

## ARIC Manuscript Proposal # 3372

**PC Reviewed:** 4/9/19                      **Status:** \_\_\_\_\_                      **Priority:** 2  
**SC Reviewed:** \_\_\_\_\_                      **Status:** \_\_\_\_\_                      **Priority:** \_\_\_\_\_

**1.a. Full Title:** Weight change and risk of venous thromboembolism over 9 years in the ARIC cohort.

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

**2. Writing Group:**

Writing group members: Simone French, Pamela Lutsey, Wayne Rosamond, Richard MacLehose, Mary Cushman, Aaron Folsom

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

**First author:** Simone French

Address: 1300 South Second Street Suite 300

Division of Epidemiology & Community Health University of Minnesota

Phone: 612-626-8594

E-mail: frenc001@umn.edu

**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: Aaron Folsom

Address: same as above                      Phone: 612-626-8862

E-mail: folso001@umn.edu

**3. Timeline:** March-May 2019 data analysis and interpretation; background and methods writing

June-July 2019 results and discussion writing; circulate to co-authors for feedback; revise as needed

August 2019 journal submission and revision process

**4. Rationale:** Obesity is a major risk factor for venous thromboembolism (VTE—deep vein thrombosis or pulmonary embolism). Only one previous prospective cohort study that we are aware of has examined weight change as a risk factor for VTE (Horvel, Braekkan & Hansen, 2016). That study found that obesity and weight gain were independently associated with higher risk of future (unprovoked) VTE. Highest risk for VTE was observed in obese participants who gained 7.5 kg or more. Additional analyses that examined weight change with incident cancer as a competing event found that weight loss among overweight/obese participants was associated with higher risk of provoked VTE.

**5. Main Hypothesis/Study Questions:** The proposed research examines weight change over a 9-year period in ARIC (V1-V4) and its association with future VTE (after V4). It is hypothesized that weight gain, independent of baseline weight status, will be associated with higher risk of future VTE compared with stable weight. A significant interaction between baseline weight and weight gain is expected, with the highest risk observed among those with obesity at baseline and weight gain over the follow up period.

**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 analysis of VTE incidence after V4 in ARIC.

Independent variable: weight change from baseline (1987-89) to ARIC clinic visit 4 (1996-98). Categorical weight change from baseline to visit 4 will be used in the analysis.

Covariates: Visit 1 age, gender, race, smoking status, physical activity, height and weight; Visit 3 physical activity; Visit 4 smoking;

Dependent variable: VTE occurrence after Visit 4 through 2015.

Exclusions: participants with Visit 4 VTE history or anticoagulant use; cancer diagnosis/treatment within 5 yrs of visit 4.

Follow up defined as time elapsed between visit 4 and incident VTE, death, date of last contact or December 31 2015.

Cox proportional hazards regression models will be used to estimate hazard ratios with 95% confidence intervals for VTE for categories of weight change. Stable weight will be the reference category. Weight loss and weight gain will be the comparison categories. Categories of weight change (Visit 4 - Visit 1) will be defined a priori and consistent with Horvel, Braekkan & Hansen, 2016. Reference category: weight stable (0 - +7.4 kg); Weight gain ( $\geq 7.5$  kg); Weight Loss ( $\leq -0.1$  kg). Marginal structural model weights will be used to adjust for potential confounding by time-varying confounders, such as physical activity and smoking. Physical activity change (Visit 1 and Visit 3) will be examined in exploratory analyses for its independent association with VTE incidence.

Stratified analysis will examine the association between weight change category and incident VTE by baseline body mass index (normal weight; overweight; obese). Interactions between baseline weight status and weight gain categories over time will be examined.

Sensitivity analyses will be conducted to examine results with post V4 censoring of cancer diagnosis/treatment and other conditions that "provoked" VTE; and with adjustment for post V4 use of anticoagulants and smoking.

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.csc.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)? Note: I am working with the authors of the manuscripts below.

Cushman M, O'Meara ES, Heckbert SR, Zakai NA, Rosamond W, Folsom AR. 2016. Body size measures, hemostatic and inflammatory markers and risk of venous thrombosis: the longitudinal investigation of thromboembolism etiology. *Thromb Res* 2016 144: 127-132.

Wattanakit K, Lutsey PL, Bell EJ, Gornik H, Cushman M, Heckbert SR, Rosamond WD, Folsom AR. 2012. Association between cardiovascular disease risk factors and occurrence of venous thromboembolism: A time-dependent analysis. *Thromb Haemost* 2012 108: 508-515.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? \_\_\_x\_\_\_ Yes \_\_\_ No

11.b. If yes, is the proposal

\_\_\_x\_\_\_ A. primarily the result of an ancillary study (list number\* 2001.16\_\_LITE\_\_)

\_\_\_ 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/>

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 <http://publicaccess.nih.gov/> are posted in <http://www.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to PubMed central.

#### References

Horvel LD, Braekkan SK, Hansen J-B. Weight change and risk of venous thromboembolism: The Tromso Study. Plos One 2016 11(12): e0168878.doi:10.1371/journal.pone.0168878