1. **Full Title**: Association of dietary calcium intake with the incidence of cardiovascular heart disease and stroke in the ARIC Study.

   **Abbreviated Title (Length 26 characters)**: Calcium and CHD/Stroke Incidence

2. **Writing Group (list individual with lead responsibility first):**

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   **Other authors**:
   Eric Nowicki, MPH, RD is a doctoral student in the Epidemiology Department at UNC whose dissertation project will investigate the association of dietary calcium, dairy foods, and calcium supplementation with anthropometry as well as metabolic syndrome risk factors and incidence.

   June Stevens, PhD is a professor in the Departments of Nutrition and Epidemiology at UNC. She is an ARIC study investigator who specializes in nutrition and obesity epidemiology.

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3. **Timeline**: Immediately following approval, data set preparation and analysis will begin. The manuscript will be completed within six months of approval.

4. **Rationale**: 
Coronary heart disease and stroke are the first and third leading causes of death in the United States (CDC, 2003). That is, cardiovascular disease, which both heart disease and stroke are components of, claims over 950,000 lives each year in America. The major risk factors associated with heart disease and stroke are high blood cholesterol, high blood pressure, tobacco use, poor nutrition, and physical inactivity. Therefore, research must focus on ways to eliminate or reduce these risk factors in order to improve the health and prevent death.

Recent research evidence suggest mechanics by which dietary calcium may produce hypotensive, hypolipidemic, and anti-obesity effects. The influence of calcitrophic hormones on intracellular calcium has been proposed to link blood pressure and dietary calcium (Zemel, 2001). Low dietary calcium intake elicits influx of 1,25 dihydroxyvitamin D and parathyroid hormone to increase intracellular calcium and thereby increases vascular smooth muscle and blood pressure. Conversely, high calcium intake appears to suppress vascular smooth muscle and decreases blood pressure.

Similarly, intracellular calcium regulation may also influence lipolysis and lipogenesis and overall adiposity. Elevated intracellular calcium levels resulting from low dietary calcium intake occur in a variety of cells including adipocytes. Parikh and Yahovski (2003) propose that increased intracadipocyte calcium concentrations may increase lipogenesis and inhibit lipolysis thereby increasing overall adiposity.

In addition, dietary calcium may also affect adiposity via decreasing triacylglycerol absorption in the gastrointestinal tract. The interaction of calcium and saturated fatty acids may result in formation of insoluble calcium fatty acid soaps and thereby reduce fat absorption (Shahkalili, 2001). Despite these insights into the mechanism of dietary calcium, the studies to date have mainly focused upon blood pressure and dietary calcium intake. In particular, three meta-analyses have been conducted which all support the antihypertensive effect of high dietary calcium intake. (McCarron, 1999; Griffith, 1998; Birkett, 1998).

Over the past four years, dietary calcium intake has been uncovered as a potential modulator of energy metabolism and thereby may be an important target for reducing obesity risk. High calcium consumption has been proposed by M. Zemel to attenuate adipocyte lipid accretion and weight gain by inhibiting lipogenesis and promoting lipolysis, lipid oxidation, and thermogenesis. To date, several animal studies, observational studies and clinical trials have supported an association between high calcium intake and decreased adiposity. However, while the observational studies, such as CARDIA and HERITAGE, have suggested the inverse association of calcium intake and body composition, these studies are limited in size and generalizability.

Few studies have investigated the lipid-lowering effects of calcium or the impact of calcium on coronary heart disease and stroke. Yacowitz first exposed the lipid lowering potential of calcium (1965), finding decrease in both serum cholesterol and triglycerides given calcium supplementation. However, subsequent studies have been limited and inconsistent. The inconsistencies of findings are speculated to be due to high fat/cholesterol of the dairy intake. However, several longitudinal analyses recently conducted support the inverse relationship of calcium intake and lipid levels. Analysis the Quebec Family Study data showed negative coorelation of calcium with LDL, total, and total:HDL cholesterol (Jacqmain, 2003). Likewise, an inverse association between calcium intake and hyperlipidemia was reported in the analysis of the CARDIA study (Pereira, 2002).

To date, only two studies have specifically investigated the relationship of dairy food consumption and stroke incidence. The Honolulu Heart Program analysis conducted by Abbott et al (1996) showed a two-fold increase in thromboembolic stroke for non milkers as opposed to those who consumed two or more glasses per day. Likewise, Iso et al. (1999) found that all three mineral abundant in milk, Ca, Mg, and K, were associated with reduced relative risk for ischemic stroke.
Only one study has looked at coronary heart disease incidence and mortality in relation to calcium intake. The 28 yr prospective cohort study of Dutch civil servants and their wives (Van Der Vijver, 1992) did not find statistically significant associations of CHD mortality and low calcium intake. Despite the insignificant findings in this particular study, the severe lack investigations of CHD and stroke with calcium intake indicate a need for more research.

Furthermore, there is a need for continued exploration of the relationship of dietary calcium intake upon blood lipids, coronary heart disease, and stroke, and within the context of obesity. Investigation of the ARIC cohort will allow these analyses to be conducted in a large, biethnic, longitudinal population.

5. Main Hypothesis/Study Questions:

The following associations will be looked at amongst race-gender groups after adjusting for confounding factors. Additional analyses will consider these associations with stratification via obesity status as well as fat content of calcium intake.

   a. Is there an association between dietary calcium intake and incidence of coronary heart disease
   b. Is there an association between dietary calcium intake and incidence of stroke?
   c. Is there an association between dietary calcium intake and plasma lipid levels?
   d. Is there an association between dietary calcium intake and hypertensive blood pressure status?

6. Data (variables, time window, source, inclusions/exclusions):

   Exclusion Criteria
   ARIC study subjects will be excluded from analysis given lack of baseline or final dietary data, unusually low or high dietary intake values (<600 kcal/day or >6,000 kcal/day), and/or pregnancy within 6 months of baseline or any exam date.

   Variables
   Identification information
      ✓ Participant identification number
      ✓ Visit date
      ✓ ARIC site

   Demographics
      ✓ Ethnicity
      ✓ Gender
      ✓ Date of birth

   Anthropometrics
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.cscce.unc.edu/ARIC/search.php

Manuscript Proposal #1005
Eric Nowicki. Associations of dietary calcium, dairy foods, and calcium supplementation with anthropometry. (May 7, 2004)
Manuscript Proposal #1006  
Eric Nowicki. Associations of dietary calcium, dairy foods, and calcium supplementation with the incidence of metabolic syndrome and its components. (May 7, 2004)

Manuscript Proposal #461D  
Wang C. Dietary patterns and blood pressure over time in middle aged adults: the Atherosclerosis Risk in Communities (ARIC) study (January 10, 2003)

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)?

11. 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.