Anthropometry, Body Fat, and Venous Thromboembolism
A Danish Follow-Up Study

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Background—Obesity, measured as body mass index, is associated with venous thromboembolism (VTE). Body mass index is a marker of excess weight and correlates well with body fat content in adults; however, it fails to consider the distribution of body fat. We assessed the association between anthropometric variables and VTE.

Methods and Results—From 1993 to 1997, 27 178 men and 29 876 women 50 to 64 years of age were recruited into a Danish prospective study (Diet, Cancer, and Health). During 10 years of follow-up, the outcome of VTE events was identified in the Danish National Patient Registry and verified by review of medical records. Body weight, body mass index, waist circumference, hip circumference, and total body fat were measured at baseline. We used Cox proportional hazard models to assess the association between anthropometry and VTE. Age was used as a time axis, with further adjustment for smoking, physical activity, height, hypertension, diabetes mellitus, cholesterol, and, among women, use of hormone replacement therapy. We verified 641 incident VTE events and found monotonic dose-response relationships between VTE and all anthropometric measurements in both sexes. In mutually adjusted analyses of waist and hip circumference, we found that hip circumference was positively associated with VTE in women but not in men, whereas waist circumference was positively associated with VTE in men but not in women.

Conclusions—All measurements of obesity are predictors of the risk for VTE. Positive associations were found between VTE and body weight, body mass index, waist circumference, hip circumference, and total body fat mass. **(*Circulation*. 2009;120:1850-1857.)**

Key Words: venous thromboembolism ■ anthropometry ■ obesity ■ follow-up studies

Obesity is an established risk factor for venous thromboembolism (VTE), ie, deep venous thrombosis (DVT) and pulmonary embolism (PE).[1–6] The body mass index (BMI; ie, weight in kilograms divided by the square of height in meters) is commonly used as a measurement of obesity, and the majority of previous studies of the association between obesity and VTE used BMI as the exposure. BMI is a marker of excess body weight and correlates well with body fat content in adults; however, it fails to consider the distribution of body fat.

Clinical Perspective on p 1857

The distribution of body fat predicts the risk of arterial thrombotic events, such as coronary heart disease (CHD). Central obesity, measured as waist circumference or waist-to-hip ratio, is a better predictor of CHD than general obesity as measured with BMI, whereas peripheral obesity, measured as hip circumference, is not a predictor of CHD[7,8]; however, only a few studies have evaluated the association between VTE and anthropometric measures other than BMI. One study evaluated the association between VTE and central obesity in men and study found that a waist circumference >100 cm was associated with a higher risk of VTE than a waist circumference <100 cm.[4] Recently, Steffen et al[9] studied the association between VTE and the metabolic syndrome, which is defined by the presence of 3 or more of the following factors: Central obesity (ie, waist circumference >102 cm for men and >88 cm for women), dyslipidemia, hypertension, and diabetes mellitus. They evaluated the different features of the metabolic syndrome and found a positive association between central obesity and risk of VTE in both sexes.

In a follow-up study, we aimed to assess the associations between anthropometric variables (body weight, BMI, waist circumference, and hip circumference) and VTE among middle-aged men and women. We also included measurement of bioelectrical impedance, from which total body fat mass can be calculated.[10–12]

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Methods

The Diet, Cancer, and Health Cohort

From December 1993 to May 1997, 80 996 men and 79 729 women 50 to 64 years of age were invited to participate in the Danish prospective study entitled Diet, Cancer, and Health. The study has been described in detail elsewhere.[13] Eligible cohort members were born in Denmark, were living in the urban areas of Copenhagen and Aarhus, and were not, at the time of invitation, registered with a previous diagnosis of cancer in the Danish Cancer Registry. Participants were identified from computerized records of the Civil Registration System in Denmark, which since 1968 has included all Danish residents.[14] The information includes a unique personal identification number in addition to name, address, and vital status. The Diet, Cancer, and Health study and the present substudy were approved by the regional ethics committees in Copenhagen and Aarhus and by the Danish Data Protection Agency.

Identification of Outcome

Incident VTE events among participants were identified by linking the Diet, Cancer, and Health cohort with the Danish National Patient Registry by use of the civil registration number of the study participants. The Danish National Patient Registry has collected nationwide data on all nonpsychiatric hospital admissions since 1977. Since 1995, discharges from emergency departments and outpatient clinics have also been included in the registry.[15] On the basis of the entire available hospital discharge history of each participant, we identified those who were registered with a discharge diagnosis of VTE (International Classification of Diseases, Revision 8 codes 450.99, 451.00, 451.08, 451.09, and 451.99, and International Classification of Diseases, Revision 10 codes I26 and I80.1 through I80.9; revision 9 was never used in Denmark). Participants with a discharge diagnosis of VTE before enrollment into the Diet, Cancer, and Health cohort were excluded. We reviewed medical records from participants with a first-time VTE diagnosis in the Danish National Patient Registry from the time of enrollment into the Diet, Cancer, and Health study until June 30, 2006. Information about symptoms, results of biochemical analyses, and diagnostic tests, including duplex ultrasound, Doppler ultrasound, venography, echocardiography, ventilation-perfusion lung scan, and computed tomography scan, were obtained. A VTE diagnosis was considered verified when typical clinical symptoms (unilateral swelling of leg, sagittal leg pain, discoloration of the leg, dyspnea, chest pain, hyperventilation, increased plasma D-dimer, or hemoptysis) were combined with confirmatory diagnostic test results (ultrasound, venography, echocardiography, ventilation-perfusion lung scan [Prospective Investigation of Pulmonary Embolism Diagnosis criteria], or computed tomography scan). Only objectively verified VTE events were included in the present study. Concurrent DVT and PE were registered as PE. In addition, events were classified as idiopathic or secondary (provoked) according to information from medical records. An event was regarded as secondary when any of the following criteria were registered in the medical record: A cancer diagnosis before or within 3 months after admission with VTE, surgery, trauma, travel (at least 5 hours' duration), acute medical disease with bed rest for at least 3 days (stroke, acute myocardial infarction, exacerbation of chronic lung disease, infection, or activity in collagenous disease), immobilization, use of a central vein catheter, or other provoking factors that were present within the 3 months before the VTE. An event was regarded as idiopathic when the physician concluded that no provoking factors could be identified or when the health of the patient was described as good without information that indicated secondary VTE. The event was registered as unclassified when information in medical records was sparse.

In the present study, we also included participants who died of VTE. We identified VTE deaths by linkage with the Danish National Death Registry (until 2003) and by review of death certificates from participants who died between 2003 and 2006. Only participants with autopsy-verified VTE were included as VTE deaths.

Data on Anthropometry and Lifestyle Factors

Data on anthropometry were obtained by trained laboratory technicians at 2 study clinics in Aarhus and Copenhagen at the time of enrollment into the Diet, Cancer, and Health study. All measurements were performed in a standardized manner. Measurement of bioelectrical impedance was obtained with a BIA 101-F device (Akern/RJL, Florence, Italy) at a single frequency (50 Hz) with the participant lying relaxed on a couch; arms and leg were not in contact with any other body part. The legs were 45° apart, and arms were 30° from the torso. Sensing electrodes were placed over the right wrist and ankle; current electrodes were placed over the metacarpals and metatarsals. The reliability and validity of the impedance method have been investigated in a Danish population (35 to 65 years of age) by use of a 4-compartment model with counting of potassium and total body water (dilutometry).[10] The equation obtained from that study was used to calculate total body fat mass. Blood pressure was measured in the right arm with automatic devices (Takeda UA-751 and UA-743, Takeda Pharmaceutical Co Ltd, Osaka, Japan) with participants in a supine position after a minimum of 5 minutes of rest.

Information on sociodemographic and lifestyle characteristics (tobacco consumption and physical activity) and medication use (use of hormone replacement therapy) was obtained from standardized detailed questionnaires at study entry. The questionnaires were optically scanned into a computer, and in subsequent interviews performed by trained laboratory technicians, information was amended as necessary. Immediately after the baseline interview, a blood sample was drawn from each participant, and total cholesterol was determined. Participants for whom information on 1 or more confounder or exposure variables was missing were excluded from the analysis.

Statistical Analysis

We assessed the association between the anthropometric variables and the risk of VTE separately for men and women using Cox proportional hazards regression. Age was used as the time axis to prevent confounding by age, with entry time defined as the subject's age at recruitment and exit time defined as age at VTE or censoring because of death, emigration, or June 30, 2006, whichever came first. Weight, BMI, waist circumference, hip circumference, and body fat mass were analyzed as continuous variables. Smoking, physical activity, height, hypertension, hypercholesterolemia, diabetes mellitus, and use of hormone replacement therapy (women only) were considered as potential confounders. Therefore, in addition to the crude models, we included adjustment for these variables. The following exposures were included as dichotomous covariates: Use of hormone replacement therapy (user, nonuser), physical activity (above or below 30 minutes of sport per day, including cycling), hypertension (systolic blood pressure $\geq$140 mm Hg, diastolic blood pressure $\geq$90 mm Hg, or self-reported use of antihypertensive medication), diabetes mellitus (self-reported), height, and cholesterol (in mmol/L) as continuous variables, along with smoking habit (in categories of nonsmoker, former smoker, smoker $<$15 g/d, smoker 15 to 25 g/d, and smoker $>$25 g/d). In addition, waist circumference was analyzed after adjustment for BMI, and waist circumference and hip circumference were analyzed with mutually adjusted models. Model adequacy was assessed graphically with a log-log plot and by use of a log-rank test based on Schoenfeld residuals and was found to be appropriate in all analyses. The associations between anthropometry and subtypes of VTE (ie, idiopathic and secondary VTE and PE) were assessed similarly. We used Stata version 9.2 (Stata Corp, College Station, Tex) for the statistical analyses.

All anthropometric variables were categorized in quartiles according to the exposure distribution among cases with VTE.[16] Hazard ratios of VTE were assessed by Cox regression, with the lowest quartile used as the reference level. We further computed the hazard ratios of VTE per 1 SD of the anthropometric variables.

In secondary analyses, we assessed the association between VTE and categories of hip circumference and waist circumference stratified according to quartiles of BMI, to evaluate the hazard ratio of

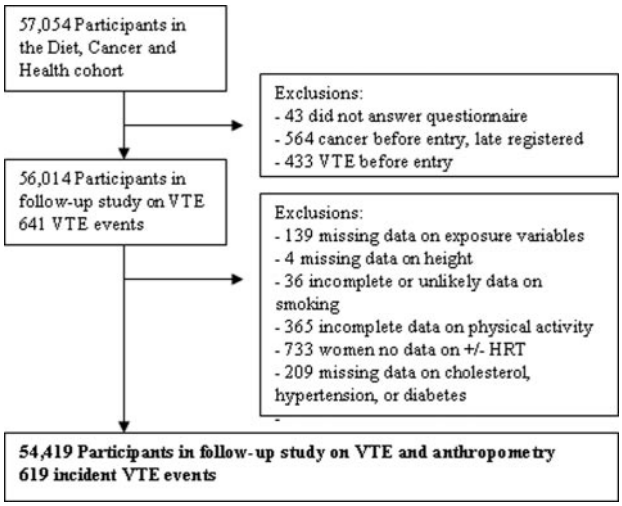

Figure. Inclusions and exclusions before analysis of the association between anthropometric variables and VTE. HRT indicates hormone replacement therapy.

VTE according to differences in waist and hip circumference in normal-weight persons. These analyses were stratified by sex and adjusted for age (with age as the time axis).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Study Population and Case Ascertainment

In total, 27 178 men and 29 876 women accepted the invitation to participate in the study (Figure). All but 43 individuals answered the questionnaire and participated in the subsequent interview. We excluded 564 participants who were later identified in the Danish Cancer Registry as having a cancer diagnosis before the study invitation or in the weeks between invitation and the baseline examination. We also excluded 433 participants with a diagnosis of VTE before enrollment into the Diet, Cancer, and Health study, which left 56 014 participants for the follow-up study on VTE. Table 1 provides baseline characteristics of the participants.

The median follow-up time was 10.2 years, with an interquartile range from 9.6 to 10.8 years. During follow-up, we identified and verified 617 incident VTE events by review of medical records. Of these, 58% (n=358) were DVT and 42% (n=259) were PE. Confirmed VTE events were characterized as idiopathic in 49% of cases (n=306) and secondary in 49% (n=300). The remaining 2% (n=11) could not be classified owing to sparse information. Of the 56 014 participants, 4084 died during the follow-up period. We found 24 participants with an autopsy-proven PE diagnosis without a prior verified VTE event during follow-up. The autopsy-verified events were not classified. Thus, in total, 641 confirmed VTE events were identified among participants during follow-up. The incidence rate of VTE was 1.15 (95% confidence interval 1.06 to 1.24) per 1000 person-years.

Analyses

The analyses were based on the 54 737 participants for whom we had complete information on all exposure and confounder variables. Table 2 shows the crude and adjusted hazard ratios for the anthropometric variables according to the different types of VTE (total VTE, idiopathic VTE, secondary VTE, and PE). We found statistically significant positive associations between VTE and all measurements of body size, including body weight, BMI, total body fat mass, waist circumference, and hip circumference, among both men and women. The associations were the same according to different types of VTE. Adjustment for potential confounding had no substantial implications. The mutually adjusted analysis of waist circumference and hip circumference showed a statistically significant positive association between VTE and waist circumference in men but not in women. Conversely, the association between VTE and hip circumference showed a statistically significant association in women but not in men. In the analysis of waist circumference adjusted for BMI, we found a statistically significant positive association in men but no association in women (Table 2).

Table 1. Baseline Characteristics of Participants in the Follow-Up Study on VTE and Anthropometry

	Women	Men
No. of participants	29 340	26 674
Age, y	56 (51–64)	56 (51–64)
Weight, kg	67 (53–91)	82 (65–105)
Height, cm	164 (155–174)	177 (166–188)
Body mass index, kg/m^2	24.8 (19.9–33.7)	26.2 (21.5–33)
Total body fat, kg	23 (13–41)	22 (12–36)
Waist circumference, cm	80 (67–103)	95 (81–114)
Hip circumference, cm	101 (89–118)	100 (90–112)
Total cholesterol, mmol/L	6.2 (4.5–8.4)	5.9 (4.3–7.9)
Systolic blood pressure, mm Hg	136 (106–175)	140 (114–177)
Education, basic school, %*		
7 y	31.4	34.8
8–10 y	50.2	41.5
≥11 y	18.5	23.7
Education after basic school, %		
None	19.3	10.0
<3 y	31.7	13.8
3–4 y	37.7	42.0
≥4 y	11.3	34.1
Smoking status, %		
Never smoked	43.7	25.7
Former smoker	23.5	34.6
Current smoker, <15 g/d	15.4	10.7
Current smoker, 15–25 g/d	14.9	17.5
Current smoker, >25 g/d	2.6	11.6
Activity >0.5 h/d, %	41	38
Hormone replacement therapy, %	31	Not applicable

Values are median (5th to 95th percentiles) unless otherwise stated.
*Education based on 3 categories of duration of basic school (starting at age of 6 to 7 years): 7 years, 8–10 years, ≥11 years.

Table 2. Anthropometry and VTE

	Women, HR (95% CI)				Men, HR (95% CI)			
	All VTE (n=259)	Idiopathic VTE (n=109)	Secondary VT (n=133)	PE (n=126)	All VTE (n=360)	Idiopathic VTE (n=182)	Secondary VTE (n=160)	PE (n=124)
Weight (kg)								
Crude	1.03 (1.02–1.04)	1.03 (1.02–1.05)	1.02 (1.01–1.04)	1.04 (1.03–1.05)	1.02 (1.02–1.03)	1.02 (1.01–1.03)	1.03 (1.02–1.04)	1.03 (1.02–1.04)
Adjustment 1	1.03 (1.02–1.04)	1.03 (1.02–1.05)	1.03 (1.01–1.04)	1.04 (1.02–1.05)	1.02 (1.01–1.03)	1.02 (1.00–1.03)	1.02 (1.01–1.04)	1.03 (1.02–1.05)
Adjustment 2	1.03 (1.02–1.04)	1.03 (1.02–1.05)	1.03 (1.01–1.04)	1.04 (1.03–1.05)	1.02 (1.01–1.03)	1.02 (1.01–1.03)	1.03 (1.01–1.04)	1.04 (1.02–1.05)
BMI (kg/m^2)								
Crude	1.07 (1.04–1.09)	1.08 (1.04–1.12)	1.06 (1.02–1.09)	1.09 (1.06–1.13)	1.06 (1.03–1.09)	1.05 (1.02–1.09)	1.07 (1.03–1.11)	1.10 (1.05–1.14)
Adjustment 1	1.08 (1.06–1.11)	1.09 (1.05–1.13)	1.07 (1.04–1.11)	1.10 (1.07–1.14)	1.07 (1.04–1.10)	1.06 (1.03–1.10)	1.08 (1.04–1.12)	1.11 (1.06–1.15)
Adjustment 2	1.08 (1.05–1.11)	1.09 (1.05–1.13)	1.07 (1.04–1.11)	1.11 (1.07–1.14)	1.07 (1.04–1.10)	1.07 (1.03–1.11)	1.08 (1.04–1.13)	1.12 (1.07–1.17)
Body fat (kg)								
Crude	1.04 (1.02–1.05)	1.04 (1.02–1.06)	1.03 (1.02–1.05)	1.05 (1.03–1.07)	1.03 (1.02–1.05)	1.03 (1.02–1.05)	1.04 (1.02–1.06)	1.05 (1.03–1.07)
Adjustment 1	1.04 (1.03–1.05)	1.04 (1.02–1.06)	1.04 (1.02–1.05)	1.05 (1.03–1.07)	1.03 (1.02–1.05)	1.03 (1.01–1.05)	1.04 (1.02–1.06)	1.05 (1.03–1.08)
Adjustment 2	1.04 (1.02–1.05)	1.04 (1.02–1.06)	1.04 (1.02–1.05)	1.05 (1.03–1.07)	1.03 (1.02–1.05)	1.04 (1.02–1.05)	1.04 (1.02–1.06)	1.06 (1.04–1.08)
Waist (5 cm)								
Crude	1.14 (1.09–1.20)	1.14 (1.06–1.23)	1.12 (1.05–1.20)	1.21 (1.13–1.29)	1.15 (1.10–1.21)	1.15 (1.07–1.22)	1.18 (1.10–1.26)	1.21 (1.12–1.31)
Adjustment 1	1.14 (1.09–1.20)	1.14 (1.06–1.23)	1.13 (1.06–1.21)	1.21 (1.13–1.29)	1.14 (1.09–1.20)	1.15 (1.07–1.23)	1.17 (1.09–1.26)	1.22 (1.12–1.32)
Adjustment 2	1.14 (1.08–1.20)	1.13 (1.04–1.22)	1.14 (1.06–1.22)	1.21 (1.13–1.30)	1.15 (1.10–1.21)	1.16 (1.08–1.24)	1.18 (1.09–1.27)	1.25 (1.15–1.36)
Adjustment 2+hip	1.02 (0.94–1.10)	0.95 (0.84–1.07)	1.02 (0.91–1.14)	1.09 (0.97–1.22)	1.18 (1.08–1.28)	1.23 (1.09–1.38)	1.15 (1.00–1.31)	1.25 (1.08–1.44)
Adjustment 2+BMI	0.97 (0.88–1.08)	0.87 (0.73–1.02)	1.00 (0.86–1.17)	1.03 (0.89–1.19)	1.17 (1.03–1.32)	1.22 (1.03–1.45)	1.17 (0.98–1.40)	1.18 (0.96–1.45)
Hip (5 cm)								
Crude	1.20 (1.14–1.27)	1.25 (1.15–1.34)	1.18 (1.09–1.28)	1.26 (1.18–1.35)	1.19 (1.11–1.28)	1.16 (1.05–1.28)	1.25 (1.13–1.38)	1.28 (1.14–1.43)
Adjustment 1	1.21 (1.15–1.28)	1.25 (1.16–1.36)	1.20 (1.11–1.30)	1.26 (1.17–1.36)	1.17 (1.08–1.26)	1.14 (1.02–1.27)	1.23 (1.11–1.38)	1.28 (1.14–1.44)
Adjustment 2	1.21 (1.14–1.28)	1.25 (1.15–1.36)	1.20 (1.11–1.31)	1.27 (1.18–1.37)	1.17 (1.09–1.27)	1.15 (1.03–1.28)	1.23 (1.11–1.38)	1.30 (1.15–1.48)
Adjustment 2+waist	1.19 (1.08–1.30)	1.30 (1.14–1.50)	1.18 (1.04–1.35)	1.18 (1.04–1.34)	0.96 (0.85–1.10)	0.90 (0.75–1.07)	1.05 (0.87–1.27)	1.00 (0.81–1.24)

Hazard ratios (HRs) with 95% confidence intervals (CIs). Age as time axis (crude: age adjusted).

Adjustment 1: physical activity, smoking categories, height, and use of hormone replacement therapy (women only). Adjustment 2: Adjustment 1 plus hypertension, diabetes mellitus, and cholesterol.

Table 3 shows the hazard ratios for VTE according to quartiles of the anthropometric variables. The analyses show a statistically significantly higher hazard ratio for VTE in the highest quartile than the lowest quartile for all anthropometric variables in both sexes. The analyses showed monotonic dose-response relationships. Table 4 shows the hazard ratios for VTE according to categories of hip circumference and waist circumferences stratified for quartiles of BMI. It appeared that the risk of VTE was higher in normal-weight persons with high hip circumference than in persons with low hip circumference. Sex-specific hazard ratios of VTE according to 1 SD showed no preferable anthropometric measure of obesity for assessing the risk of VTE (online-only Data Supplement Table I).

Discussion

In this large prospective study, we found statistically significant positive associations between VTE and all measurements of obesity for both men and women. The hypothesis tested was that central obesity might be a better predictor of VTE than peripheral obesity measured as hip circumference (as has been shown in CHD), but the results showed that both peripheral and central obesity were strong risk factors for VTE. However, the anthropometric variables were only surrogate measures for the actual regional fat deposits and not independent measurements. Therefore, these results do not exclude differences between different types of fat tissues, but they do indicate a distinction between VTE and CHD, because no association has been found between hip circumference and CHD.

Strengths and Limitations of the Present Study

This prospective study included 641 incident VTE events and was one of the largest prospective studies on VTE. Data on anthropometry were collected prospectively by trained laboratorial technicians. All VTE events were validated by review of medical records by a physician familiar with VTE (MTS), and we included only objectively verified incident VTE events. The hospital system in Denmark is financed by taxation, and almost every Danish inhabitant with VTE symptoms is admitted to and examined in a hospital. The medical record included information on visits from both outpatient and inpatient clinics. Obviously, there will be VTE events among participants that we missed. For example, because of a very low frequency of autopsy in Denmark (6% of all deaths in 2001), an unknown number of the participants died of PE. However, obesity is unlikely to influence the chance of an autopsy being performed, and thus, selection bias because of autopsy performance is not a likely explanation of the present findings.

The data on anthropometry were not available during review of medical records, and therefore, information bias is

Table 3. Hazard Ratio (95% Confidence Interval) of VTE by Quartiles of Anthropometric Variables

	Women	Level, Women	Men	Level, Men
Weight (kg)				
Lowest	1	<64	1	<77
Lower-middle	1.24 (0.88–1.76)	64–72	1.15 (0.85–1.55)	77–85
Upper-middle	1.91 (1.34–2.74)	72–80	1.58 (1.16–2.15)	85–94
Highest	2.27 (1.57–3.28)	>80	1.88 (1.35–2.62)	>94
BMI (kg/m^2)				
Lowest	1	<23.7	1	<24.4
Lower-middle	1.45 (1.03–2.05)	23.7–26.3	0.98 (0.73–1.31)	24.4–26.8
Upper-middle	1.81 (1.27–2.56)	26.3–29.9	1.32 (0.98–1.79)	26.8–29.4
Highest	2.82 (1.96–4.04)	>29.9	1.72 (1.27–2.33)	>29.4
Waist (cm)				
Lowest	1	<77	1	<91
Lower-middle	1.34 (0.96–1.88)	77–84	1.04 (0.78–1.39)	91–98
Upper-middle	1.58 (1.11–2.25)	84–92	1.36 (1.00–1.83)	98–105
Highest	1.92 (1.35–2.73)	>92	2.00 (1.47–2.72)	>105
Hip (cm)				
Lowest	1	<98	1	<97
Lower-middle	1.45 (1.02–2.04)	98–103	0.98 (0.73–1.31)	97–102
Upper-middle	1.67 (1.18–2.37)	103–110	1.34 (1.00–1.80)	102–105
Highest	2.54 (1.78–3.64)	>110	1.43 (1.05–1.93)	>105
Fat weight (kg)				
Lowest	1	<20	1	<19
Lower-middle	1.15 (0.81–1.63)	20–26	1.18 (0.88–1.59)	19–23
Upper-middle	1.62 (1.14–2.30)	26–33	1.34 (0.99–1.81)	23–29
Highest	2.33 (1.62–3.34)	>33	1.89 (1.39–2.57)	>29

Adjusted for age, physical activity, smoking categories, height, cholesterol, hypertension, diabetes mellitus, and use of hormone replacement therapy (women only).

not a likely explanation of our findings, because the reviewer was blinded with regard to exposure. However, it can be a challenge to diagnose DVT in persons with obese legs, in whom it may be impossible to make a conclusive ultrasound examination; therefore, obesity might cause a lack of verification of DVT diagnosis. This would tend to underestimate the effects of obesity. Nevertheless, the association between anthropometric measurements and PE was similar to the association for VTE. Using Cox regression, we assumed that those people who died had the same risk of VTE as those who did not die. If those who died had a higher risk of VTE, our assumption would tend to underestimate the effect of obesity. Detailed information on a range of potential confounding factors was available in the present study. Adjustment for these factors in the statistical analyses had only a minor impact on the risk estimates, which indicates that residual confounding was not a likely explanation of the observed associations.

Comparison With Other Studies

Few studies have evaluated the association between VTE and measures of obesity other than BMI. The findings of the present study are in accordance with the results from large-scaled epidemiological studies of BMI and VTE.[1–3,6] In a recent large case-control study, Pomp et al[5] also found a positive association between VTE and body weight in addition to BMI. They found a monotonic dose-response relationship, as we identified in the present study.[5]

We also found a statistically significant positive association between waist circumference and VTE in both men and women. This finding is in agreement with a small study of men born in 1913, in which Hansson et al[4] found a higher risk of VTE in men with waist circumference >100 cm than in men with waist circumference <100 cm. Steffen et al[9] assessed the association between VTE and the metabolic syndrome. They found a positive association between VTE and central obesity in both sexes. In addition, they found that the metabolic syndrome and its other features did not appear important in the cause of VTE. This finding is in agreement with a study by Ray et al,[17] who analyzed the association between VTE and the different features of the metabolic syndrome and found that central obesity was associated with VTE, whereas no association existed between VTE and diabetes mellitus, hypertension, or dyslipidemia. Recently, Borch et al[18] confirmed the findings that obesity is the pivotal risk factor for VTE among the features of the metabolic syndrome. Other studies evaluated the associations between VTE and dia-

Table 4. Hazard Ratio (95% Confidence Interval) of VTE According to Categories of Hip Circumference and Waist Circumference Stratified for Quartiles of BMI

	Lowest BMI (≤24 kg/m^2)	Lower-Middle BMI (24.1–26.7 kg/m^2)	Upper-Middle BMI (26.71–29.5 kg/m^2)	Highest BMI (>29.5 kg/m^2)
Hip circumference ≤97 cm				
No. of cases	113	37	14	0
HR (95% CI)	1.27 (0.88–1.85)	1 (Reference)	1.52 (0.82–2.82)	…
Hip circumference 97.5–102 cm				
No. of cases	37	73	51	8
HR (95% CI)	1.18 (0.75–1.87)	1.40 (0.94–2.08)	1.70 (1.11–2.59)	1.28 (0.60–2.75)
Hip circumference 102.5–108 cm				
No. of cases	9	46	66	36
HR (95% CI)	1.51 (0.72–3.14)	1.73 (1.12–2.67)	1.65 (1.11–2.47)	1.66 (1.05–2.62)
Hip circumference ≥108.5 cm				
No. of cases	1	3	28	115
HR (95% CI)	…	…	2.22 (1.35–3.65)	2.89 (1.99–4.20)
Waist circumference ≤80 cm				
No. of cases	77	27	13	1
HR (95% CI)	0.84 (0.54–1.30)	1 (Reference)	2.47 (1.28–4.79)	…
Waist circumference 80–88 cm				
No. of cases	49	37	23	8
HR (95% CI)	1.26 (0.77–2.06)	0.99 (0.60–1.64)	1.22 (0.70–2.12)	1.78 (0.81–3.93)
Waist circumference 88–102 cm				
No. of cases	33	89	88	38
HR (95% CI)	1.51 (0.87–2.60)	1.30 (0.81–2.08)	1.43 (0.91–2.27)	1.35 (0.82–2.21)
Waist circumference ≥102 cm				
No. of cases	1	6	35	112
HR (95% CI)	…	2.34 (0.94–5.81)	1.95 (1.13–3.35)	2.42 (1.54–3.78)

HR indicates hazard ratio; CI, confidence interval.

Age as time axis, with stratification for sex. There were 637 cases with information on BMI, waist circumference, and hip circumference.

betes mellitus, hypertension, and dyslipidemia. Goldhaber et al[3] investigated the risk of PE in women and found no association with diabetes or dyslipidemia; a positive association with hypertension was identified. Tsai et al[6] found no association with hypertension or dyslipidemia, and after adjustment for BMI, there was no association with diabetes. Glynn et al[2] analyzed VTE in men and found no association with hypertension, dyslipidemia, or diabetes. No data on waist circumference were included in these studies, but the results indicate that the effect of the metabolic syndrome on VTE risk may be entirely due to obesity. We performed adjustment for hypertension, diabetes mellitus, and cholesterol, but the addition of these variables to the model did not change our estimates, which indicates that the mechanism of obesity is not mediated by these covariates.

To the best of our knowledge, no studies have investigated the association between peripheral obesity, measured as hip circumference, and VTE. We found a statistically significant positive association between VTE and hip circumference both in men and in women; however, this effect of peripheral obesity could be caused indirectly by central obesity, because when people become very obese, fat accumulates all over the body, and thus, persons with a large hip circumference also have a large waist circumference.[19] On the other hand, no association has been found between hip circumference and CHD.[7,8] To eliminate the effect of waist circumference in the analysis of hip circumference, as well as the effect of hip circumference in the analysis of waist circumference, we performed mutually adjusted analyses. When hip circumference was adjusted for waist circumference, the association between hip circumference and VTE was eliminated for men but was still significant for women. In contrast, when waist circumference was adjusted for hip circumference, the association between waist circumference and VTE was eliminated for women but was still significant for men. These differences may be explained by the sex-specific distribution of fat. In general, men accumulate fat around the abdomen, and women accumulate fat on the hips. Therefore, in women, hip circumference is more informative than waist circumference when predicting the risk of VTE because the variation in hip circumference is highest, whereas waist circumference is more informative than hip circumference in men because the variation in waist circumference is highest. However, the correlation coeffi-

cients between waist and hip circumference were 0.80 in men and 0.75 in women, and thus, the results might reflect collinearity and not biology. In secondary analysis of combined measurements of hip circumference and BMI, we confirmed that a high hip circumference was associated with a higher risk of VTE even in normal-weight persons, in contrast to studies of CHD.[7,8] Waist circumference adjusted for BMI has been shown to be an approximation of intra-abdominal fat content.[20] We therefore analyzed the hazard ratio of waist circumference adjusted for BMI as a model to assess the effect of intra-abdominal fat. We found a statistically significant positive association in men but no association in women, which indicates that intra-abdominal fat is only a risk factor in males. However, this model includes a redistribution of masses, because when we investigate the hazard ratio of higher waist circumferences with equal BMI, other body compartments must concomitantly be smaller. The hazard ratio we found using this model may indicate the effect of more intra-abdominal fat, diminished hip circumference, less muscle mass, or a combination of these factors.

We also found statistically significant positive associations between idiopathic VTE and all measurements of obesity. These data underscore the fact that the effect of obesity on VTE risk was not mediated solely through diseases caused by obesity.

The mechanisms responsible for the association between VTE and obesity are unknown. The association between arterial thrombosis and obesity is explained in part by the strong association between central obesity and hypertension, type 2 diabetes mellitus, and dyslipidemia, all of which are major risk factors for atherosclerosis and arterial thrombosis[2,7,8]; however, these factors are not established risk factors for VTE.[2–4,6] Therefore, the effect of obesity on VTE risk may be mediated by other mechanisms. The present data suggest that fat mass, independent of its distribution in the body, is positively associated with VTE. This is biologically plausible, because adipose tissue is more than an energy-storage organ; it is also metabolically active, secreting several biologically active substances. A number of these substances are associated with procoagulant activity or inhibition of fibrinolysis, ie, interleukin-6, tumor necrosis factor-α, tissue factor, and plasminogen activator inhibitor-1.[19,21–23] Enlarged fat cells produce a higher amount of these substances than normal-sized fat cells.[22,24,25] It is therefore plausible that both peripheral and central obesity are risk factors for VTE due to fat-cell biosynthesis; however, the present study was not designed to evaluate the validity of this proposed mechanism. Estrogen produced by fat cells might also be a potential mediator of VTE risk, because the plasma estrogen level is positively associated with obesity.[26] In addition, obesity might be associated with venous stasis, which promotes venous thrombosis; however, this association is hypothetical and not well established. Further studies are warranted on this topic.

In conclusion, we found statistically significant positive associations between weight, BMI, waist circumference, hip circumference, and total fat mass and VTE in both sexes. Further studies are needed to explain the mechanism underlying the associations.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The distribution of body fat predicts the risk of coronary heart disease, and central obesity consistently has been shown to be a risk factor for coronary heart disease, whereas peripheral obesity (measured as high hip circumference) appears to protect against coronary heart disease. The importance of fat distribution with regard to the risk of venous thromboembolism (VTE), ie, deep venous thrombosis and pulmonary embolism, has not been evaluated. In a 10-year follow-up study of 56 014 middle-aged men and women, which included 641 verified incident events of VTE, we evaluated the risk of VTE according to different measurements of fat distribution in the body. Our results show that all measurements of obesity are positively associated with VTE in both sexes. We also showed that a higher hip circumference in normal-weight persons was associated with a higher risk for VTE, which is in contrast to studies on coronary heart disease. We found statistically significant positive associations between idiopathic (unprovoked) VTE and all measurements of obesity. The associations between VTE and the anthropometric measurements persisted after adjustment for hypertension, diabetes mellitus, or hypercholesterolemia, which shows that the effect of obesity was not mediated solely by these factors.

Anthropometry, Body Fat, and Venous Thromboembolism. A Danish Follow-Up Study

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Supplementary table 1. Hazard ratios [95% Confidence interval] for venous thromboembolism (VTE) according to one standard deviation of the anthropometric measure. Age was used as time axis (crude estimate age adjusted). Adjusted for physical activity, smoking categories, height, cholesterol, hypertension, diabetes and use of hormone replacement therapy (women only).

	Women				***Men***			
	All VTE (n=259)	**Idiopathic VTE** (n=109)	**Secondary VTE** (n=133)	**PE** (n=126)	**All VTE** (n=360)	**Idiopathic VTE** (n=182)	**Secondary VTE** (n=160)	**PE** (124)
	HR	HR	HR	HR	HR	HR	HR	HR
Weight, 1sd								
Crude	1.40 [1.27-1.55]	1.47 [1.27-1.70]	1.35 [1.17-1.55]	1.58 [1.39-1.80]	1.34 [1.22-1.46]	1.30 [1.14-1.48]	1.39 [1.21-1.59]	1.46 [1.25-1.69]
Adjusted	1.41 [1.27-1.57]	1.46 [1.24-1.73]	1.37 [1.17-1.60]	1.57 [1.36-1.81]	1.31 [1.18-1.46]	1.29 [1.11-1.50]	1.37 [1.17-1.60]	1.55 [1.31-1.85]
BMI, 1sd								
Crude	1.33 [1.20-1.47]	1.37 [1.18-1.60]	1.29 [1.12-1.49]	1.48 [1.29-1.69]	1.23 [1.12-1.35]	1.22 [1.07-1.39]	1.28 [1.11-1.47]	1.40 [1.20-1.62]
Adjusted	1.40 [1.26-1.55]	1.45 [1.24-1.71]	1.36 [1.17-1.58]	1.56 [1.36-1.80]	1.28 [1.16-1.41]	1.27 [1.11-1.46]	1.34 [1.16-1.55]	1.50 [1.28-1.75]
Body fat, 1sd								
Crude	1.36 [1.23-1.51]	1.39 [1.19-1.62]	1.33 [1.16-1.54]	1.54 [1.35-1.76]	1.30 [1.18-1.42]	1.29 [1.13-1.47]	1.34 [1.17-1.54]	1.48 [1.28-1.71]
Adjusted	1.38 [1.24-1.53]	1.40 [1.19-1.65]	1.37 [1.18-1.59]	1.55 [1.34-1.78]	1.29 [1.17-1.43]	1.30 [1.13-1.49]	1.34 [1.16-1.55]	1.55 [1.32-1.81]
Waist, 1sd								
Crude	1.33 [1.20-1.48]	1.32 [1.11-1.56]	1.31 [1.12-1.52]	1.52 [1.32-1.76]	1.33 [1.21-1.47]	1.33 [1.16-1.51]	1.39 [1.20-1.59]	1.48 [1.26-1.72]
Adjusted	1.33 [1.19-1.50]	1.31 [1.09-1.56]	1.33 [1.13-1.56]	1.54 [1.31-1.79]	1.33 [1.20-1.47]	1.34 [1.16-1.54]	1.39 [1.19-1.61]	1.55 [1.31-1.83]
Hip, 1sd								
Crude	1.37 [1.25-1.51]	1.45 [1.26-1.66]	1.35 [1.18-1.55]	1.51 [1.33-1.70]	1.27 [1.15-1.39]	1.22 [1.07-1.40]	1.35 [1.17-1.54]	1.38 [1.19-1.61]
Adjusted	1.40 [1.26-1.54]	1.48 [1.27-1.72]	1.39 [1.20-1.60]	1.53 [1.34-1.75]	1.24 [1.12-1.37]	1.20 [1.04-1.39]	1.33 [1.15-1.55]	1.43 [1.21-1.69]