ARIC Manuscript Proposal # 1679

PC Reviewed: 8/10/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Leg length and incident venous thromboembolism: The Longitudinal Study of Thromboembolism Etiology (LITE)

b. Abbreviated Title (Length 26 characters): Leg length and VTE

2. Writing Group:

Writing group members: Pamela L. Lutsey, Aaron R. Folsom, Susan R. Heckbert, Mary Cushman, and Weihong Tang; other interested investigators are welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _PLL_ **[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:

Venous thromboembolism (VTE) is associated with significant morbidity and mortality, with an incidence of approximately 1 per 1,000 person-years, and a case-fatality rate of about 10%[1-3]. Recently, several cohorts have reported that height is positively associated with VTE risk[3-7]. In general, individuals in the greatest sex-specific quartile of height were at about 1.5 to 2 times greater risk of VTE than those in the lowest height quartile. Authors of these studies have speculated that the positive association seen between height and risk of VTE could occur as a consequence of either 1) taller people simply having longer veins, thus a greater area where a thrombus could occur, and/or 2) greater hydrostatic pressure among taller individuals[8, 9]. In LITE, the vast majority of deep vein thromboses occurred in the lower extremities (91%), with only 7% occurring in the upper extremities, and 2% occurring at an 'other' site[2].

In contrast, tall stature is has generally been associated with lower risk of coronary heart disease (CHD) and stroke[4, 10-18]. As expected, given the intrinsic correlation between height and leg length, greater leg length has also generally been found to be inversely related to cardiovascular risk factors and morbidity[19-21]. The most commonly proposed explanations for these associations are that height (and leg length) are markers of early childhood environment[22, 23], and as early childhood nutrition and/or socioeconomic status influences adult height, early childhood environment may impact CHD and stroke outcomes. Height is, however, highly genetically regulated[24], and it is also possible that height and CHD risk have shared genetic factors.

Although a number of recent studies have explored the association of height to risk of VTE[3-7], it is unknown whether leg length is associated with VTE risk. Using LITE data, we propose to more carefully scrutinize the observation that height is a VTE risk factor by specifically evaluating the relation of leg length to risk of VTE. Further, we will explore whether leg length is associated with risk of incident VTE independently of height.

5. Main Hypothesis/Study Questions:

We hypothesize that:

1) Leg length will be positively associated with incident VTE, and that this association will persist even after accounting for total height.

2) Trunk length (as assessed in ARIC and CHS by length of the torso, neck, and head) will be unrelated to VTE risk.

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).

<u>Study Design</u>

The analysis will be prospective. Incident VTE has been identified through hospital discharge diagnosis codes, and validated by medical record review.

Inclusions/Exclusion

We will exclude participants with self-reported prevalent VTE at baseline.

Variables

Outcome variables: Total VTE, idiopathic VTE, secondary VTE. Additionally, we will explore an outcome variable including DVTs originating in the lower extremities and all PEs (excluding DVTs in arm and other non-leg sites).

Exposure variables: Leg length, trunk length, and height.

At baseline, height, and seated height were measured. Seated height will approximate trunk length. Leg length will be computed as total height minus seated height.

Potential confounding and mediating factors: Age, sex, race, study (i.e. ARIC, CHS), education, physical activity (Baecke score), diabetes, markers of childhood SES assessed at ARIC visit 4 (i.e. parental education, parental home ownership), VTE genetic risk factor (i.e. factor V Leiden, factor II G20210A, and ABO blood type) and select markers of coagulation (e.g. factor VIII and aPTT).

Data Analysis

Baseline characteristics of participants will be described using means and proportions. Cox proportional hazards regression will be used to assess the relation between leg length and incident VTE, with adjustment for pertinent covariates.

Our first model will adjust for age, sex, race, and study (i.e. ARIC or CHS). A second model will additionally adjust for education, physical activity (Baecke score), waist circumference, and diabetes. If in preliminary analyses we find that markers of VTE genetic risk factors (i.e. factor V Leiden, factor II G20210A, and ABO blood type) and markers of coagulation (e.g. factor VIII and aPTT) are related to height, we will explore additionally adjusting for these markers, which may be on the causal pathway between height and VTE. We will also evaluate the impact of adjusting for markers of childhood SES assessed at ARIC visit 4, namely parental education, and parental home ownership. This analysis will, by necessity, be limited to those who participated at ARIC Visit 4. Interactions of the leg length and VTE relationship by age, sex, race, and study will be evaluated by adding cross-product terms to the models.

Two strategies will be used to evaluate whether leg length is associated with incident VTE independently of height:

1) Standard approach: We will standardize leg length and height per 1 standard deviation, and then include them simultaneously in the models as continuous variables. The anthropometric measure with the stronger association, as determined by the beta coefficients and confidence intervals, is more likely to be the anthropometric measure influencing VTE risk in this cohort. If strong relations are observed for both leg length and height in the same model, it implies that they are independently related to VTE risk.
2) Residual method[25]: 'Height adjusted leg length" will be computed as the residuals from a linear regression model with leg length as the dependent variable and

height as the independent variable. The leg length residuals by definition provide a measure of leg length uncorrelated with height, thereby isolating the variation in height due to leg length. 'Height adjusted leg length' will then be entered into the Cox models.

In secondary analyses, using the same methods as above, we will explore trunk length as an exposure, and VTE subtypes (i.e. idiopathic, secondary, and PE/DVTs of leg origin) as outcomes.

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 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? __X*__ Yes ____ No
*VTE genetic risk factors will only be included in the models if they are found to be related to height.

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"?
__X__ 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/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)?

MS#1082: Interrelations of Obesity with Hemostatic and other Risk Factors for Venous Thrombosis: the LITE study

As part of this analysis Dr. Mary Cushman proposes looking at the relation of height to risk of incident VTE. She did not propose to look at leg length, thus there is no overlap. Please note that Dr. Cushman is also a coauthor on this manuscript proposal.

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: 1998.03)

___ 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

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