Original Contribution

Body Height and Risk of Venous Thromboembolism

The Tromsø Study

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An association between body height and venous thromboembolism (VTE) has been suggested by previous studies including males only. The aim of this prospective cohort study was to investigate the sex-specific impact of body height on risk of VTE in a general population. Risk factors, including body height and weight, were registered for 26,727 subjects aged 25–96 years who participated in the Tromsø Study (Norway) in 1994–1995. Incident VTE events were registered through September 1, 2007. There were 462 VTE events during a median 12.5 years of follow-up. Body height was a risk factor for VTE in men, but not in women. Multivariable hazard ratios per 10 cm, adjusted for age, body mass index, diabetes, smoking, and hormone therapy (women), were 1.34 (95% confidence interval: 1.09, 1.64) for men and 1.13 (95% confidence interval: 0.91, 1.40) for women. Hazard ratios by quartiles of body height revealed that men in the upper quartile ($>$181 cm) had a 1.99-fold (95% confidence interval: 1.35, 2.92) increased risk of VTE compared with men in the lowest quartile ($<$173 cm) (*P* for trend across quartiles = 0.002). There was no significant trend (*P* = 0.2) across quartiles of body height for women. Study findings revealed that body height is a sex-specific risk factor for VTE in men.

body height; risk factors; venous thromboembolism

Abbreviations: CI, confidence interval; HR, hazard ratio; VTE, venous thromboembolism.

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is a common multifactor disease, with serious short-term and long-term complications and a potentially fatal outcome (1). The annual incidence is approximately 1–3 per 1,000 adults in developed countries (1, 2), and VTE is the third most common cardiovascular disease (3, 4). Even though surgery, trauma, hospitalization, malignancy, immobilization, pregnancy, use of estrogens, and inherited thrombophilia are associated with VTE events (1, 5), 30%–50% of the events still are not associated with obvious predisposing factors (6, 7).

Several investigations have consistently shown that anthropometric measures of obesity, such as body mass index and waist circumference, are strong and independent risk factors for VTE in population-based studies (8–10), in outpatients (11), and in patients discharged from hospitals (12).

In contrast, the impact of other anthropometric measures, such as body height, on risk of VTE has received little attention. In the mid-19th century, Virchow acknowledged blood stasis as a major contributor to venous thrombosis (13), and body height was later shown to affect venous pressure dynamics (14, 15). Thus, it is likely that body height may affect risk of VTE.

Data from the Physicians' Health Study (3), including only male physicians, showed that taller men had an increased risk of VTE. Similar findings were reported in a cohort of Swedish men (16). To the best of our knowledge, no study has addressed the sex-specific impact of body height on risk of VTE. Thus, we wanted to investigate whether body height was an independent risk factor for VTE in men and women. To address this question, we performed a prospective, population-based study of 26,727 adults, of

whom 47.5% were males, and assessed the impact of body height on the incidence of VTE in sex-stratified analysis.

MATERIALS AND METHODS

Study population

Participants were recruited from the fourth survey of the Tromsø Study (conducted in 1994–1995), a single-center, prospective, population-based study with repeated health surveys of inhabitants of Tromsø, Norway. All inhabitants older than age 24 years were invited, and 27,158 participated (77% of the eligible population). Data were collected by physical examination, blood samples, and self-administered questionnaires. The study was approved by the regional committee for research ethics, and all participants gave their informed, written consent. Subjects who did not consent to medical research ($n = 300$) and those not officially registered as inhabitants of the municipality of Tromsø ($n = 43$) were excluded from the study. Furthermore, subjects with a known history of VTE ($n = 47$) and those with missing values for body height ($n = 41$) were excluded. Therefore, 26,727 subjects were included in our study. Incident VTE events among the study participants were recorded from the date of enrollment through the end of follow-up, September 1, 2007.

Baseline measurements

Body height and weight were measured with subjects wearing light clothing and no shoes. Height was measured to the nearest centimeter and weight to the nearest 0.5 kg. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Information on self-reported diabetes and current smoking was collected from a self-administered questionnaire. The smoking-related questions were, Do you yourself smoke: cigarettes or cigars/cigarillos or a pipe daily? (yes = yes to any of these questions, no = no to all of these questions). Information on estrogen treatment for birth control or hormone replacement therapy was obtained from women by a self-administered questionnaire, generating the combined variable hormone therapy.

Identification and validation of VTE

All first lifetime VTE events were identified by searching the hospital discharge diagnosis registry, the autopsy registry, and the radiology procedure registry at the University Hospital of North Norway from date of enrollment in the Tromsø Study (1994–1995) to September 1, 2007. All hospital care and relevant diagnostic radiology in the Tromsø municipality are provided exclusively by this hospital. The relevant discharge codes were *International Classification of Diseases*, Ninth Revision, codes 325, 415.1, 451, 452, 453, 671.3, 671.4, and 671.9 for 1994–1998 and *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision, codes I80.0–I80.3, I80.8, I80.9, I81, I82.0–I82.3, I82.8, I82.9, I67.6, O22.3, O22.5, O87.1, O87.3, I26.0, and I26.9 for 1999–2007.

The hospital discharge diagnosis registry included diagnoses from outpatient clinic visits and hospitalizations. An additional search was conducted of the computerized index of autopsy diagnoses, and cases diagnosed with VTE as either a cause of death (part 1 of the death certificate) or a significant condition (part 2 of the death certificate) were identified. We also searched the radiology database to identify cases with objectively confirmed VTE that may have been missed because of coding errors in the hospital discharge diagnosis registry. All relevant diagnostic procedures performed at the Department of Radiology to diagnose VTE during the 13-year period were systematically reviewed by trained personnel, and cases with confirmed VTE were identified.

The medical records for each VTE case derived from the hospital discharge diagnosis registry, the autopsy registry, or the radiology procedure registry were reviewed by trained personnel. An episode of VTE was confirmed and registered as a validated VTE event when all 4 of the following conditions were satisfied: 1) confirmation by diagnostic procedures including compression ultrasonography, venography, spiral computed tomography, perfusion-ventilation scan (high or moderate probability for pulmonary embolism), pulmonary angiography, or autopsy; 2) indication on the medical record that a physician had diagnosed deep vein thrombosis or pulmonary embolism; 3) presence of signs and symptoms consistent with deep vein thrombosis or pulmonary embolism; and 4) treatment of the patient with anticoagulants (heparin, warfarin), thrombolytic therapy, or vascular surgery. For patients derived from the autopsy registry, a VTE event was recorded when the autopsy record indicated pulmonary embolism as cause of death or as a significant condition contributing to death.

On the basis of the presence of provoking factors at the time of diagnosis, the VTE event was classified as unprovoked (no provoking factors) or provoked (≥ 1 provoking factors). Major surgery, trauma, or an acute medical condition (acute myocardial infarction, ischemic stroke, or major infectious disease) within 8 weeks prior to the event; active cancer at the time of the event; and marked immobilization (bed rest for longer than 3 days, confinement to wheelchair, or long-distance travel exceeding 4 hours within the last 14 days prior to the event) were considered provoking factors.

Statistical analyses

For each participant, person-years of follow-up were accrued from the date of enrollment in 1994–1995 through the date that a VTE event was first diagnosed, from the date that the participant died or migrated from the municipality of Tromsø, or through the end of the study period—September 1, 2007. Statistical analysis was carried out by using SPSS version 15.0 software (SPSS Inc., Chicago, Illinois). The significance level was 0.05. Age-adjusted incidence rates with 95% confidence intervals were calculated by using Poisson regression models. Cox proportional hazards regression models were used to estimate age-adjusted and multivariable hazard ratios, with 95% confidence intervals, for VTE. In the multivariable model, hazard ratios were adjusted for age, body mass index, smoking, self-reported

diabetes, and estrogen use (women). We modeled body height as a continuous variable and determined hazard ratios for VTE per 10-cm increase in body height. We also estimated hazard ratios for VTE by quartiles of body height, using the lowest quartile as the reference group. Statistical interactions of body height with age and sex were tested by using cross-product terms. Hazard ratios were also estimated separately for unprovoked and provoked VTE. The proportional hazards assumption was verified by evaluating the parallelism between the curves of the log-log survivor function for quartiles of body height.

RESULTS

The mean age at baseline was 47 years (standard deviation, 15), and 52.5% ($n = 14,020$) were women. There were 462 validated first-ever VTE events during 289,116 person-years of follow-up (median, 12.5 years). The overall crude incidence rate of VTE was 1.6 per 1,000 person-years. We found a statistically significant interaction between body height and sex ($P = 0.003$), and sex-specific analyses were conducted.

Characteristics of the VTE events are shown in Table 1. A total of 41.8% ($n = 193$) events were unprovoked VTE, and 64.3% of the events presented as clinical deep vein thrombosis, whereas 35.7% of the participants had pulmonary embolism with or without concurrent deep vein thrombosis. We found no obvious sex differences in the distribution of type of venous thrombosis or provoking factors (Table 1).

Characteristics of potential confounders across quartiles of body height are shown in Table 2. Age and body mass index decreased significantly with increasing quartiles of body height for both women and men (all P for trend < 0.001). The proportion of smokers and hormone therapy users increased linearly with body height among women ($P < 0.001$), whereas the proportion of smokers decreased among men ($P = 0.03$). The proportion of subjects with diabetes decreased significantly with body height among women ($P < 0.001$) and nonsignificantly among men ($P = 0.06$) (Table 2).

Age-adjusted incidence rates of VTE per 1,000 person-years were 1.02 (95% confidence interval (CI): 0.87, 1.19) among women and 1.17 (95% CI: 1.01, 1.36) among men. The age- and multivariable-adjusted risk of total VTE increased significantly by increasing height among men, but not among women (Table 3). Age-adjusted hazard ratios per 10 cm were 1.34 (95% CI: 1.09, 1.64) for men and 1.06 (95% CI: 0.86, 1.31) for women. Further adjustments for body mass index, diabetes mellitus, smoking, and hormone therapy (women) did not substantially affect the risk estimates. Multivariable hazard ratios increased across quartiles of height (P for trend $= 0.002$) for men. Men in the upper quartile had a 2-fold increased risk of VTE compared with men in the lower quartile (hazard ratio (HR) $= 1.99$, 95% CI: 1.35, 2.92). We found no association of VTE across quartiles of height for women (P for trend $= 0.2$) (Table 3).

To investigate whether body height had a differential impact on risk of unprovoked and provoked VTE, we estimated hazard ratios for unprovoked and provoked VTE in

Table 1. Characteristics of Venous Thromboembolism Events, the Tromsø Study, Norway, 1994–2007

	Women ($n = 243$)		Men ($n = 219$)	
	No.	%	No.	%
Deep vein thrombosis	158	65.0	139	63.5
Pulmonary embolism	85	35.0	80	36.5
Unprovoked event	101	41.6	92	42.0
Clinical risk factors				
Estrogens (HRT, oral contraceptives)	355	14.4		
Heredity[a]	9	3.7	4	1.8
Pregnancy	3	1.2		
Other medical conditions[b]	60	24.7	40	18.3
Provoking factors				
Surgery	43	17.7	36	16.4
Trauma	18	7.4	13	5.9
Acute medical conditions	33	13.6	37	16.9
Cancer	58	23.9	48	21.9
Immobilization (bed rest for >3 days, confinement to wheelchair)	45	18.5	35	16.0
Other[c]	8	3.3	11	5.0

Abbreviation: HRT, hormone replacement therapy.

[a] Reported family history of venous thromboembolism in first-degree relative(s) before age 60 years.

[b] Other diseases within the previous year (myocardial infarction, ischemic stroke, heart failure, inflammatory bowel disease, chronic infections, chronic obstructive pulmonary disease, or myeloproliferative disorders).

[c] Other provoking factors described by a physician in the medical record (e.g., intravascular catheter).

continuous and quartile-based models (Table 4). For men, multivariable hazard ratios per 10-cm increase in body height were similar for unprovoked (HR = 1.33, 95% CI: 0.97, 1.81) and provoked (HR = 1.35, 95% CI: 1.04, 1.76) VTE. The risk of unprovoked ($P = 0.04$) and provoked ($P = 0.02$) VTE increased linearly for men in quartile-based analysis, and men in the upper quartile of body height exhibited a 2-fold increased risk of both unprovoked (HR = 2.00, 95% CI: 1.11, 3.59) and provoked (HR = 1.99, 95% CI: 1.20, 3.31) VTE compared with men in the lowest quartile. For women, body height was a risk factor for neither unprovoked nor provoked VTE in continuous and quartile-based models (Table 4).

DISCUSSION

The purpose of our prospective cohort study was to investigate the impact of body height on the risk of VTE in a general population. In continuous and quartile-based analysis, the risk of total VTE was significantly increased for men, but not for women. Risk estimates for unprovoked and provoked VTE were similar for men, and men in the upper quartile of body height (>181 cm) had a 2-fold increased

Table 2. Baseline Characteristics of Participants by Quartile of Body Height, the Tromsø Study, Norway, 1994–2007

	Height Quartile[a]												P for Trend
	1			2			3			4			
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	
Women													
Height, cm			155 (4)			162 (1)			165 (1)			172 (3)	<0.001
Age, years			55 (17)			48 (15)			45 (14)			41 (11)	<0.001
BMI, kg/m^2			25.8 (4.6)			25.0 (4.2)			24.5 (4.1)			23.9 (3.8)	<0.001
Smoking	1,157	32.4		1,284	38.0		1,226	38.0		1,443	37.6		<0.001
Diabetes	118	3.3		55	1.6		47	1.5		39	1.0		<0.001
Hormone therapy	381	10.7		414	12.3		419	13.0		548	14.3		<0.001
Men													
Height, cm			168 (4)			175 (1)			179 (1)			186 (3)	<0.001
Age, years			52 (16)			48 (14)			44 (13)			42 (12)	<0.001
BMI (kg/m^2)			25.7 (3.3)			25.7 (3.3)			25.6 (3.3)			25.3 (3.3)	<0.001
Smoking	1,246	38.2		1,312	38.5		1,016	36.8		1,178	36.0		0.03
Diabetes	71	2.2		57	1.7		38	1.4		53	1.6		0.06

Abbreviations: BMI, body mass index; SD, standard deviation.
[a] Quartile body height range, cm: women—1: <160, 2: 160–163, 3: 164–167, 4: >167; men—1: <173, 2: 173–177, 3: 178–181, 4: >181.

risk of total VTE, unprovoked VTE, and provoked VTE compared with men in the lowest quartile (<173 cm). In accordance with 2 previous cohort studies (3, 16), we confirmed that taller men had an increased risk of VTE, and our extended sex-stratified analysis revealed that this association was specific for men and was attributable to both unprovoked and provoked VTE. The observation of an association between taller height and risk of VTE in 2 separate and large cohort studies with equivalent risk estimates suggests that body height may become a recognized risk

Table 3. Age-adjusted Incidence Rates and Age- and Multivariable-adjusted Hazard Ratios for Total Venous Thromboembolism by Body Height in Participants in the Tromsø Study, Norway, 1994–2007[a]

	Total Venous Thromboembolism							
	No. of Person-Years	No. of Events	IR[b]	95% CI	HR[b]	95% CI	HR[c]	95% CI
Women								
Quartile 1 (<160 cm)	38,125	97	0.99	0.75, 1.31	1.00		1.00	
Quartile 2 (160–163 cm)	37,416	55	0.88	0.66, 1.19	0.89	0.63, 1.24	0.93	0.66, 1.30
Quartile 3 (164–167cm)	35,472	48	1.03	0.77, 1.40	1.04	0.73, 1.49	1.12	0.78, 1.61
Quartile 4 (>167 cm)	41,819	43	1.10	0.81, 1.49	1.11	0.75, 1.65	1.24	0.84, 1.84
P for trend					0.6		0.2	
Height per 10 cm	152,833	243			1.06	0.86, 1.31	1.13	0.91, 1.40
Men								
Quartile 1 (<173 cm)	33,861	57	0.84	0.61, 1.14	1.00		1.00	
Quartile 2 (173–177 cm)	36,832	67	1.18	0.90, 1.55	1.39	0.97, 1.98	1.41	0.99, 2.01
Quartile 3 (178–181 cm)	30,350	38	1.04	0.75, 1.45	1.23	0.81, 1.87	1.23	0.81, 1.87
Quartile 4 (>181 cm)	35,239	57	1.68	1.29, 2.18	1.99	1.36, 2.93	1.99	1.35, 2.92
P for trend					0.002		0.002	
Height per 10 cm	136,283	219			1.34	1.09, 1.64	1.34	1.09, 1.64

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate.
[a] The table presents HRs by quartile of height and by a 10-cm increase in height modeled as a continuous variable.
[b] Adjusted for age.
[c] Adjusted for the following covariates at baseline: age, body mass index, self-reported diabetes, smoking, and hormone therapy (women).

Table 4. Age-adjusted Incidence Rates and Age- and Multivariable-adjusted Hazard Ratios for Unprovoked and Provoked Venous Thromboembolism[a] by Body Height in Participants in the Tromsø Study, Norway, 1994–2007[b]

	Unprovoked Venous Thromboembolism								Provoked Venous Thromboembolism							
	No. of Person-Years	No. of events	IR[c]	95% CI	HR[c]	95% CI	HR[d]	95% CI	No. of Person-Years	No. of Events	IR[c]	95% CI	HR[c]	95% CI	HR[d]	95% CI
Women																
Quartile 1 (<160 cm)	37,758	37	0.45	0.30, 0.69	1.00		1.00		37,882	60	0.53	0.36, 0.77	1.00		1.00	
Quartile 2 (160–163 cm)	37,193	24	0.44	0.28, 0.68	0.96	0.57, 1.61	1.01	0.60, 1.71	37,247	31	0.45	0.30, 0.67	0.85	0.54, 1.31	0.88	0.57, 1.37
Quartile 3 (164–167cm)	35,338	27	0.64	0.43, 0.95	1.39	0.83, 2.33	1.51	0.90, 2.53	35,263	21	0.42	0.27, 0.66	0.80	0.48, 1.33	0.86	0.51, 1.43
Quartile 4 (>167 cm)	41,610	13	0.35	0.20, 0.60	0.76	0.39, 1.49	0.87	0.44, 1.70	41,721	30	0.75	0.52, 1.08	1.42	0.87, 2.30	1.58	0.97, 2.58
P for trend					0.9		0.7						0.4		0.2	
Height per 10 cm	151,899	101			0.91	0.66, 1.26	0.99	0.71, 1.37	152,113	142			1.19	0.90, 1.57	1.26	0.95, 1.67
Men																
Quartile 1 (<173 cm)	33,669	24	0.37	0.23, 0.60	1.00		1.00		33,699	33	0.47	0.31, 0.70	1.00		1.00	
Quartile 2 (173–177 cm)	36,535	27	0.50	0.33, 0.76	1.32	0.76, 2.29	1.33	0.76, 2.31	36,675	40	0.69	0.48, 0.98	1.44	0.91, 2.29	1.48	
Quartile 3 (178–181 cm)	30,162	16	0.45	0.27, 0.75	1.20	0.63, 2.29	1.18	0.62, 2.25	30,228	22	0.60	0.39, 0.92	1.26	0.73, 2.18	1.27	0.73, 2.20
Quartile 4 (>181 cm)	34,993	25	0.75	0.51, 1.12	2.01	1.12, 3.61	2.00	1.11, 3.59	35,046	32	0.94	0.66, 1.34	2.00	1.20, 3.33	1.99	1.20, 3.31
P for trend					0.04		0.04						0.02		0.02	
Height per 10 cm	135,359	92			1.33	0.97, 1.81	1.33	0.97, 1.81	135,648	127			1.35	1.04, 1.76	1.35	1.04, 1.76

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate.

[a] Provoked venous thromboembolism: presence of 1 or more provoking factors including major surgery, trauma, or acute medical condition (acute myocardial infarction, ischemic stroke, or major infectious disease) within 8 weeks prior to the event; active cancer at the time of the event; and marked immobilization (bed rest for longer than 3 days, confinement to wheelchair, or long-distance travel exceeding 4 hours within the last 14 days prior to the event).

[b] The table presents HRs by quartile of height and by a 10-cm increase in height modeled as a continuous variable.

[c] Adjusted for age.

[d] Adjusted for the following covariates at baseline; age, body mass index, self-reported diabetes, smoking, and hormone therapy (women).

factor for VTE in men. Our findings also suggest that taller height may be an unrecognized confounder for the increased risk of VTE in men versus women reported in some cohort studies (8, 10).

In the Physicians' Health Study, 18,662 male physicians were followed for up to 21 years, and 358 self-reported incident VTE events were registered (3). The study showed for the first known time that taller men had an unexpected increased risk of VTE (HR per 10 cm = 1.35, 95% CI: 1.15, 1.59). Because of the magnitude and precision of the association of height with greater risk of VTE, the authors suggested that the observed association could not be explained by chance (3). In the cohort of 6,958 Swedish men followed for up to 28 years, men taller than 179 cm (upper quartile) had a 1.5-fold higher risk of VTE compared with men shorter than 172 cm. To our knowledge, this finding has not been investigated and confirmed until now in cohort studies including both men and women.

The pathophysiologic mechanism(s) beyond the sex-specific increased risk of VTE with body height in men is unknown. However, we can likely assume that sex-specific differences in venous architecture and pressure dynamics are involved. The common femoral vein diameter is reported to be smaller in women than in men (14), independent of age, height, and body mass index in multivariable analysis. Greater body height is associated with higher resting venous pressure during quiet standing (15, 17, 18). Furthermore, women have lower resting venous pressure during quiet standing (15), require a shorter time to achieve minimal venous pressure during exercise (15), and have higher common femoral vein velocity at rest and after a standardized Valsalva maneuver (14). The apparent sex differences in venous pressure and velocity disappeared after adjustment for anthropometric factors such as body height, body mass index, and calf circumference (14, 15). Thus, it is likely that venous stasis associated with sex-specific differences in height may contribute, at least in part, to increased risk of VTE with body height in men.

Average body height in the Norwegian population increased substantially during the last century (19), most probably because of improved socioeconomic conditions, including better nutritional status. Age was a major confounder of the association between body height and VTE because elderly men were shorter and were thereby underrepresented in the upper quartile of body height, and because advanced age was strongly associated with risk of VTE (8).

The main strengths of our study are its prospective design, large number of participants recruited from a general population with a high attendance rate, long-term follow-up, and validated VTE events. All hospital care and radiologic imaging in the region is exclusively provided by a single hospital, which enhances the possibility of a complete VTE register. Furthermore, the exposure variable of interest (body height) and the major confounder (age) are not modifiable risk factors, and thus nondifferential misclassification of true associations is avoided even when the time between exposure and disease manifestation is long.

However, the study has some limitations. Information on diabetes mellitus, smoking, and hormone therapy was obtained from a self-administered questionnaire without validation. Modifiable risk factors, such as body weight, are a potential limitation of cohort studies, especially when the time between exposure and disease manifestation is long. This type of nondifferential misclassification generally leads to underestimation of the true associations. Information on concomitant medical treatment was not available in our study and therefore was not taken into account.

In conclusion, our prospective cohort study revealed a sex-specific increased risk of both unprovoked and provoked VTE for taller men. The confirmation of an association between taller height and risk of VTE in 3 separate and large cohort studies may suggest that body height is a true risk factor for VTE in men and should be considered for optimal risk stratification and treatment.

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