**ARIC Manuscript Proposal #2579**

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| **PC Reviewed: 7/13/15** | **Status: A** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: Genetic risk score for height and the incidence of venous thromboembolism: a prospective study

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

**2. Writing Group**:
Writing group members:

Nicholas Roetker
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Susan Heckbert
Mary Cushman
Aaron Folsom

Other interested investigators are welcome to join the writing group

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


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**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).


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## 3. Timeline:

Start Summer 2015

## 4. Rationale:

Taller body height is associated with greater risk of VTE.[1–9] An analysis of the Longitudinal Investigation of Thromboembolism Etiology (LITE) found that leg length and body height modeled separately were each associated positively with risk of VTE in risk factor-adjusted models [HR (95% CI) per 1-SD increment in leg length and height: 1.18 (1.09, 1.29) and 1.14 (1.05, 1.24), respectively].[8] The physiologic explanation underpinning this increased risk remains to be identified; some proposed mechanisms include greater venous surface area, a greater number of venous valves, and greater hydrostatic pressure in taller people.[8]

A number of studies have found genetic variants related to height,[10–18] the most recent of which was a meta-analysis that found 697 SNPs explaining 20% of the heritability for height.[18] It is unclear whether the genetically-related component of height is related with VTE risk. Finding this out would provide evidence as to whether the frequently observed association between greater height and increased VTE risk is causal.

Given that over 9,000 ARIC and over 3,000 CHS participants of European ancestry have genotyping data, LITE represents a valuable setting in which to explore the connection between the genetics of height and VTE risk. We will use the height SNPs from the meta-analysis as an instrument for height and determine how the instrument is related with risk of VTE. We will also find the direct association between the GRS for height and risk of VTE.

## 5. Main Hypothesis/Study Questions:

1a. Higher genetically predicted height will be associated with increased risk of VTE.

1b. The positive association between higher measured height and VTE will be attenuated with inclusion of genetically predicted height in the model.

2. Higher genetic risk score (GRS) for height will be associated with greater hazard of 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).

**Design:** prospective cohort
**Endpoints:** VTE incidence

**Exposure:** height genetic risk score
**Inclusion:** 9,349 ARIC and 3,388 CHS participants of European ancestry who provided consent for genotyping.
**Exclusions:** prevalent VTE at baseline, use of anti-coagulants at baseline, no consent for DNA use, missing height SNPs or visit 1 measured height
**Covariates:** age, sex, HRT, BMI, diabetes, eGFR, CRP, factor VIII, and aPTT
**Analysis:** First we will reconfirm that measured height is associated with VTE risk using a Cox model adjusting for age, sex, and waist circumference. After excluding SNPs showing evidence of linkage disequilibrium ($R^2 > 0.1$), we will create a weighted GRS for each participant by taking $\sum$(meta-analysis SNP beta value * # of allele copies) over all the SNPs.

We will check that two assumptions for Mendelian randomization are met: the GRS is associated with height, and the GRS is not associated with other VTE risk factors (i.e., no confounding and no pleiotropy).

Then we will do the following, separately by ARIC and CHS:

Analysis 1) perform an instrumental variable analysis using the weighted GRS for height as the instrument, phenotypic height as the exposure, and VTE outcome, adjusting for sex and age (in Stata)

Analysis 2) perform a Cox regression with weighted GRS as the exposure and time to VTE as the outcome, adjusting for sex and age

In additional models, we will adjust Analysis 2 for measured height and other VTE risk factors. We will also check the association of each of the height SNPs with VTE risk, correcting for multiple testing with Bonferroni correction.

If an association is observed, we will seek replication in additional cohorts.

**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?**
**__x__ 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"?**
**__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)?**

None

**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/

**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.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

**References**


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