusion
We will exclude participants with missing or implausible energy intakes. Further, participants will be excluded if they had prevalent GBD at baseline, or if they failed to complete the 1994-1996 medical history phone interview. The logic for the non-dietary exclusions, which ties into our desire to use the same GBD definition as previously used in ARIC\textsuperscript{18,19}, is outlined in the outcome variable section of this proposal.

In sensitivity analyses we will also exclude individuals with prevalent CVD and prevalent diabetes at baseline, as participants may have changed their diet after being diagnosed with these conditions.

Variables

Outcome variable: Hospitalized GBD has been previously defined in the ARIC cohort by Boland, Folsom, \textit{et al.}\textsuperscript{18,19} We plan to use the same definition as employed previously.

“Information regarding prevalent gallbladder disease at baseline was ascertained retrospectively during the medical history phone interview (1994–96). During the interview, participants were asked, “Have you ever been diagnosed by a doctor as having gallstones or a gallbladder attack?” and “At what age were you first told you had a gallbladder problem?” Those who responded “Yes” to the first item and whose response to the second item was an age younger than their age at the baseline visit were defined as having prevalent gallbladder disease at baseline. If a participant failed to complete the follow-up medical history interview, their baseline status was set to missing. Individuals with prevalent gallbladder disease or missing status at baseline were excluded from analysis. Among those with no prevalent gallbladder disease at baseline, incident cases were those having one of the following hospital discharge codes, assigned according to the International Classification of Diseases 9th revision (ICD-9), between the baseline examination and the end of 1996: 574.x, 575.x (except 575.8), 51.2x, 51.41, or 51.96. These codes generally include cholelithiasis, acute or chronic cholecystitis, and cholecystectomy, but do not include cancer of the gallbladder. Person-years (PY) of follow-up was calculated for each participant by taking the date of last known status through December 31, 1996 (noncases) or the date of the qualifying gallbladder disease hospitalization (cases) and subtracting the date of the baseline clinic exam. In addition to this verified hospitalization definition, we also examined self-report of gallbladder disease after the baseline exam using the two items from the follow-up medical history phone interview.”

Despite the fact that substantial time has passed since the end of follow-up in the Boland, Folsom, \textit{et al.}\textsuperscript{18,19} manuscripts, we intend to use the same follow-up end date (Dec 31, 1996) in our analyses. The reason for this decision is two-fold:

First, since the ARIC study began, the manner in which cholecystectomies are performed has changed dramatically, such that now most are done laparoscopically on an outpatient basis, as opposed to through open surgery\textsuperscript{2}. Outpatient cholecystectomies would be missed by ARIC cohort hospital surveillance. By ending follow-up at 1996, we will be capturing events before the shift from inpatient to outpatient cholecystectomies. Were we to include more contemporary events, we would be misclassifying individuals who had outpatient cholecystectomies as non-events. This misclassification would likely be differential, as participants with fewer comorbidities would be more liable to have cholecystectomies performed on an outpatient basis.
Secondly, the 1994-1996 health history questionnaire asked about GBD history, and age of first diagnosis. This data is useful in assessing the quality of our event ascertainment. In their previous work, Boland, Folsom, et al\textsuperscript{18} reported that cross-classification of hospitalization and self-reported case status yielded 97% agreement and a Kappa coefficient of 0.57.

Through 1996, Boland, Folsom, et al identified 397 events\textsuperscript{18}. While our primary analysis will end follow-up at the end of 1996, we will also conduct sensitivity analyses which, in order to increase power, will end follow-up December 31, 2000.

Exposure variables: We intend to use food groups that have been previously defined within the ARIC dataset\textsuperscript{20}. Dietary patterns will be created in our analytic set via principal components analysis. The patterns will be based on individual food items, including the associated frequency and portion size information. Varimax rotation will be used to create uncorrelated factors, and to enhance interpretability. Given our prior dietary pattern work in ARIC, we anticipate identifying ‘Western’ and ‘Prudent’ dietary patterns.

We acknowledge that measurement error is a problem of dietary data; however in ARIC reliability data for food groups and dietary patterns, needed for making corrections, is not available. Our interpretation of findings will take this limitation into account.

Potential confounding and mediating factors: Age, sex, race, center, education, income, energy intake (kcal/day), smoking status (former, current, never), pack-years (continuous), vitamin supplements (yes/no), physical activity (Baecke score), fasting serum insulin, HDL cholesterol, triglycerides and use of diabetes medications, fibrates, and statins.

Data Analysis Summary
Baseline characteristics of participants will be described using means and proportions. The dietary patterns and major food groups will be categorized into quintiles. Given their nonnormal distribution of consumption, intake of fish, coffee, alcohol, regular soda, and diet soda will be categorized based on their observed distributions.

Cox proportional hazards regression will be used to assess the relation between diet and incident GBD. Hazard ratios will be obtained by entering the quintiles (or categories) into the models as indicator variables, using the lowest intake category as the referent. To test the trend across levels of consumption, quintiles will be entered into the models as continuous terms. For categories, we will create ordinal variables to designate the categories and enter the ordinal variables into the models as continuous terms.

Model 1 will adjust for age, sex, race, center, education, income, and energy intake. Model 2 will adjust for Model 1 covariates, BMI, and non-dietary lifestyle factors, such as smoking, physical activity, and HRT use. In a mediation model (Model 3) we will further adjust for fasting serum insulin, HDL cholesterol, triglycerides, and use of diabetes medications, fibrates, and statins. This model aims to determine whether diet-GBD associations are mediated by metabolic abnormalities. In a final model (Model 4), we will account for dietary intercorrelation by adjusting for multiple food groups.
simultaneously. Interactions of the diet-GBD relationship by sex, race, and BMI will be evaluated by adding cross-product terms to the models.

In sensitivity analyses we will explore the use of cumulative average diet, as opposed to baseline diet. We will also evaluate the impact of omitting from our analyses individuals with prevalent diabetes and prevalent CVD at baseline.

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 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.csec.unc.edu/ARIC/search.php

      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)?

   There are only 2 ARIC proposals which use GBD as an outcome.
      MS# 675: Risk factors for incident gallstone disease.
      MS# 973: Apolipoprotein E polymorphism and cholelithiasis in a large, population-based cohort: The Atherosclerosis Risk in Communities (ARIC) Study.

      Diet was not used as an exposure in either of these, now published, manuscripts, thus there is no overlap.

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 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.

References


