Anthropometric Measures of Obesity and Risk of Venous Thromboembolism
The Tromsø Study
Knut H. Borch, Sigrid K. Brækkan, Ellisiv B. Mathiesen, Inger Njølstad, Tom Wilsgaard, Jan Størmer, John-Bjarne Hansen

Objectives—The purpose of this study was to assess the impact of various obesity measures on identification of subjects at risk and their respective risk estimates for VTE in a prospective population-based study.

Methods and Results—Measures of body composition such as body mass index (BMI), waist circumference (WC), hip circumference (HC), and waist-hip ratio (WHR) were registered in 6708 subjects aged 25 to 84 years, who participated in the Tromsø Study (1994–1995). Incident VTE-events were registered during follow-up until September 1, 2007. There were 222 VTE-events during a median of 12.3 years of follow-up. All measures of obesity exhibited significantly increased HR for VTE in multivariable models with highest risk estimates for WC in both genders. The risk of VTE increased across quartiles of BMI, WC, and HC in both genders, but not for WHR. WC identified more subjects at risk using established criteria for obesity. WC had the highest area under the curve in both genders in ROC analysis, and WC above ROC-derived cut-off values (WC ≥85 cm in women and ≥95 cm in men) were associated with HRs of 1.92 (95% CI: 1.05 to 3.48) in women and 2.78 (95% CI: 1.47 to 5.27) in men.

Conclusions—Our findings indicate that WC is the preferable anthropometric measure of obesity to identify subjects at risk and to predict risk of VTE. (Arterioscler Thromb Vasc Biol. 2010;30:121-127.)

Key Words: cardiovascular disease • obesity • thrombosis

The prevalence of obesity has increased dramatically in populations of developed countries during the last decades and has become a major challenge to public health and health care systems because of its associations with chronic diseases such as cardiovascular diseases and diabetes. In the U.S. population, 64.5% were overweight (BMI: ≥25 kg/m²) and 30.5% obese (BMI ≥30 kg/m²) in 2000. As excess body fat is an important risk factor for VTE, the search for the optimal anthropometric measure of obesity is pivotal to identify individuals at risk, imply public health and individual risk stratification, and subsequently modify exposure to prevent associated diseases in the future.

Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) is a common disease with serious short- and long-term complications and potential fatal outcome. The incidence of VTE is 1 to 2 per 1000 person-years, increasing significantly with age. VTE is the third most common life-threatening cardiovascular disease in the United States. Several studies have shown that obesity, mostly assessed by BMI, is a strong and independent risk factor of VTE in population-based studies, and in patients discharged from hospitals. Recent studies on arterial cardiovascular disease indicate that abdominal measures of obesity such as waist circumference (WC) and waist-hip ratio (WHR) are more strongly associated to metabolic risk factors, myocardial infarction, and mortality than BMI, but controversy exists on which anthropometric measure should be preferred when assessing cardiovascular risk associated with excessive body weight. Data from the Physicians’ Health Study indicated that BMI is a stronger predictor for VTE than coronary heart disease and stroke, but despite strong evidence for an association between BMI and VTE, few studies have assessed the relationship between other measures of obesity and VTE. A prospective study among middle-aged men identified WC as an independent predictor for VTE and increased WC and WHR have been reported in case–control studies among patients with unprovoked VTE and recurrent VTE, respectively.

To our knowledge, no study has compared the impact of various anthropometric measures of obesity on the risk of VTE. We used data from a prospective population-based...
study to assess the impact of BMI, WC, hip circumference (HC), and WHR on risk estimates for VTE, the risk estimates across quartiles of each anthropometric measure, and their optimal cut-off values for risk stratification.

Methods

Study Population

The fourth survey of the Tromsø Study was carried out in 1994 to 1995 and comprised 2 screening visits with an interval of 4 to 12 weeks. All inhabitants born before 1970 were invited to the first visit. All participants born in 1920 to 1939 and 5% to 10% samples of subjects born 1940 to 1970 and 1910 to 1919 were invited to a more extensive second visit. A total of 7965 subjects attended both visits. The response rates were 74% in women and 77% in men. The study was approved by the regional committee for research ethics and all participants gave their informed written consent to participate. Subjects who did not consent to medical research (n=110), subjects not officially registered as inhabitants of the municipality of Tromsø at the date for the second examination (n=16), subjects with prior VTE (n=20), and subjects with missing values of one or more of the examined variables (n=78) were excluded. Furthermore, 1033 women only participating in a substudy (Bone Mineral Density study) with limited measurements and registrations were excluded. Hence, a total of 6708 subjects were included in our study and followed from the date of enrolment in 1994 to 1995 through the end of the study period, September 1, 2007.

Measurements

Baseline information was collected by physical examination, non-fasting blood samples, and self-administered questionnaires. Height and weight were measured with subjects wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m²). WC was measured in centimetres at the umbilical line. HC was measured at the widest point at the hips. WHR ratios were calculated by dividing WC by HC. Information on self-reported diabetes and current smoking was collected from a self-administered questionnaire.

Blood pressure was recorded with an automatic device (Dinamap Vital Signs Monitor 1846, Critikon Inc) by trained personnel. Participants rested for 2 minutes in a sitting position, and then 3 readings were taken on the upper right arm separated by 2-minute intervals. The average of the last 2 readings was used in the analysis. Nonfasting blood samples were collected from an antecubital vein, serum prepared by centrifugation after 1 hour respite at room temperature and analyzed at the Department of Clinical Chemistry, University Hospital of North Norway. Serum total cholesterol and triglycerides were analyzed by enzymatic colorimetric methods and commercially available kits (CHOD-PAP for cholesterol and GPO-PAP for triglycerides: Boeringer Mannheim, Germany). Serum HDL-cholesterol was measured after precipitation of lower-density cholesterol was measured in centimetres at the umbilical line. HC was measured at the widest point at the hips. WHR ratios were calculated by dividing WC by HC. Information on self-reported diabetes and current smoking was collected from a self-administered questionnaire.

Blood pressure was recorded with an automatic device (Dinamap Vital Signs Monitor 1846, Critikon Inc) by trained personnel. Participants rested for 2 minutes in a sitting position, and then 3 readings were taken on the upper right arm separated by 2-minute intervals. The average of the last 2 readings was used in the analysis. Nonfasting blood samples were collected from an antecubital vein, serum prepared by centrifugation after 1 hour respite at room temperature and analyzed at the Department of Clinical Chemistry, University Hospital of North Norway. Serum total cholesterol and triglycerides were analyzed by enzymatic colorimetric methods and commercially available kits (CHOD-PAP for cholesterol and GPO-PAP for triglycerides: Boeringer Mannheim, Germany). Serum HDL-cholesterol was measured after precipitation of lower-density lipoproteins with heparin and manganese chloride. Determination of glycated hemoglobin (HbA1c) in EDTA whole blood was based on an immunoturbidimetric assay (UNIMATES, P Hoffmann-La Roche AG). The HbA1c percent value was calculated from the HbA1c/Hb ratio.

Registry of Venous Thrombosis

All first lifetime events of VTE 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 enrolment in the Tromsø study (1994–1995) to September 1, 2007. All hospital care and relevant diagnostic radiology in the Tromsø municipality is provided exclusively by this hospital. The relevant discharge codes were ICD-9 codes 425, 451.1, 451, 452, 453, 671.3, 671.4, 671.9 for the period 1994 to 1998 and ICD-10 codes I80.0–I80.3, I80.8, I80.9, 181, 182.0–182.3, 182.8, 182.9, I67.6, O22.3, O22.5, O87.1, O87.3, I26.0 and I26.9 for the period 1999 to 2007. The hospital discharge diagnosis registry included diagnoses from outpatient clinic visits and hospitalizations. An additional search through the computerized index of autopsy diagnoses was conducted, and cases diagnosed with VTE either as cause of death (part 1 of the death certificate) or as 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 due to 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) confirmed by diagnostic procedures including compression ultrasonography, venography, spiral computed tomography (spiral CT), perfusion-ventilation scan (high or moderate probability for PE), pulmonary angiography, or autopsy; (2) the medical record indicated that a physician had made a diagnosis of DVT or PE; (3) signs and symptoms consistent with DVT or PE were present, and (4) the patient underwent treatment 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 PE as cause of death or as a significant condition contributing to death.

Based on 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 acute medical condition (acute MI, ischemic stroke, or major infectious disease) within 8 weeks before event, active cancer at time of event, marked immobilization (bed rest for longer than 3 days, wheelchair, or long distant travels exceeding 4 hours within the last 14 days before event) were considered provoking factors.

Statistical Analyses

For each participant, person-years of follow-up were accrued from the date of enrolment in the Tromsø Study through the date a VTE-event was diagnosed, the date participant died or officially moved from the municipality of Tromso, or through the end of the study period, September 1, 2007. During the follow-up period, 484 persons moved from the municipality of Tromso and 1403 persons died.

Statistical analysis was carried out using SPSS version 15.0 (SPSS Inc). Statistical differences between groups were tested by Student t test for continuous variables and by χ² for categorical variables. General linear models for univariate analysis of variance were used for age and gender adjustments of continuous variables, whereas logistic regression was used for adjustments of dichotomous variables. Pearson product-moment correlation was used to assess the strength and direction of the linear relationships between the anthropometric measures. Gender specific Cox-proportional hazards regression models were used to estimate hazard ratios (HR) with 95% confidence intervals (CI) for VTE by 1 standard deviation (SD) increase in the anthropometric measurements and to assess the risk of VTE associated with established definitions of obesity. For BMI (kg/m²), overweight was defined as BMI 25 to 29.9 kg/m² and obesity as BMI ≥30 kg/m² in both genders.23,24 For WC (cm), abdominal overweight was defined as ≥80 cm in women and ≥94 cm in men and abdominal obesity was defined as ≥88 cm in women and ≥102 cm in men.23,24 For WHR (ratio), obesity was defined as ≥0.85 in women and ≥0.95 in men.23 Cox-proportional hazard regression was also used to calculate gender specific age-adjusted HR across quartiles of the different anthropometric measures. The proportional hazard assumption was verified by evaluating the parallelism between the curves of the log-log survivor function for
There were 222 validated first VTE events registered during 72,088 person-years of follow-up (median 12.3 years). The incidence of VTE was 3.08 per 1000 person-years in the study population. Characteristics of VTE events are shown in Table 1. A total of 88 events (39.6%) were unprovoked. Among the subjects with incident VTE, 63.1% had DVT and 36.9% had pulmonary embolism, with or without concurrent DVT. Except for women-specific risk factors such as estrogen supplementation and pregnancy/puerperium, clinical risk factors and provoking factors were distributed equally between genders (data not shown).

Baseline characteristics of subjects with and without incident VTE events during follow-up are shown in Table 2. Individuals with VTE during follow-up were significantly older ($P<0.001$) than those without VTE. Anthropometric measures of obesity such as body weight (kg), BMI (kg/m$^2$), WC (cm), HC (cm), and WHR were higher in subjects who suffered a VTE-event. Men with VTE during follow-up had significantly higher systolic and diastolic blood pressure ($P<0.001$) and higher prevalence of diabetes mellitus (DM) ($P=0.035$). In women, no significant differences between subjects with and without VTE were seen with regard to smoking, blood pressure, total cholesterol, HDL-cholesterol, triglycerides, HbA1c levels, or prevalence of DM.

Simple correlation analysis of relations between various anthropometric measures in men and women revealed strong and similar age-adjusted correlation coefficients among genders with the exception that BMI was stronger correlated with HC in women than men ($r=0.85$ and

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### Table 1. Characteristics of VTE Patients (n=222) at the Time of the VTE Event: the Tromsø Study (1994–2007)

| Provoking factors | F | M | F | M
|------------------|---|---|---|---
| Heredity*        | 2.3 (5) | 2.4 (5) | 2.3 (5) | 2.4 (5)
| Other medical conditions† | 23.4 (52) | 23.4 (52) | 23.4 (52) | 23.4 (52)
| Estrogens (HRT, oral contraceptives)‡ | 12.5 (14) | 12.5 (14) | 12.5 (14) | 12.5 (14)

Values are percentages, with numbers in brackets.

*VTE event in one or more first-degree relatives before age of 60 years.
†Other diseases within the previous year (myocardial infarction, ischemic stroke, heart failure, inflammatory bowel disease, chronic infections, chronic obstructive pulmonary disease, or myeloproliferative disorders).
‡In women only.
§Some patients had more than one provoking factor at the time of the event.
||Other provoking factors described by a physician in the medical record, (eg intravascular catheter).

different categories of the variables. Optimal cut-off values for the anthropometric measures were defined as the value with shortest distance to perfect sensitivity in a logistic regression-based empirical receiver operating characteristic (ROC) curve.

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### Table 2. Baseline Characteristics of Subjects With (+VTE) and Without (−VTE) Incident VTE During Follow-Up (Age-Adjusted): the Tromsø Study (1994–2007)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Women</th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>+VTE (n=112)</td>
<td>65.1±6.5</td>
<td>60.7±10.3</td>
<td>&lt;0.001</td>
<td>+VTE (n=110)</td>
<td>63.7±6.9</td>
</tr>
<tr>
<td>BW, kg</td>
<td>71.9±11.5</td>
<td>67.6±11.8</td>
<td>&lt;0.001</td>
<td>84.5±12.4</td>
<td>79.9±12.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.3±4.3</td>
<td>25.9±4.4</td>
<td>0.001</td>
<td>26.9±3.3</td>
<td>26.0±3.4</td>
<td>0.01</td>
</tr>
<tr>
<td>WC, cm</td>
<td>88.6±10.3</td>
<td>85.0±11.1</td>
<td>&lt;0.001</td>
<td>98.0±8.8</td>
<td>95.0±9.4</td>
<td>0.001</td>
</tr>
<tr>
<td>HC, cm</td>
<td>105.8±8.9</td>
<td>103.4±9.1</td>
<td>0.005</td>
<td>105.4±6.0</td>
<td>103.2±6.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WHR, ratio</td>
<td>0.84±0.07</td>
<td>0.82±0.07</td>
<td>0.014</td>
<td>0.93±0.06</td>
<td>0.92±0.06</td>
<td>0.083</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>25.6 (26)</td>
<td>31.1 (1030)</td>
<td>0.231</td>
<td>29.9 (32)</td>
<td>34.3 (1120)</td>
<td>0.347</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>141±23</td>
<td>140±23</td>
<td>0.483</td>
<td>145±22</td>
<td>140±19</td>
<td>0.004</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>81±13</td>
<td>79±13</td>
<td>0.158</td>
<td>84±12</td>
<td>81±11</td>
<td>0.038</td>
</tr>
<tr>
<td>Total-C, mmol/L</td>
<td>7.07±1.32</td>
<td>6.89±1.35</td>
<td>0.122</td>
<td>6.41±1.10</td>
<td>6.52±1.2</td>
<td>0.349</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.58±0.42</td>
<td>1.65±0.44</td>
<td>0.085</td>
<td>1.35±0.35</td>
<td>1.36±0.40</td>
<td>0.665</td>
</tr>
<tr>
<td>TAG, mmol/L</td>
<td>1.52±0.86</td>
<td>1.47±0.87</td>
<td>0.528</td>
<td>1.59±0.75</td>
<td>1.66±1.00</td>
<td>0.494</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.6±0.95</td>
<td>5.5±0.68</td>
<td>0.096</td>
<td>5.48±0.66</td>
<td>5.46±0.67</td>
<td>0.708</td>
</tr>
<tr>
<td>DM, %</td>
<td>3.1 (6)</td>
<td>2.6 (116)</td>
<td>0.683</td>
<td>6.1 (9)</td>
<td>2.9 (110)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Values are means±1SD or percentage with numbers in brackets.

BW indicates body weight; BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; Total-C, total cholesterol; HDL-C, HDL-cholesterol; TAG, triglycerides; DM, diabetes mellitus.
and that BMI was stronger correlated with WHR in men than women (r = 0.60 and r = 0.38, respectively) (data not shown).

Hazard ratios for VTE by 1SD increase in anthropometric measures of obesity are shown in Table 3. The risk estimates for VTE were similar and significant for most anthropometric measures among both genders when modeled as continuous variables, with WC exhibiting the highest risk among women, whereas HC and WC had the higher risk estimates in men (Table 3). In quartile-based analysis (Figure) adjusted for age, smoking, systolic blood pressure, total cholesterol, HDL cholesterol, diabetes mellitus, and estrogen supplementation (women only), a linear increase in risk of VTE appeared in men and women for BMI, WC, and HC, whereas no association was found across quartiles of WHR in any gender. The adjusted risk estimates for VTE (Figure) among subjects in the upper quartile of BMI compared to the lower quartile were 2.14 (95% CI: 1.13 to 4.05) versus 2.12 (1.14 to 3.94) in women and men, respectively. For WC HRs were 2.02 (95% CI: 1.07 to 3.85) versus 2.85 (95% CI: 1.44 to 5.67) and for HC 1.80 (95% CI: 0.97 to 3.34) versus 1.95 (95% CI: 1.11 to 3.44). In ROC-analysis, WC had the higher area under the curve in both genders (Table 4). In women, a WC cut-off point of 85 cm had sensitivity of 0.68 and specificity of 0.57, whereas in men a cut-off value of 95 cm had sensitivity of 0.64 and specificity of 0.54. In a multivariable model adjusted for age, smoking, systolic blood pressure, total cholesterol, HDL cholesterol, diabetes mellitus, and estrogen supplementation (women only) using the lower quartiles as reference group, a WC above the cut-off value yielded HRs of 1.92 (95% CI: 1.05 to 3.48) in women and 2.78 (95% CI: 1.47 to 5.27) in men.

Risk assessment of total VTE by different levels of overweight and obesity in men and women are shown in Table 5. In men, 12%, 22%, and 29% were obese according to the criteria for BMI, WC, and WHR, respectively. Corresponding figure for women were 17%, 37%, and 29%, respectively. With the exception of BMI and WHR in men, all established criteria for obesity were associated with increased risk of total VTE. The risk estimates for the association between obesity and total VTE were highest for WC. Risk estimates for provoked and unprovoked VTE across categories of anthropometric measures did not differ significantly from total VTE (data not shown).

### Table 3. Gender-Specific Hazard Ratios (HR) for Venous Thromboembolism (VTE) With 95% Confidence Intervals (95% CI) by 1SD Increase in the Anthropometric Measures: the Tromsø Study (1994–2007)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean</th>
<th>SD</th>
<th>BMI, kg/m²</th>
<th>Age-Adjusted HR (95% CI)</th>
<th>Multivariable* HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (n=3396)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.0</td>
<td>4.4</td>
<td>1.30 (1.11–1.53)</td>
<td>1.26 (1.04–1.52)</td>
<td></td>
</tr>
<tr>
<td>WC, cm</td>
<td>85.1</td>
<td>11.1</td>
<td>1.35 (1.14–1.60)</td>
<td>1.33 (1.09–1.62)</td>
<td></td>
</tr>
<tr>
<td>HC, cm</td>
<td>103.4</td>
<td>9.1</td>
<td>1.26 (1.07–1.49)</td>
<td>1.21 (1.00–1.46)</td>
<td></td>
</tr>
<tr>
<td>WHR</td>
<td>0.82</td>
<td>0.07</td>
<td>1.23 (1.06–1.43)</td>
<td>1.21 (1.03–1.43)</td>
<td></td>
</tr>
<tr>
<td>Men (n=3312)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.1</td>
<td>3.4</td>
<td>1.26 (1.06–1.51)</td>
<td>1.21 (1.00–1.47)</td>
<td></td>
</tr>
<tr>
<td>WC, cm</td>
<td>95.1</td>
<td>9.4</td>
<td>1.37 (1.15–1.64)</td>
<td>1.32 (1.09–1.60)</td>
<td></td>
</tr>
<tr>
<td>HC, cm</td>
<td>103.1</td>
<td>6.2</td>
<td>1.38 (1.15–1.65)</td>
<td>1.33 (1.10–1.61)</td>
<td></td>
</tr>
<tr>
<td>WHR</td>
<td>0.92</td>
<td>0.06</td>
<td>1.21 (1.02–1.43)</td>
<td>1.15 (0.96–1.38)</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, smoking, systolic blood pressure, total cholesterol, HDL cholesterol, diabetes mellitus, and estrogen supplementation (women).
A recent cohort study suggested obesity, assessed by BMI, to be a stronger predictor for VTE than for other cardiovascular diseases such as myocardial infarction and stroke. The present study was conducted to compare the impact of different anthropometric measures of obesity on risk of VTE with regard to risk estimates and identification of subjects at risk. Most anthropometric measures of obesity were significantly associated with risk of VTE, with WC exhibiting high-risk estimates in both genders. WC yielded highest risk estimates for VTE and number of subjects at risk using established criteria for obesity measured by BMI, WC, and WHR. Furthermore, ROC-analysis revealed that WC had the greater area under the curve and ROC-derived cut-off points (WC ≥85 cm in women and ≥95 cm in men) rendered 46.8% of the female and 50.2% of the male population at 2- to 3-fold increased risk of VTE, suggesting that criteria for abdominal obesity should be modified to imply optimal risk stratification and subsequent modification to prevent VTE in the future. Our findings suggest that WC is preferable to other anthropometric measures of obesity to identify subjects at risk and predict VTE in both genders.

BMI has been the preferred anthropometric measure of obesity for decades and consistently been shown to be a risk factor of VTE in prospective studies and case–control studies. Accordingly, BMI was shown to be a risk factor of VTE when modeled as a continuous variable and in quartile-based analysis in our study with most pronounced impact in women. However, BMI lack discriminatory power to differentiate between body fat and lean body mass which may cause misclassification of subjects. The latter phenomenon may have contributed to the observation that obesity (BMI ≥30 kg/m²) was not an independent risk factor of VTE in men. Likewise, quartile-based analysis revealed that only men and women in the upper quartile of BMI (BMI ≥28.2 kg/m²) had increased risk of VTE. Along with lower risk estimates of VTE for BMI and lower area under the curve in ROC-curve analysis, these considerations suggest that BMI is inferior to WC as an anthropometric measure of obesity to identify subjects at risk and to assess risk of VTE.

WC is a simple measure of abdominal visceral adipose tissue unrelated to height, but closely related to BMI and total body fat. Furthermore, WC has been reported to be more closely associated with cardiovascular risk factors and all-cause mortality than BMI. Similarly, WC has also been shown to be the best indicator of change in intra-abdominal fat during weight loss. Previously, abdominal obesity, assessed by WC ≥100 cm, was shown to increase the relative risk of VTE 3.9-fold in middle-aged Swedish men. In our study, we confirmed that increased WC is a substantial risk factor of VTE in men and provided extended data suggesting that WC is also a risk factor of VTE in women. Furthermore, case–control studies in patients with unprovoked VTE and risk.

### Table 4. ROC-Curve Analysis With Area Under the Curve (AUC), 95% CI, and Suggested Cut-Off Values for Anthropometric Measures: the Tromsø Study (1994–2007)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Women</th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>95% CI</td>
<td>Cut-Off Value</td>
<td>AUC</td>
<td>95% CI</td>
<td>Cut-Off Value</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.628</td>
<td>0.578–0.678</td>
<td>26.7</td>
<td>0.572</td>
<td>0.519–0.625</td>
<td>25.9</td>
</tr>
<tr>
<td>WC, cm</td>
<td>0.640</td>
<td>0.592–0.689</td>
<td>85</td>
<td>0.609</td>
<td>0.559–0.659</td>
<td>95</td>
</tr>
<tr>
<td>HC, cm</td>
<td>0.602</td>
<td>0.550–0.653</td>
<td>102.5</td>
<td>0.594</td>
<td>0.540–0.649</td>
<td>103.5</td>
</tr>
<tr>
<td>WHR</td>
<td>0.602</td>
<td>0.549–0.654</td>
<td>0.84</td>
<td>0.575</td>
<td>0.522–0.628</td>
<td>0.92</td>
</tr>
</tbody>
</table>

### Table 5. Gender-Specific Hazard Ratios (HR) for Total Venous Thromboembolism (VTE) with 95% Confidence Intervals (95% CI) by Established Criteria for Obesity: the Tromsø Study (1994–2007)

<table>
<thead>
<tr>
<th>Total VTE</th>
<th>Women (n=3396)</th>
<th></th>
<th></th>
<th>Men (n=3312)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>Events</td>
<td>HR (95% CI)*</td>
<td>n (%)</td>
<td>Events</td>
<td>HR (95% CI)*</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25</td>
<td>1534 (45.2)</td>
<td>29</td>
<td>Ref</td>
<td>25–29.9</td>
<td>1276 (37.6)</td>
</tr>
<tr>
<td>≥30</td>
<td>586 (17.3)</td>
<td>35</td>
<td>2.36 (1.37–4.07)</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WC, cm</td>
<td>&lt;80</td>
<td>1130 (33.3)</td>
<td>17</td>
<td>Ref</td>
<td>80–87.9</td>
<td>1008 (29.7)</td>
</tr>
<tr>
<td>≥88</td>
<td>1258 (37.0)</td>
<td>67</td>
<td>2.53 (1.42–4.52)</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHR</td>
<td>&lt;0.85</td>
<td>2414 (71.1)</td>
<td>63</td>
<td>Ref</td>
<td>0.85–0.85</td>
<td>982 (28.9)</td>
</tr>
<tr>
<td>≥0.85</td>
<td>739 (22.3)</td>
<td>38</td>
<td>2.08 (1.24–3.46)</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, smoking, systolic blood pressure, total cholesterol, HDL cholesterol, diabetes mellitus, and estrogen supplementation (women only).
recurrent VTE\textsuperscript{22} have also reported increased WC among VTE patients. Current cut-off values for WC proposed by Lean et al\textsuperscript{25} were originally derived by their ability to predict corresponding measures of obesity assessed by BMI (overweight 25.0 to 29.9 and obesity $\geq$30) and not on basis of empirical relation to risk factors or related diseases.\textsuperscript{24,25} In our study, women with WC $\geq$85 cm and men with WC $\geq$95 cm had a 1.9-fold and 2.8-fold increased risk of VTE, respectively. Likewise, middle-aged Swedish men in the upper quintile of WC (WC $\geq$95 cm) experienced a 2.6-fold increased risk of VTE during 26 years of follow-up.\textsuperscript{20} Thus, these empirical data on the relation between WC and risk of VTE may advocate for lowering of the present action levels for WC with subsequent weight reduction to prevent development of associated diseases such as VTE.

The mechanism(s) by which abdominal obesity increases the risk of venous thrombosis in not fully understood. Abdominal obesity is associated with raised intra-abdominal pressure and reduced venous blood flow velocity which may render blood more susceptible to thrombosis.\textsuperscript{32,33} Visceral adipose tissue, estimated by increased waist circumference in our study, is highly metabolic active, releasing increased amounts of proinflammatory-, proatherogenic- and prothrombotic substances.\textsuperscript{11} It remains to be settled to what extent these mechanisms contribute to the risk of VTE by obesity.

Previous studies have shown that high HC is associated with a favorable metabolic profile\textsuperscript{34} and protects against myocardial infarction (MI).\textsuperscript{14} In contrast, high HC was associated with increased risk of VTE in both genders in our study. However, ROC-curve analysis yielded lower area under the curve compared to WC in both genders, suggesting that HC is less attractive to assess risk of VTE than WC. In accordance, middle-aged men who suffered a VTE had higher HC at baseline than those who did not experience a VTE-event during follow-up, but HC did not turn out to be an independent risk factor in multivariable analyses.\textsuperscript{20} Likewise, a case–control study among patients with recurrent VTE reported a nonsignificant increase in HC among the VTE patients.\textsuperscript{22} The reason(s) for the apparent opposite impact of HC on risk of MI and VTE are not known, but may reflect different pathophysiological mechanism(s), complex interpretations of HC which encompass bone structure, gluteal muscle, and subcutaneous adipose tissue.\textsuperscript{34}

WHR has been shown to be a less accurate measure of intra-abdominal fat than WC.\textsuperscript{29,35} Despite this, data from the INTERHEART-study revealed WHR to have the strongest relation with risk of MI and it was suggested that WHR should be the preferred anthropometric measure of obesity to assess risk of MI.\textsuperscript{14} However, the impact of WHR as a risk factor of VTE is expected to be diluted because of the opposite effect of HC on risk of MI and VTE. As expected, WHR turned out to be a weaker risk factor of VTE than each of its components and only showed significance treated as a continuous variable among women (table 3). Similarly, increased WHR was reported in a case–control study among patients with recurrent VTE,\textsuperscript{22} despite a nonsignificant increase in HC among VTE patients.

The main strengths of our study are its prospective design; large number of participants recruited from a general population with high attendance rate, long-term follow-up, and validated VTE events. All hospital care and radiological imaging in the region is exclusively provided by a single hospital, which enhances the possibility of a complete VTE registry. However, the study has some limitations. Modifiable risk factors, such as anthropometric measures of obesity, are a potential limitation of cohort studies, especially when the time between acquisition of data and disease manifestation is very long. However, this type of nondifferential misclassification generally leads to underestimation of the true associations. Because of limited number of VTE events in our cohort, we did not have statistical power to assess potential different impact of anthropometric measures of obesity on risk of unprovoked and provoked VTE.

In conclusion, our study indicates that WC is the preferable anthropometric measure of obesity for assessing risk of VTE attributable to high risk estimates in both genders and its ability to identify subjects at risk. Furthermore, our findings may suggest cut-off values for WC by which weight reduction is recommended.

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Disclosures

None.

References


Anthropometric Measures of Obesity and Risk of Venous Thromboembolism: The Tromsø Study
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