1.a. **Full Title**: Diet and Incidence of Venous Thromboembolism: The LITE Study

b. **Abbreviated Title (Length 26 characters)**: Diet and VTE

2. **Writing Group**:
   Writing group members: So Yun Yi, Lyn M. Steffen, Pam Lutsey, Mary Cushman, Aaron R. Folsom

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

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3. **Timeline**: Analysis: 3 months; Writing the manuscript: 6 months

4. **Rationale**:  
   Venous thromboembolism (VTE), which is defined as pulmonary embolism (PE), deep vein thromboembolism (DVT), or both, is caused by many modifiable and/or unmodifiable factors. In efforts to identify modifiable risk factors for VTE, studies have been conducted over the past decade or so about the association between dietary intake and incident VTE. Yet, results across studies have been inconsistent and some dietary factors have been understudied.  
   In an early publication, Steffen and colleagues reported greater intakes of folate, vitamin B6, n-3 fatty acids, fruit/vegetables, and fish were inversely associated with the incidence of VTE in
ARIC, while red/processed meat and the Western dietary pattern were positively associated (1). ARIC participants have since been followed for another 14 years, and cases of VTE have more than doubled. Therefore, we propose to examine whether the diet-VTE associations are consistent over time.

Further, we will examine nutrients, foods, and beverages relative to VTE reported in other studies. To date, at least 10 studies have examined the associations between dietary intake and incidence of VTE; however, results were not consistent across studies. Nutrient intakes, including folate, vitamin B6, vitamin E, n-3 fatty acids, and fiber, were inversely associated with incidence of VTE (1-3). Intakes of foods and beverages, including fruit, vegetables, fish, and coffee, were inversely associated with incident VTE (1, 4-8), while red and processed meat and diet soda were positively associated (1, 2, 6). The Mediterranean diet pattern was inversely associated with incidence of PE (9), while the Western diet pattern was positively associated (1, 2). Associations were null for nutrients vitamin B12, and saturated fatty acids, foods and beverages whole grain, refined grain, meat, dairy, sugar sweetened beverages, and the prudent and the DASH diet patterns (1, 2, 4-6).

5. Main Hypothesis/Study Questions:

1. Nutrient intakes:
   a. Folate, vitamin B6, n-3 fatty acids, vitamin E and fiber are inversely associated with risk of developing VTE.
   b. Vitamin B12 are not associated with risk of developing VTE

2. Food and beverage intakes:
   a. Fruit, vegetables, and fish are inversely associated with risk of developing VTE.
   b. Red and processed meat, sugar-sweetened beverages, and diet soda are positively associated with risk of developing VTE.
   c. Whole grain, refined grain, poultry, nuts, dairy products, and coffee are not associated with risk of developing VTE.

3. Diet patterns:
   a. The Western diet pattern is positively associated with risk of developing VTE.
   b. The Healthy Food Score is inversely associated with risk of developing VTE.

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: Prospective (VTE follow-up from 2002 to 2015 in relation to diet from visits 1 and 3)

Exclusion criteria: Because we have already examined VTE before Jan 1, 2002, as reported by Steffen et al (1), these cases will be excluded; other exclusions include missing or outlying dietary intake (lower and upper 1% of distribution), anticoagulant use at visit 4, and not white or black.
Exposure variables: The 66-food item food frequency questionnaire (FFQ) was administered at visit 1 and visit 3 and these diet data will be averaged. Nutrient intake: n-3 fatty acids, folate, vitamin B6, vitamin B12, vitamin E, and fiber; Food intake: whole grains, refined grains, red and processed meat, fish/seafood, poultry, nuts, fruit, vegetables, dairy products, sugar-sweetened beverages, diet beverages, and coffee; Dietary patterns: PCA derived prudent/Western dietary patterns and the Healthy Food score (10).

Outcome: Incident DVT of leg or PE not related to cancer. Cancer-related VTE and non-leg DVT cases will be censored at time of event.

Confounding factors (at visit 4 when present, otherwise as indicated): age, sex, race, field center, education (V1), smoking (status and pack-years), drinking status, energy intake (averaged V1+V3), physical activity (V3), BMI, and diabetes.

Analysis Plan:
After description of the data, Cox proportional hazards regression analyses will be used to examine the association between quintiles of dietary intake (nutrients, foods, or diet patterns) and risk of developing VTE, adjusting for confounding factors.
Model 1 will be adjusted for age, sex, race, field center, education, and energy intake.
Model 2 will be adjusted for Model 1 + smoking, drinking status, physical activity.
(Nutrient models will be adjusted for selected macro and micro nutrient intakes; foods will be adjusted for the Healthy Food Score (minus the food group exposure of interest)).
Model 3 will be adjusted for model 2 + BMI, diabetes
We will explore race and sex interactions by including cross-product terms in the models.

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 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 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 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.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)?

ARIC manuscript proposal #1016

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  \textbf{X} Yes    ____ No

11.b. If yes, is the proposal
\textbf{X} A. primarily the result of an ancillary study (list number* \_2001.16\_)
___ 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 \url{https://www2.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 \url{http://publicaccess.nih.gov/} are posted in \url{http://www.cscc.unc.edu/aric/index.php}, under Publications, Policies & Forms. \url{http://publicaccess.nih.gov/submit_process_journals.htm} shows you which journals automatically upload articles to PubMed central.

References