Published in final edited form as:
Thromb Haemost. 2011 July 4; 106(1): 113–120. doi:10.1160/TH11-02-0100.

Longer legs are associated with greater risk of incident venous thromboembolism independent of total body height: The Longitudinal Study of Thromboembolism Etiology (LITE)

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Abstract

Several studies have reported that taller individuals are at greater risk of venous thromboembolism (VTE). We hypothesized that longer leg length would be positively associated with incident VTE, and would explain the height association. LITE ascertained VTE in a prospective population-based sample of 21,860 individuals aged 45 and older. Leg length was measured as standing height minus sitting height. Cox regression models were adjusted for age, race, sex, waist circumference, diabetes, and factor VIII. To evaluate whether leg length was associated with VTE risk independent of height we standardized leg length and height per 1 standard deviation (SD), and then included them simultaneously in Cox regression models. A total of 641 incident VTE cases accrued over a median follow-up of 16 yrs. Participants in the highest quintile of leg length were at 59% (95% CI: 22%-108%) greater risk of VTE, relative to the lowest quintile. For height, risk was 45% (12%-88%) greater for those in the highest quintile, compared to the lowest. When leg length and height were modeled simultaneously leg length remained associated with VTE risk (HR per 1 SD: 1.21 (1.04-1.40) while height was unrelated (HR per 1 SD: 1.00 (0.86-1.16). To conclude, participants with longer legs were at greater risk of incident VTE, and leg length explained the relation of height to VTE. It remains to be established whether this finding is due to greater venous surface area, a larger number of venous valves, or greater hydrostatic pressure among individuals with longer legs.

Keywords

height; leg length; venous thromboembolism; Atherosclerosis Risk in Communities Study (ARIC); Cardiovascular Health Study (CHS)

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Disclosures: We have no conflicts to declare.

Introduction

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 cohort studies reported that height is positively associated with VTE risk(3-8). In general, individuals in the greatest quantile of height were at about 1.5 to 2 times greater risk of VTE than those in the lowest height quantile. Possible physiologic explanations include taller people having greater venous surface area or more venous valves where a thrombus could occur, and/or greater hydrostatic pressure(9, 10). Along with the fact that most VTE originate in the legs, these explanations would lead to a hypothesis that leg length is the important factor rather than simply height.

Although a number of recent studies reported the association of height with risk of VTE(3-8), it is unknown whether leg length is specifically associated with VTE risk, or whether leg length is the reason for an association of height with VTE. Using LITE data, we further studied the association of height with VTE risk by evaluating the relation of leg length to risk of VTE. We hypothesized that leg length would be positively associated with risk of incident VTE, and would explain the height association. We also hypothesized that torso length would be unrelated to VTE risk.

Materials & Methods

Study Design

The Longitudinal Study of Thromboembolism Etiology (LITE) is a prospective study of VTE occurrence in two population-based cohorts: the Atherosclerosis Risk in Communities (ARIC) study(11) and the Cardiovascular Health Study (CHS) (12, 13). Extensive cardiovascular disease risk factor information was collected in both studies, generally in a similar fashion, using standard measures. Local institutional review boards approved the study protocols, and all participants gave informed consent.

The ARIC study is a multi-center population-based prospective cohort study investigating the etiology and natural history of atherosclerosis in middle-aged adults(11). Participants were recruited from four US communities: Forsyth County, NC; Jackson, MS; suburbs of Minneapolis, MN; and Washington County, MD. The study cohort included 15,972 white and black men and women aged 45-64 years at baseline, in 1987-1989.

CHS is a population-based longitudinal study of coronary heart disease and stroke in adults aged 65 years and older(12, 13). A total of 5,201 men and women sampled from Medicare eligibility lists were recruited in 1989 to 1990 from four U.S. communities: Forysth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA. An additional 687 African-American participants were recruited from 1992 to 1993.

Exposure & Covariate Assessment

Age, sex, and race were self-reported. Anthropometrics were taken with participants dressed in light clothing and without shoes. Standing height was measured using a wall-mounted ruler. Seated height was measured with the participant seated on a stool against a wall-mounted ruler. Trunk length was estimated as seated height minus stool height. Leg length was estimated as standing height minus trunk length. Weight was quantified using a balance scale. Waist and hip circumferences were measured to the nearest centimeter with the participant standing; waist circumference at the level of the umbilicus, and hip circumference at the maximum protrusion of the gluteal muscles. Height and circumference measurements were to the nearest centimeter in ARIC, and nearest half-centimeter in CHS.

Prevalent diabetes was defined as fasting blood glucose ≥126 mg/dL, nonfasting blood glucose ≥200 mg/dL, physician diagnosis of diabetes, or being on diabetes medication. Factor VIII was assessed at baseline soon after phlebotomy, using published methods(14, 15).

VTE Identification and Classification

ARIC participants were contacted annually by telephone or through clinic visits, and CHS participants were contacted twice a year, alternating clinic visits and telephone calls. Hospitalizations were identified by participants or proxy reports in both ARIC and CHS, by surveillance of local hospital discharge lists in ARIC, and by a search of Medicare records in CHS. For each hospitalization identified, all ICD-9-CM discharge codes were recorded.

All records with ICD-9-CM codes indicating possible VTE (415.1×, 451, 451.1×, 451.2, 451.8×, 451.9, 453.0, 453.1, 453.2, 453.8, 453.9, 996.7×, 997.2, and 999.2, and procedure code 38.7) were identified, copied, and independently reviewed by two physicians (ARF and MC) (16). Deep vein thrombosis (DVT) was defined on the basis of duplex ultrasound or venogram or, in rare cases, by impedance plethysmography, computed tomography, or autopsy. Definite PE required ventilation/perfusion scanning showing multiple segmental or subsegmental mismatched perfusion defects, or a positive pulmonary angiogram, computed tomography, or autopsy(16). Events were further classified as idiopathic or secondary (occurring within 90 days of major trauma, surgery, hospitalization, or marked immobility or associated with active cancer or chemotherapy). Incident VTE was defined as the first occurrence of validated deep-vein thrombosis or pulmonary embolism from baseline through the end of follow-up; December 31, 2005 for ARIC and December 31, 2001 for CHS.

Statistical Analysis

Excluded from the analysis were participants who at baseline self-reported prevalent VTE (n = 630), were taking anticoagulants (n = 185), or had missing sitting height data (n = 142), resulting in an analytic dataset of 20,773 participants. Baseline characteristics of the participants were described using means and proportions, stratified by sex-specific leg length quintile. Partial correlation coefficients, adjusted for age, sex, race and study were computed to describe the interrelation of height, leg length, and torso length.

Cox proportional hazards regression was used to assess the prospective relation between leg length and incident VTE, with adjustment for pertinent covariates. Person years accumulated from the participant's baseline exam until incident VTE, death, loss-to-follow-up, or for ARIC participants the end of 2005, and for CHS participants the end of 2001. Our first model adjusted for age, sex, race, and study (i.e. ARIC or CHS). Model 2 additionally adjusted for other VTE risk factors in LITE: waist circumference, diabetes status and factor VIII level. VTE subtypes (i.e. idiopathic, secondary) were also analyzed as outcomes. Interactions of leg length with sex, race, and study were evaluated by including cross-product terms in the VTE models. The proportional hazards assumption was tested by examining whether the ln(-ln) survival curves for the leg length quintiles were parallel. There was no evidence of violation.

Leg length, height, and torso length were represented in a number of ways in the Cox models. Given the differing range of values between men and women for leg length and height, sex-specific quintiles and standard deviations were computed. As there was not statistical evidence of an interaction of the leg length and VTE relation by sex, the sex-specific quintiles and standard deviations were re-combined. In this way, we evaluated the relation of leg length and height relative to others of the same gender. The absolute relations of leg length and height to VTE risk are also presented, per 5 cm leg length increment, and 10 cm height increment.

To describe the overall relation of leg length, height, and torso length to incident VTE, hazard ratios (95% CIs) were obtained by entering the quintiles into the models as indicator variables, using the lowest quintile as the referent. Tests of the linear trend across the quintiles were conducted by including the quintiles in the models as a continuous term. Two analytic strategies were used to evaluate whether leg length explained the previously reported association between height and VTE:

1. Mutual adjustment: We standardized leg length and height per 1 standard deviation, and then included the standardized variables simultaneously in the models, as continuous variables. The anthropometric measure with the stronger association, as determined by its beta coefficient and confidence interval, is more likely to be the anthropometric measure influencing VTE risk in this analysis. If strong relations were observed for both leg length and height in the same model, it would imply that they were independently related to VTE risk.

   Model stability may be disturbed if covariates have a high degree of collinearity(17). Given our intention of including leg length and height in the same models, we evaluated 'tolerance' in order to confirm that including both measures in the models was reasonable. Tolerance for a variable is defined as $1 - R^2$, where R^2 is obtained from the regression of the variable on all other regressors in the model(18). A tolerance of ≤0.10 was set as the criterion for an unacceptable level of multicollinearity(19). Our models were deemed acceptable according to the tolerance criterion.

2. Residual method(20): "Leg length adjusted for height" was 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. 'Leg length adjusted for height' was then entered into the Cox models as the main exposure variable.

Results

At baseline, the 20,773 LITE participants were on average 59 years old, 45% were male, and 24% African American. Among men, the mean (SD) leg length was 83.9 (4.8) cm and the mean height was 175.3 (6.7) cm, while in women the mean leg length was 76.5 (4.4), and height 161.3 (6.3) cm. Participants with longer legs tended to be younger, black, diabetic, and have a greater mean waist circumference, waist-to-hip ratio, body weight, and factor VIII level (Table 1). After adjustment for age, race, and study there was no remaining evidence of a relation between leg length and factor VIII levels in either men (p-trend = 0.32) or women (p-trend = 0.17). Leg length, torso length, and height were highly inter-correlated, adjusting for age, sex, race, and study: leg length and height r = 0.83; torso length and height r = 0.73, leg length and torso length r = 0.24 (p<0.0001 for all).

A total of 641 incident VTE events accrued over a maximum follow-up of 19.1 years in ARIC (median = 16.9 years) and 13.1 years in CHS (median = 11.6). Of the events, 234 (37%) were categorized as idiopathic VTE, and 407 (63%) as secondary VTE.

Separate relations of leg length and height quintiles to VTE

Relations of leg length quintiles, and height quintiles, to incident VTE risk are presented in Table 2. In demographic-adjusted models, longer legs were associated with greater risk of incident VTE (p-trend < 0.0001) as was greater height (p-trend = 0.0003), while torso length was unrelated (p-trend = 0.19). There was no evidence of interaction by sex, race or study (ARIC vs. CHS) ($p_{interaction} > 0.10$ for all). Though there was not a statistically significant interaction, associations tended to be stronger in the ARIC cohort than in CHS.

LITE participants in the highest sex-specific quintile of leg length were at 64% (95% CI: 27%, 112% greater risk of VTE relative to those in the lowest quintile, after adjustment for demographics. Additional adjustment for waist circumference, diabetes status, and factor VIII attenuated the relation of leg length to incident VTE only slightly, with participants with legs in the longest quintile being at 59% (95% CI: 22%, 108%) greater risk. Associations were somewhat stronger for idiopathic VTE than for secondary VTE, and for women than for men, despite there not being a statistically significant sex-interaction. Relations of height quintile to risk of incident VTE followed a pattern similar to those of leg length quintile and VTE risk, however the magnitudes of associations tended to be smaller (Table 2). In contrast, there was no evidence to suggest a relation between torso length and VTE risk. In the fully-adjusted model, the HRs (95% CIs) across increasing quintiles of torso length were 1.00 (reference), 1.02 (0.79, 1.33), 0.86 (0.66, 1.12), 1.04 (0.81, 1.34), 1.07 (0.81, 1.42); p-trend = 0.62.

Evaluation of whether leg length explains relations between height and VTE

Adjusted for age, sex, race, and study, longer legs were associated with greater risk of VTE [HR (95% CI) for 1 sex-specific SD] [1.21 (1.11, 1.31)] as was greater height [1.17 (1.08, 1.27)] (Table 3). When leg length and height were modeled simultaneously, per 1 SD, greater leg length continued to be associated with increased VTE risk [1.21 (1.04, 1.40)] while height was unassociated [1.00 (0.86, 1.16)]. With additional adjustment for waist circumference, diabetes status, and factor VIII, the relation of leg length to VTE persisted [1.23 (1.05, 1.44)], while height remained unassociated [0.96 (0.82, 1.11)]. As shown in the table, results of analyses stratified by sex mirrored those for overall VTE, with both leg length and height being related to VTE when modeled separately, but only leg length being associated with VTE when modeled simultaneously.

'Leg length adjusted for height' was also positively related to VTE risk in models adjusted for demographics [HR (95% CI) for 1 sex-specific SD (men: 2.86 cm; women 2.79 cm) 1.14 (1.04, 1.26)] and other VTE risk factors [1.16 (1.05, 1.27)]. Relations were similar between the sexes, as presented here for the fully-adjusted model: men [1.17 (1.02, 1.35)], women [1.14 (1.00, 1.31)].

Secondary Analyses

We additionally explored using quintiles based on the entire LITE distribution, rather than stratified by sex. As expected given the broader range (leg length median Q1 = 72 cm, median Q5 = 87 cm), HRs were larger when leg length was derived from the entire LITE sample than when created separately by sex. For total VTE, the HR for extreme quintiles of leg length in the demographic adjusted model was 1.99 (1.43, 2,76), while the HR for the fully adjusted models was 1.78 (1.28, 2.48).

To make our results comparable to those previously published relating height to VTE, using a continuous variable we also represented height per 10 cm, and leg length per 5 cm. In the fully-adjusted model, each 5 cm greater leg length was associated with a HR of 1.20 (1.10, 1.32) in the entire cohort, and of 1.16 (1.01, 1.32) in men and 1.25 (1.10, 1.42) in women. The fully-adjusted HR for VTE associated with 10 cm greater height was 1.22 (1.07, 1.38) for all of LITE, while it was 1.12 (0.93, 1.35) in men and 1.30 (1.09, 1.55) in women.

Lastly, in sensitivity analyses we substituted alternate measures of obesity (i.e. waist-to-hip ratio, body weight) for waist circumference, and the results were essentially unchanged (data not shown).

Discussion

In this sample of 20,773 middle-aged and older participants of the LITE study, people with longer legs and greater overall height were at increased risk of incident VTE, while torso length was unrelated to VTE risk. After adjustment for VTE risk factors, LITE participants in the highest quintile of leg length were at 59% greater risk of VTE, relative to their counterparts in the lowest quintile of leg length. For idiopathic VTE, those in the highest quintile of leg length were at 86% greater risk, while for secondary VTE those in the highest quintile were at 45% greater risk. By specifically focusing on the leg length component of height, which we hypothesized to be the aspect of height physiologically linked to VTE risk, we were able to more thoroughly scrutinize the height and VTE association. Both analytic approaches employed suggested that leg length explained the positive relation between height and VTE risk.

The consistency with which prior cohort studies have reported greater height to be associated with elevated risk of VTE is striking(3-8), with those in the highest quantile of height being at 1.5 to 2-fold greater risk of VTE, relative to those in the lowest category. As with previously published studies, the height and VTE relationship remained in LITE after adjustment for obesity and other VTE risk factors. Our findings were somewhat stronger among women than men. This is counter to some prior studies that have shown a stronger association of height to VTE among men than among women(5, 8), though height has been previously reported to be associated with VTE risk among female participants of the Iowa Women's Health Study(3). Two prior studies also stratified by VTE type, and found the relation of height to be similar for idiopathic and secondary VTE(3, 5).

Physiologically, several mechanisms may explain the observation that longer legs and greater height are associated with higher VTE risk. First, greater body height is associated with higher resting venous pressure during quiet standing(10). The common femoral vein diameter is also larger among taller individuals, though flow velocity was unrelated to height(9). Given that flow rate is the product term of diameter and velocity, taller individuals would have a higher venous flow rate. Both greater hydrostatic pressure and a higher flow rate may increase venous damage, and possibly VTE. In an experimental rat model, induced venous hypertension was associated with significant venous distension and venous valve damage(21). An alternate explanation is that taller people simply having longer veins, thus a greater area where a thrombus could occur. A related possibility is that taller people have more venous valves. Venous thrombi are thought to originate in the valve pocket, which is the area between a valve leaflet and the vessel wall(22). Height is, however, highly genetically regulated(23), and it is also possible, though unlikely, that height and VTE risk have shared genetic determinants. Lastly, in accordance with the mechanisms proposed above, the lack of relation between leg length and factor VIII levels in our data once we accounted for demographics suggests that leg length is more likely to influence VTE risk through blood stasis or changes in the vascular wall than through hypercoagability, at least as determined by factor VIII levels.

Although VTE is a significant cause of morbidity and mortality(1-3), VTE is rare relative to other major cardiovascular conditions, and therefore VTE risk estimation is unlikely cost-effective on a population-wide basis. Recurrent VTE, however, occurs frequently. Approximately 8% of individuals with incident VTE experience a recurrent event within 1 year of their initial diagnosis(1), and the long-term cumulative risk of VTE recurrence is about one-third over 8-10 years(3, 24, 25). Given the high cumulative incidence of recurrent VTE, the relation of leg length to recurrent VTE events should be explored since leg length could be simply and inexpensively measured in practice.

Strengths of this study include the prospective design, systematic case validation, and the large, population-based, biethnic sample from a wide geographic distribution in the USA. Further, both leg length and height are determined in childhood and adolescence(26, 27), and are therefore unlikely to be highly confounded by adult behaviors and characteristics that cause VTE. A weakness of this study is that leg length was not directly measured in either ARIC or CHS; rather it was calculated as standing height minus sitting height. Minor error in our leg length estimation likely occurred because measures of seated height would include greater soft tissues (i.e. muscle and adiopose tissue) of the gluteal region in obese than non-obese participants(28, 29). This would result in systematic underestimation of leg length among obese participants. Given the direction of our finding, that taller individuals are at increased risk of VTE, this measurement error most likely attenuated our HR estimates toward the null. Further, adjustment for measures of obesity such as waist circumference, body weight, and waist-to-hip ratio did not appreciably impact the associations.

To conclude, in this biethnic sample of men and women, longer legs were associated with greater risk of incident VTE and explained relations between height and VTE. Our findings extend the results of previous studies which have reported associations between height and VTE by isolating the association to leg length, which is the component of height physiologically hypothesized to influence VTE risk. It is remains to be established whether this finding is due to greater surface area, a larger number of venous valves, greater hydrostatic pressure among individuals with longer legs, or an unknown mechanism. Attempts should be made to replicate these findings in individuals with prior VTE events, as leg length, like obesity status(24, 25, 30), could potentially aid in prediction of recurrent VTE risk.

Acknowledgments

The LITE study was funded by National Heart, Lung, and Blood Institute (NHLBI) grant R01 HL59367. The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C. CHS was funded by NHLBI contracts N01-HC-80007, N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, N01-HC-45133, and NHLBI grant number U01 HL080295 with additional contribution from the National Institute of Neurological Disorders and Stroke. The authors thank the staff and participants of the ARIC and CHS studies for their important contributions.

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Nomenclature and abbreviations

VTE	venous thromboembolism
LITE	Longitudinal Study of Thromboembolism
BMI	body mass index
SD	standard deviation
HR	hazard ratio
CI	confidence interval

Requested information

What is known on this topic?	**1**	Greater height has been associated with an increased risk of VTE.
	2	Associations of leg length length to VTE have not been reported previously.
What this paper adds.	**1**	We demonstrate that longer legs are associated greater risk of incident VTE.
	2	Using 3 different analytic methods, we show that longer legs are associated with greater risk of incident VTE after accounting for total body height.
	3	Leg length may be a simple and inexpensive screening tool for VTE risk.

Table 1

Baseline participant characteristics stratified by sex and leg length quintile: The LITE Study

	Sex-Specific Leg Length Quintiles					
<u>Men</u>	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**p-trend**
Median, cm	79	82	84	86	90	
Range, cm	(32 - 80)	(81 - 82)	(83 - 84)	(85 - 87)	(88 - 103)	
N	2116	1528	1535	2056	2001	
Demographics						
Age, mean years ± SD	60.3 ± 10.0	59.1 ± 10.1	59.3 ± 9.9	58.9 ± 9.7	58.4 ± 9.8	<0.0001
African American, n (%)	233 (11.0)	218 (14.3)	258 (16.8)	481 (23.4)	764 (38.2)	<0.0001
Physiologic Characteristics						
Standing height, cm ± SD	168 ± 5	173 ± 4	175 ± 4	178 ± 4	183 ± 5	<0.0001
Torso length, cm ± SD	90.1 ± 4.2	91.1 ± 3.8	91.4 ± 3.8	91.9 ± 4.0	92.2 ± 4.2	<0.0001
Waist circumference, cm ± SD	97.4 ± 10.8	98.5 ± 10.5	98.3 ± 10.9	99.3 ± 11.1	99.7 ± 11.1	<0.0001
Waist-to-hip ratio ± SD	0.97 ± 0.05	0.96 ± 0.05	0.96 ± 0.06	0.96 ± 0.06	0.96 ± 0.06	0.001
Body weight, lbs ± SD	78.5 ± 13.1	82.0 ± 13.2	83.1 ± 13.6	85.6 ± 14.4	88.4 ± 14.5	<0.0001
Prevalent diabetes, n (%)	296 (14.1)	224 (14.8)	205 (13.4)	259 (12.7)	280 (14.2)	0.46
Factor VIII, % ± SD	125 ± 35	124 ± 37	124 ± 36	125 ± 37	128 ± 40	0.009
<u>Women</u>						
Median, cm	71	74	76	79	82	
Range, cm	(37 - 72)	(73 - 75)	(76 - 77)	(78 - 80)	(81 - 106)	
N	1948	2840	2186	2553	2010	
Demographics						
Age, mean years ± SD	59.1 ± 9.9	58.9 ± 10.0	58.6 ± 10.2	58.7 ± 9.9	58.3 ± 10.0	0.009
African American, n (%)	190 (9.8)	473 (16.7)	520 (23.8)	859 (33.7)	1086 (54.0)	<0.0001
Physiologic Characteristics						
Standing height, cm ± SD	154 ± 4	158 ± 4	161 ± 4	164 ± 4	169 ± 5	<0.0001
Torso length, cm ± SD	83.7 ± 4.0	84.4 ± 3.7	85.0 ± 4.0	85.2 ± 4.1	85.4 ± 4.3	<0.0001
Waist circumference, cm ± SD	92.6 ± 14.8	93.3 ± 15.4	93.8 ± 15.4	94.5 ± 14.8	98.1 ± 16.0	<0.0001
Waist-to-hip ratio ± SD	0.89 ± 0.08	0.89 ± 0.09	0.89 ± 0.08	0.90 ± 0.08	0.91 ± 0.09	<0.0001
Body weight, kg ± SD	66.6 ± 14.4	69.2 ± 15.1	71.1 ± 15.5	73.1 ± 15.5	79.0 ± 17.8	<0.0001
Prevalent diabetes, n (%)	221 (11.4)	293 (10.4)	252 (11.6)	322 (12.7)	317 (16.1)	<0.0001

	Sex-Specific Leg Length Quintiles					
Factor VIII, % ± SD	129 ± 36	128 ± 38	132 ± 40	133 ± 41	139 ± 45	<0.0001

Table 2

Baseline leg length and height quintiles* and risk of incident VTE: The LITE study 1987-2005

Leg Length Quintile		**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**p-trend**
Men	Median, cm	79	82	84	86	90	
	Range, cm	(32 - 80)	(81 - 82)	(83 - 84)	(85 - 87)	(88 - 103)	
Women	Median, cm	71	74	76	79	82	
	Range, cm	(37 - 72)	(73 - 75)	(76 - 77)	(78 - 80)	(81 - 106)	
	N events	99	108	127	141	166	
	N total	4064	4368	3721	4609	4011	
All VTE							
	Model 1	1.00	1.03 (0.78, 1.35)	1.40 (1.07, 1.82)	1.23 (0.95, 1.60)	1.64 (1.27, 2.12)	<0.0001
	Model 2	1.00	1.07 (0.81, 1.41)	1.39 (1.06, 1.82)	1.25 (0.96, 1.63)	1.59 (1.22, 2.08)	0.0004
VTE Type							
Idiopathic	Model 1	1.00	0.89 (0.56, 1.41)	1.31 (0.85, 2.03)	1.15 (0.75, 1.77)	1.80 (1.19, 2.73)	0.002
	Model 2	1.00	0.95 (0.59, 1.52)	1.39 (0.89, 2.17)	1.21 (0.78, 1.89)	1.86 (1.21, 2.87)	0.003
Secondary	Model 1	1.00	1.11 (0.79, 1.56)	1.46 (1.04, 2.03)	1.28 (0.92, 1.78)	1.56 (1.12, 2.17)	0.007
	Model 2	1.00	1.14 (0.80, 1.61)	1.38 (0.98, 1.95)	1.27 (0.91, 1.78)	1.45 (1.03, 2.04)	0.03
Sex-Stratified							
Men	Model 1	1.00	0.93 (0.62, 1.40)	1.17 (0.80, 1.71)	0.98 (0.68, 1.42)	1.41 (1.00, 1.99)	0.07
	Model 2	1.00	0.96 (0.64, 1.46)	1.19 (0.80, 1.76)	0.97 (0.66, 1.42)	1.39 (0.97, 1.99)	0.11
Women	Model 1	1.00	1.19 (0.80, 1.75)	1.72 (1.17, 2.53)	1.59 (1.08, 2.33)	2.02 (1.36, 2.99)	<0.0001
	Model 2	1.00	1.20 (0.81, 1.78)	1.64 (1.11, 2.42)	1.59 (1.08, 2.34)	1.85 (1.24, 2.77)	0.0008
Height Quintile		**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**p-trend**
Men	Median, cm	167	172	175	178	184	
	Range, cm	(142 - 169)	(170 - 173)	(174 - 176)	(177 - 180)	(181 - 199)	
Women	Median, cm	154	158	161	164	169	
	Range, cm	(124 - 156)	(157 - 159)	(160 - 162)	(163 - 166)	(167 - 188)	
	N events	115	112	114	138	162	
	N total	4343	3811	3837	4461	4321	
All VTE							
	Model 1	1.00	1.15 (0.89, 1.49)	1.20 (0.92, 1.56)	1.28 (0.99, 1.64)	1.58 (1.23, 2.02)	0.0003
	Model 2	1.00	1.11 (0.85, 1.46)	1.17 (0.89, 1.54)	1.25 (0.96, 1.63)	1.45 (1.12, 1.88)	0.004

VTE Type							
Idiopathic	Model 1	1.00	1.02 (0.65, 1.58)	1.13 (0.73, 1.74)	1.26 (0.83, 1.90)	1.69 (1.13, 2.53)	0.006
	Model 2	1.00	1.03 (0.65, 1.63)	1.14 (0.73, 1.79)	1.30 (0.85, 2.00)	1.58 (1.04, 2.41)	0.02
Secondary	Model 1	1.00	1.23 (0.89, 1.71)	1.24 (0.90, 1.73)	1.30 (0.94, 1.78)	1.52 (1.11, 2.09)	0.01
	Model 2	1.00	1.16 (0.82, 1.64)	1.18 (0.84, 1.67)	1.23 (0.89, 1.72)	1.38 (0.99, 1.91)	0.06
Sex-Stratified							
Men	Model 1	1.00	0.90 (0.61, 1.33)	1.11 (0.76, 1.63)	1.18 (0.82, 1.70)	1.26 (0.87, 1.82)	0.09
	Model 2	1.00	0.87 (0.58, 1.31)	1.04 (0.69, 1.55)	1.07 (0.73, 1.58)	1.11 (0.75, 1.63)	0.35
Women	Model 1	1.00	1.41 (0.99, 2.01)	1.28 (0.89, 1.83)	1.37 (0.97, 1.94)	1.92 (1.37, 2.68)	0.0007
	Model 2	1.00	1.35 (0.93, 1.95)	1.30 (0.90, 1.87)	1.40 (0.98, 2.00)	1.77 (1.25, 2.51)	0.003

[*] Quintiles are sex-specific

Model 1: Adjusted for age, sex, race, and study

Model 2: Adjusted for Model 1 + waist circumference, diabetes status, and factor VIII

Table 3

Impact of mutual leg length and height adjustment on risk of incident VTE: The LITE Study 1987-2005

	HR (95% CI) per 1 SD[*]	
	Leg length	**Height**
Men	**(1 SD = 4.76 cm)**	**(1 SD = 6.73 cm)**
Women	**(1 SD = 4.39 cm)**	**(1 SD = 6.31 cm)**
All VTE Events (n = 641)		
Leg length and height modeled separately		
Model 1	1.21 (1.11, 1.31)	--
	--	1.17 (1.08, 1.27)
Model 2	1.18 (1.09, 1.29)	--
	--	1.14 (1.05, 1.24)
Leg length and height included in the same model		
Model 1	1.21 (1.04, 1.40)	1.00 (0.86, 1.16)
Model 2	1.23 (1.05, 1.44)	0.96 (0.82, 1.11)
Sex-Stratified		
Men (n = 289)		
Leg length and height modeled separately		
Model 1	1.16 (1.03, 1.31)	--
	--	1.13 (1.00, 1.27)
Model 2	1.15 (1.01, 1.30)	--
	--	1.08 (0.95, 1.23)
Leg length and height included in the same model		
Model 1	1.19 (0.95, 1.49)	0.98 (0.78, 1.23)
Model 2	1.30 (1.03, 1.65)	0.86 (0.68, 1.10)
Women (n = 352)		
Leg length and height modeled separately		
Model 1	1.25 (1.12, 1.40)	--
	--	1.21 (1.08, 1.35)
Model 2	1.21 (1.08, 1.36)	--
	--	1.18 (1.05, 1.32)
Leg length and height included in the same model		
Model 1	1.24 (1.02, 1.51)	1.01 (0.83, 1.23)
Model 2	1.20 (0.98, 1.48)	1.01 (0.83, 1.24)

[*] SDs are sex-specific

Model 1: Adjusted for age, sex, race, and study

Model 2: Adjusted for Model 1 + waist circumference, diabetes status, and factor VIII