





Overall and abdominal obesity in relation to venous thromboembolism

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Abstract

Background: Abdominal obesity has been shown to be a superior measure over overall obesity for detecting cardiovascular risk.

Objective: We conducted this study to compare the effects of overall and abdominal obesity on venous thromboembolism (VTE) and to calculate population attributable fraction for obesity for VTE.

Methods: Body mass index (BMI) and waist circumference (WC) were used to represent overall and abdominal obesity, respectively. In the cohort study, we included 74317 Swedish adults with anthropometric measures in 1997 and of whom 4332 were diagnosed with VTE until the end of 2017. A Mendelian randomization study was conducted to investigate causal associations of BMI, WC, and WC adjusted for BMI with VTE using data from FinnGen and UK Biobank study. Population attributable fraction was calculated for overall and abdominal obesity for VTE.

Results: In the cohort study, there were dose-response associations of BMI and WC with VTE. The association between BMI and VTE was attenuated largely after adjusting for WC. Among individuals with normal BMI, participants with substantially increased WC had 53% higher (hazard ratio 1.53; 95% confidence interval, 1.28, 1.81) risk of VTE compared to those with normal WC. The causality of the association of WC adjusted for BMI with VTE was confirmed in Mendelian randomization analysis. The estimated population-attributable risk due to elevated BMI and WC were 12.4% (8.4%, 16.5%) and 23.7% (18.1%, 29.4%), respectively.

Conclusions: WC might be a preferable indicator linking obesity to VTE. A large proportion of VTE cases can be prevented if the population maintained a healthy BMI and WC.

KEYWORDS

abdominal obesity, Mendelian randomization analysis, obesity, perspective cohort study, venous thromboembolism

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1 | INTRODUCTION

Venous thromboembolism (VTE) is the third most common cardiovascular disease affecting one to two individuals per thousand inhabitants in the Western world. VTE is associated with considerable morbidity and mortality as well as high health-care costs.¹⁻³

Adipose tissue, an important biomarker for obesity, not only influences body weight but also insulin resistance as well as blood lipids, blood pressure, coagulation, fibrinolysis, and inflammation, thereby leading to endothelial dysfunction and atherosclerosis.⁴ Elevated body mass index (BMI) has been identified as a risk factor for VTE in most observational population-based studies.⁵⁻⁷ The causal association between BMI and VTE has been confirmed in several Mendelian randomization (MR) studies.⁸⁻¹⁰ Abdominal obesity has been shown to be a superior measure over overall obesity for detecting cardiovascular disease risk.¹¹ However, given different etiological bases between VTE and other cardiovascular diseases and limited evidence on this topic,⁶ it remains unclear whether abdominal obesity is a better indicator linking obesity to VTE compared to overall obesity. In addition, the proportion of VTE cases that would not occur in a population if obesity were to be eliminated is unknown. Such information contributes to the prevention strategies for VTE, prediction model construction, health policy making, and resource allocation in public health. Therefore, we conducted a study to compare the effects of overall and central obesity on VTE using both prospective cohort and MR study designs and calculated population attributable fraction for overall and abdominal obesity for VTE.

2 | METHODS

2.1 | Prospective cohort study

2.1.1 | Study population

We obtained data from the Swedish Infrastructure for Medical Population-Based Life-Course and Environmental Research (SIMPLER, www.simpler4health.se), which includes data from the Cohort of Swedish Men (COSM) and the Swedish Mammography Cohort (SMC). Invited to participate in these cohorts were all men who were born between 1918 and 1952 and resided in Västmanland and Örebro counties and all women who were born between 1914 and 1948 and lived in Västmanland and Uppsala counties. In the autumn of 1997, a total of 48 850 men and 39 227 women answered a questionnaire of which 38 626 men and 35 691 women were included in the present analyses after exclusion of individuals (a) with incorrect/missing personal identity number; (b) who died before 01 January 1998; (c) with a history of cancer, VTE, or cardiovascular disease (heart failure and stroke); (d) with missing or implausible BMI information; or (e) who were underweight (BMI < 18.5 kg/m²). Information on waist circumference (WC) was missing for 12 529 participants, leaving 61 788 participants in the analyses of WC. The participants had completed a questionnaire on

Essentials

- Abdominal obesity appears to be a superior measure over overall obesity for detecting cardiovascular risk.
- Waist circumference (WC) was the preferable indicator linking obesity to venous thromboembolism (VTE).
- The estimated population attributable risk due to elevated WC was 23.7%.
- A large proportion of VTE cases can be prevented if the population maintained a healthy BMI and WC.

anthropometrics, lifestyle, and other risk factors for chronic diseases in late autumn 1997.

2.1.2 | Assessment of obesity and covariates

We obtained information on current body weight and height, WC, date of birth, sex, highest education level, smoking status and history, alcohol consumption status and history, diet, walking/bicycling time, and ever hormone therapy use (only for women) from the self-administrated questionnaire. Cancer diagnosis was based on codes in the International Classification of Diseases 9th (140--239) and 10th (C00--C97) Revisions and the information was extracted from the Swedish Cancer Registry. We constructed a dietary score using a modified version of Dietary Approaches to Stop Hypertension (mDASH) diet, which includes fruits, vegetables, nuts and legumes, whole grains, low-fat dairy products, meat, and sweetened beverages. The mDASH diet score ranged from 7 to 35 and a higher score represented a healthier dietary pattern.

BMI and WC were used to represent overall and abdominal obesity, respectively. BMI was calculated as weight in kg divided by the square of height in m. Participants were categorized into five groups based on BMI (kg/m²) corresponding to 18.5--22.4, 22.5--24.9, 25.0--27.4, 27.5--29.9, and ≥ 30.0 . In addition, participants were categorized into three groups as normal BMI in kg/m² (18.5--24.9), overweight (25.0--29.9) and obesity (≥ 30) based on World Health Organization (WHO) definition for obesity in European populations. We further grouped participants into three categorizations for normal, increased, and substantially increased WC (cm) with cutoff points <94, 94--101, and ≥ 102 for men and <80, 80--87, and ≥ 88 for women, according to WHO classification. Individuals with BMI 18.5--22.4 kg/m², men with WC < 94 cm, and women with WC < 80 cm were defined as the normal group.

2.2.1 | Venous thromboembolism ascertainment and follow-up

Outcome was defined by the clinical diagnosis caused by VTE or its two subtypes (pulmonary embolism [PE] and deep vein thrombosis

[DVT]) as the main or contributing cause. Diagnostic information was ascertained via linkage of the cohort to the Swedish National Patient Register, which covers nearly 100% of hospital-based inpatient care.¹² The register has been expanded to include outpatient physician visits from specialist public and private care providers since 2001.¹² Dates of deaths were ascertained by linkage with the Swedish Cause of Death Register. Diagnostic definitions for VTE, PE, and DVT were based on the International Classification of Diseases 9th and 10th Revisions. Detailed diagnostic codes are displayed in Table S1 in supporting information. Participants were followed up from 01 January 1998 until the date of diagnosis of VTE, date of death, or end of follow-up (ie 31 December 2017), whichever came first.

2.3 | Mendelian randomization study

2.3.1 | Instrumental variable selection

Single-nucleotide polymorphisms (SNPs) associated with BMI ($n = 312$), WC ($n = 47$), and WC adjusted for BMI ($n = 76$) at the genome-wide significance level ($P < 5 \times 10^{-8}$) were identified from meta-analyses of genome-wide association studies encompassing up to 806 834 individuals for BMI¹³ and 224 459 individuals for WC and WC adjusted for BMI.¹⁴ SNPs for each trait were independent (defined as linkage disequilibrium $R^2 < .01$). Details of the included SNPs and studies are displayed in Table S2 in supporting information.

2.4 | Outcome source

Summary-level data for the associations of the SNPs related to obesity traits with VTE were obtained from the FinnGen consortium¹⁵ with 5403 VTE cases and 130 235 non-cases of European ancestry and UK Biobank with 4620 VTE cases and 356 574 non-cases of British genetic ancestry.¹⁶ Detailed methods, such as participating biobanks/cohorts, data collection, genotyping, and data analysis are presented in FinnGen's and Neale lab's webpage.

2.5 | Statistical analysis

Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of VTE by exposure categories were estimated using Cox proportional hazard regression model with age as the underlying time scale. Analyses were first performed separately for women and men, and then combined, treating sex as a stratum variable. A multivariable model further adjusted for alcohol drinking, cigarette smoking, total energy intake, mDASH score, walking/bicycling time, education level, and ever hormone therapy use (only for women). Median values for each category of the anthropometric measures were modelled as a continuous variable to test the trend across categories. Given that cancer is a provoking risk factor for VTE, we performed

stratified analysis to explore whether there was a difference in the association between obesity and VTE between individuals without or with a cancer diagnosis during follow-up before the date of the VTE. The assumption for Cox proportional hazards model was tested using Schoenfeld residuals and found to be satisfied.

For the Mendelian randomization analyses, the inverse-variance weighted method was used as the main analysis to assess the associations of obesity and body composition with VTE. To detect and correct for possible heterogeneity and pleiotropy, we further conducted two sensitivity analyses based on the weighted median¹⁷ and MR-Egger¹⁸ methods. Odds ratios (ORs) and 95% CIs of VTE were scaled to one standard deviation (SD) increase in genetically predicted obesity traits.

Assuming a causal association between obesity and VTE,⁸⁻¹⁰ we estimated the percentage of VTE cases that could potentially be prevented if all individuals maintained a healthy BMI ranging between 18.5 to 24.9 kg/m² or a normal WC. The following formula was used to calculate the population attributable risk: $p(HR - 1)/(1 + p[HR - 1])$.¹⁹ In this formula, p is the prevalence of exposure (overweight and obesity combined and increased and substantially increased WC combined) in the population and HR is the hazard ratio for exposed versus unexposed individuals. Similarly, we estimated population attributable risk for obesity (BMI ≥ 30 kg/m²) and substantially increased WC. All statistical analyses were two-sided and performed in Stata/SE (version 15.0; StataCorp, College Station, TX, USA). $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Findings from the cohort study

During a mean follow-up of 16.7 years (1 265 566 person-years), 4332 incident VTE cases (2175 in men and 2157 in women) were ascertained. The incidence rate was 334.2 per 100 000 person-years in men and 350.9 per 100 000 person-years in women. Mean (\pm SD) of BMI was 25.8 (\pm 3.3) kg/m² in men and 25.1 (\pm 3.8) kg/m² in women. Compared with individuals with normal BMI and WC, obese individuals were less likely to have a postsecondary education, have a history of hormone therapy use (for women), and to be a current smoker. These individuals also tended to be less physically active, consumed lower amounts of alcohol, and had lower energy intake (Table 1).

Higher BMI and WC were associated with an elevated risk of VTE and there was no sex difference (Table 2). BMI and WC were positively associated with both PE and DVT, though the magnitude of the associations was larger for DVT compared to PE (Table 2). The association between WC and VTE was only slightly attenuated after adjusting for BMI, whereas the association between BMI and VTE was attenuated largely after adjusting for WC, especially for PE (Table 2). Obesity was associated with VTE both among individuals with and without cancer before VTE diagnosis,

TABLE 1 Age-standardized baseline characteristics of 74 317 Swedish women and men according to categories of body mass index and waist circumference

Characteristic ^a	BMI					WC		
	18.5--<22.5	22.5--<25.0	25.0--<27.5	27.5--<30.0	≥30.0	Normal	Increased	Substantially increased
Women (n = 35 691)								
Number of women, n	9289	10 466	7921	4220	3795	10 919	9607	9717
Age, years (SD)	60.5 ± 9.4	61.2 ± 9.1	62.2 ± 9.0	62.7 ± 8.9	61.9 ± 8.5	59.8 ± 8.8	62.0 ± 9.2	63.4 ± 9.0
Postsecondary education, %	23.9	19.7	16.3	14.6	12.9	22.2	18.4	14.8
Ever hormone therapy use, %	48.1	47.6	45.8	42.9	40.0	47.6	47.3	43.4
Current smoker, %	27.3	22.9	21.0	20.0	18.8	23.9	21.2	21.1
Alcohol consumption, g/day (SD)	7.4 ± 8.8	7.0 ± 10.6	6.7 ± 7.9	6.1 ± 7.9	6.0 ± 16.9	7.0 ± 7.7	6.8 ± 7.6	6.4 ± 11.8
Energy intake, kcal/day (SD)	1789 ± 555	1744 ± 551	1712 ± 583	1704 ± 560	1720 ± 631	1782 ± 542	1745 ± 546	1716 ± 585
mDASH diet score (SD)	19.4 ± 4.3	19.5 ± 4.3	19.4 ± 4.3	19.1 ± 4.2	18.9 ± 4.2	19.7 ± 4.3	19.4 ± 4.2	19.0 ± 4.2
Walking/bicycling ≥40 minutes/day, %	38.1	35.5	31.7	28.9	25.1	39.9	34.7	27.9
Men (n = 38 626)								
Number of men, n	5305	11 853	11 833	5869	3766	13 376	10 331	7838
Age, years (SD)	59.5 ± 10.2	59.3 ± 9.7	59.2 ± 9.3	59.4 ± 9.1	58.9 ± 8.9	58.6 ± 9.4	59.8 ± 9.5	60.8 ± 9.4
Postsecondary education, %	23.5	19.7	16.2	13.4	11.6	19.6	16.7	14.4
Current smoker, %	27.4	24.6	23.5	22.9	24.3	24.2	21.8	23.6
Alcohol consumption, g/day (SD)	14.7 ± 21.3	14.8 ± 18.7	15.6 ± 18.8	16.4 ± 23.9	16.9 ± 24.8	14.5 ± 17.3	15.3 ± 18.1	16.9 ± 23.6
Energy intake, kcal/day (SD)	2742 ± 861	2710 ± 878	2668 ± 899	2644 ± 910	2617 ± 999	2796 ± 885	2794 ± 875	2680 ± 876
mDASH diet score (SD)	19.6 ± 4.4	19.7 ± 4.2	19.6 ± 4.1	19.2 ± 4.2	18.8 ± 4.2	19.9 ± 4.2	19.6 ± 4.1	19.1 ± 4.2
Walking/bicycling ≥40 minutes/day, %	32.9	32.5	29.3	26.7	22.8	34.8	30.0	24.5

Note: Waist circumference information is missing for 5448 women and 7081 men.

Abbreviations: BMI, body mass index; mDASH, modified Dietary Approaches to Stop Hypertension; SD, standard deviation; WC, waist circumference.

^aThe categorization for normal, increased, and substantially increased waist circumference in cm were based on < 94, 94-101, and ≥ 102 for men, and <80, 80-87, and ≥88 for women.

*Age-standardized to the age distribution of the study population at baseline. Continuous variables are expressed as mean ± SD and categorical variables as percentages.

albeit with a slightly stronger association in those without cancer and WC (Figure 1). In the analysis categorizing individuals jointly by BMI and WC (Figure 2), among individuals with normal BMI, participants with substantially increased WC had 53% higher (HR 1.53; 95% CI, 1.28, 1.81) risk of VTE compared with those with normal WC. Among subgroups with the same BMI status in categorization, the risk of VTE differed in a dose-response way for individuals with different status of WC. However, the risk of VTE did not vary across groups (with CIs overlapping) with the same WC but different BMI status.

3.2 | Findings from Mendelian randomization study

Genetically predicted higher BMI, WC, and WC adjusted for BMI were associated with VTE risk in both the FinnGen consortium and UK Biobank (Figure 3). The combined ORs of VTE were 1.51 (95% CI, 1.35, 1.70), 1.61 (95% CI, 1.31, 1.98), and 1.40 (95% CI, 1.19, 1.65) for one SD increase of BMI, WC, and WC adjusted for BMI, respectively. Results were consistent across sensitivity analyses and there was no heterogeneity and pleiotropy in these analyses (Table S3 in supporting information).

TABLE 2 Hazard ratio (95% CI) of venous thromboembolism, pulmonary embolism, and deep vein thrombosis by body mass index and waist circumference in 74 317 Swedish women and men

	Women and men combined						Women			Men			
	No. of individuals	Cases %	Person-years	HR ^a	95% CI	HR ^b	95% CI	HR ^c	95% CI	HR ^b	95% CI	HR ^b	95% CI
Venous thromboembolism													
BMI (kg/m ²)													
18.5--22.4 (reference)	14 594	4.4	249 626	1.00	--	1.00	--	1.00	--	1.00	--	1.00	--
22.5--24.9	22 319	5.6	383 582	1.23	1.12--1.35	1.24	1.12--1.36	1.15	1.04--1.27	1.31	1.15--1.48	1.16	1.00--1.35
25.0--27.4	19 754	5.8	338 192	1.25	1.14--1.38	1.26	1.14--1.39	1.08	0.97--1.20	1.26	1.10--1.44	1.25	1.07--1.45
27.5--29.9	10 089	7.2	169 398	1.59	1.43--1.76	1.59	1.43--1.78	1.27	1.12--1.44	1.65	1.42--1.91	1.54	1.31--1.81
≥30.0 ^d	7561	7.7	124 772	1.76	1.58--1.98	1.76	1.57--1.97	1.36	1.19--1.55	1.90	1.63--2.20	1.62	1.35--1.94
P for trend				<.001		<.001		<.001		<.001		<.001	
Waist circumference^e													
Normal	24 295	4.4	426 746	1.00	--	1.00	--	1.00	--	1.00	--	1.00	--
Increased	19 938	5.9	341 526	1.27	1.17--1.38	1.27	1.17--1.38	1.22	1.12--1.33	1.26	1.12--1.43	1.29	1.16--1.45
Substantially increased	17 555	7.7	286 415	1.66	1.53--1.80	1.65	1.52--1.79	1.46	1.31--1.61	1.65	1.47--1.86	1.66	1.48--1.87
P for trend				<.001		<.001		<.001		.001		.001	
Pulmonary embolism													
BMI (kg/m ²)													
18.5--22.4 (reference)	14 594	2.4	251 199	1.00	--	1.00	--	1.00	--	1.00	--	1.00	--
22.5--24.9	22 319	3.2	386 525	1.24	1.09--1.41	1.25	1.10--1.43	1.17	1.03--1.34	1.40	1.18--1.66	1.13	0.93--1.37
25.0--27.4	19 754	3.1	341 251	1.16	1.02--1.33	1.17	1.03--1.34	1.02	0.88--1.18	1.11	0.92--1.43	1.20	0.99--1.45
27.5--29.9	10 089	3.9	171 425	1.50	1.30--1.73	1.51	1.30--0.74	1.24	1.05--1.46	1.59	1.29--1.95	1.44	1.17--1.78
≥30.0 ^d	7561	3.8	126 773	1.54	1.32--1.80	1.53	1.31--1.79	1.23	1.02--1.48	1.73	1.41--2.14	1.36	1.07--1.73
P for trend				<.001		<.001		<.001		<.001		<.001	
Waist circumference^e													
Normal	24 295	2.5	429 272	1.00	--	1.00	--	1.00	--	1.00	--	1.00	--
Increased	19 938	3.3	344 499	1.24	1.11--1.39	1.24	1.11--1.39	1.21	1.08--1.37	1.22	1.03--1.44	1.28	1.11--1.48
Substantially increased	17 555	4.0	290 437	1.50	1.34--1.67	1.48	1.33--1.66	1.38	1.20--1.58	1.53	1.30--1.79	1.47	1.26--1.72
P for trend				<.001		<.001		.001		<.001		<.001	

(Continues)

TABLE 2 (Continued)

	Women and men combined						Women			Men			
	No. of individuals	Cases %	Person-years	HR ^a	95% CI	HR ^b	95% CI	HR ^c	95% CI	HR ^b	95% CI	HR ^b	95% CI
Deep vein thrombosis													
BMI (kg/m ²)													
18.5--22.4 (reference)	14 594	2.2	250 856	1.00	--	1.00	--	1.00	--	1.00	--	1.00	--
22.5--24.9	22 319	2.8	386 319	1.27	1.11--1.45	1.28	1.11--1.46	1.18	1.03--1.36	1.29	1.09--1.54	1.24	1.00--1.54
25.0--27.4	19 754	3.2	340 493	1.44	1.25--1.65	1.45	1.26--1.66	1.22	1.05--1.42	1.48	1.24--1.77	1.39	1.12--1.73
27.5--29.9	10 089	4.0	170 945	1.80	1.55--2.09	1.81	1.56--2.10	1.41	1.19--1.68	1.91	1.57--2.32	1.71	1.35--2.16
≥30.0 ^d	7561	4.4	125 930	2.08	1.78--2.42	2.07	1.77--2.42	1.56	1.30--1.87	2.22	1.82--2.71	1.90	1.47--2.45
P for trend				<.001		<.001		<.001		<.001		<.001	
Waist circumference ^e													
Normal	24 295	2.2	428 924	1.00	--	1.00	--	1.00	--	1.00	--	1.00	--
Increased	19 938	3.1	344 084	1.33	1.19--1.50	1.33	1.19--1.50	1.22	1.08--1.39	1.33	1.13--1.58	1.35	1.14--1.58
Substantially increased	17 555	4.4	289 224	1.86	1.67--2.08	1.85	1.66--2.07	1.51	1.31--1.74	1.85	1.58--2.16	1.88	1.59--2.21
P for trend				<.001		<.001		<.001		<.001		<.001	

Note: There are 12 529 missing in the analysis of waist circumference and therefore, the number of individuals and cases does sum up to the total number.

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; WC, waist circumference.

^aAdjusted for age and sex.

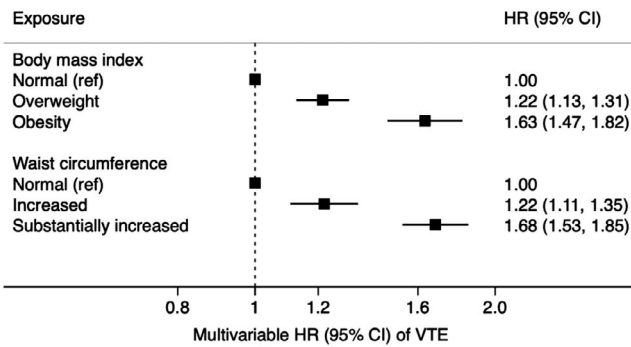
^bAdjusted for age, sex, alcohol drinking (non-drinker, former drinker, and current drinker), cigarette smoking (non-smoker, former smoker, and current smoker), total energy intake, modified Dietary Approaches to Stop Hypertension Diet score, walking/bicycling time (<20, 20-40, 40-60, and >60 mins/day), education level (representing socioeconomic status; less than high school, high school, and university and higher), and ever hormone therapy use (only for women).

^cAdditionally adjusted for BMI in analyses of WC and for WC in the analyses of BMI.

^dThe median BMI in the group was 31.9 (32.0 for women and 31.7 for men) kg/m².

^eThe categorization for normal, increased, and substantially increased waist circumference in cm were based on <94 (median 88), 94-101 (median 97), and ≥102 (median 106) for men, and <80 (median 75), 80-87 (median 83), and ≥88 (median 94) for women, respectively.

A individuals without cancer before VTE diagnosis



B individuals with cancer before VTE diagnosis

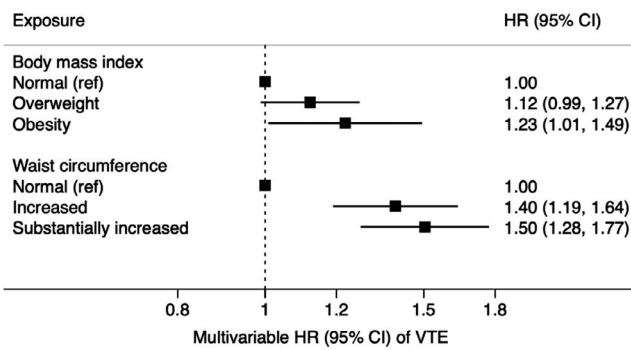


FIGURE 1 Multivariable-adjusted hazard ratio (95% CI)^a of venous thromboembolism by body mass index and waist circumference^b stratified by cancer.^c CI, confidence interval; HR, hazard ratio; VTE, venous thromboembolism. ^aAdjusted for age; sex; history of hypertension, hypercholesterolemia, diabetes, and fracture; incident cancer; alcohol drinking (non-drinker, former drinker, and current drinker); cigarette smoking (non-smoker, former smoker, and current smoker); total energy intake; modified Dietary Approaches to Stop Hypertension Diet score; walking/bicycling time (< 20, 20–40, 40–60, and >60 mins/day); education level (representing socioeconomic status; less than high school, high school, and university and higher); and ever aspirin use. ^bThe categorization for normal, increased, and substantially increased waist circumference in cm were based on <94, 94–101, and ≥102 for men, and <80, 80–87, and ≥88 for women, respectively. ^cIncident cancer before VTE diagnosis (59 018 and 15 299 individuals in cancer-free and cancer group, respectively)

3.3 | Population-attributable risk

The estimated proportion of VTE cases attributed to overweight and obesity combined (BMI ≥ 25 kg/m²; 50.3% of the study population) was 12.4% (95% CI 8.4%–16.5%) and that for obesity alone (BMI ≥ 30 kg/m²; 10.1% of the study population) was 5.1% (95% CI 3.8%–6.5%). The proportion of VTE cases attributed to increased and substantially increased WC combined (≥94 cm for men and ≥ 80 cm for women; 60.7% of the study population) was 23.7% (95% CI 18.1%–29.4%) and that for substantially increased WC (≥102 cm for men and ≥ 88 cm for women; 28.4% of the study population) was 15.6% (95% CI 12.9%–18.3%).

4 | DISCUSSION

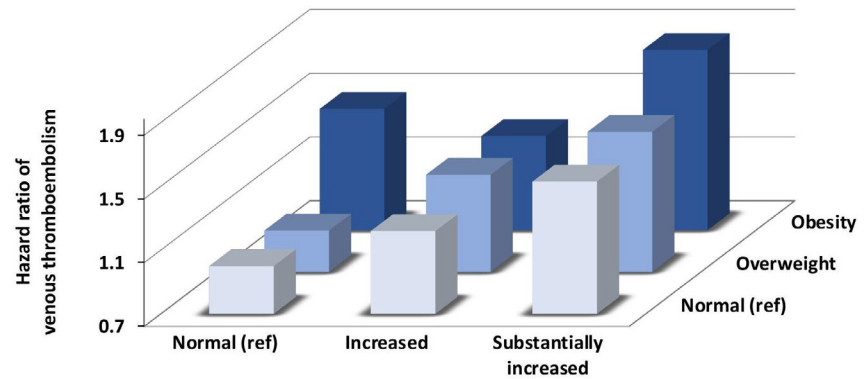
In the present study, we applied prospective cohort and MR study designs and used data from three European populations to decipher the role of overall and abdominal obesity for VTE development. We found that both WC and BMI were positively associated with VTE, but that the magnitude of the association for BMI was largely attenuated after adjusting for WC. Even among individuals with normal BMI, the risk of VTE significantly increased with increasing WC. The estimated population-attributable risk due to elevated BMI and WC were 12.4% and 23.7%, respectively.

A positive relationship between obesity and VTE has been found in previous traditional observational studies^{5–7,20–22} and MR studies.^{8–10} Results of our analyses further strengthened the evidence that obesity is a causal risk factor for VTE.

WC appears to be a better index compared to BMI for discriminating VTE risk across individuals with different obesity status, which has been revealed in a previous study with 222 incident VTE cases and a median of 12.3 years' follow-up time.⁶ In this study, WC had the highest area under the curve in receiver operating characteristic analysis compared to other obesity-related indices.⁶ In our study, we confirmed this hypothesis in a larger and longer cohort study by observing a clearer pattern for the associations between WC and VTE after the mutual adjustment for WC and BMI. In addition, our MR analysis further showed that WC adjusted for BMI was causally associated with VTE. These findings shed a light on a greater impact of the distribution of adipose tissue, especially the centralized obesity, on VTE risk compared with overall fat mass. Thus, our findings support the need for accurate identification of obesity not relying on BMI solely to understand the etiology of VTE.²³

The stronger influence of abdominal obesity may give a hint on potential mechanisms underlying the link between obesity and VTE. A population-based cohort study found that the abdominal obesity-derived risk of myocardial infarction attenuated largely, whereas the estimates for VTE remained unchanged after adjusting for atherosclerotic risk factors, such as blood pressure, serum lipids, and diabetes-related traits among 3336 women and 3043 men.²⁴ Along with the differences we observed between the effects of BMI and WC, it is assumed that the causal pathway from adiposity to VTE is more likely mediated by systemic inflammation, rather than by other obesity-related traditional risk factors for cardiovascular disease, including hypertension, blood lipids, and diabetes,²⁵ which are not clearly related to VTE. Abdominal obesity has been shown to exhibit a distinct effect on inflammation.²⁶ Results of our previous MR studies showed causal effects of inflammation-related fatty acids, especially arachidonic acid,²⁷ and tumor necrosis factor²⁸ on VTE. In addition, obesity-driven chronic inflammation and impaired fibrinolysis have been postulated to be major effector mechanisms of thrombosis.²⁹ All these facts further solidified the assumption and implied that anti-inflammation therapy might be an effective preventive strategy for VTE among obese individuals, particularly

FIGURE 2 Multivariable-adjusted hazard ratio^a of venous thromboembolism by joint categorization for body mass index and waist circumference. CI, confidence interval; HR, hazard ratio. The total population included in this analysis is 61 788 owing to missing information on WC for 12 529 participants. ^aAdjusted for age; sex; history of hypertension, hypercholesterolemia, diabetes, and fracture; incident cancer; alcohol drinking (non-drinker, former drinker, and current drinker); cigarette smoking (non-smoker, former smoker, and current smoker); total energy intake; modified Dietary Approaches to Stop Hypertension Diet score; walking/bicycling time (< 20, 20--40, 40--60, and >60 mins/day); education level (representing socioeconomic status; less than high school, high school, and university and higher); and ever aspirin use. The categorization for body mass index (normal, overweight, and obese) was defined based on 18.5--25, 25--30, and >30 kg/m². The categorization for normal, increased, and substantially increased waist circumference in cm were based on <94, 94--101, and ≥102 for men, and <80, 80--87, and ≥88 for women, respectively



Hazard ratio of venous thromboembolism			
Body mass index	Waist circumference		
	Normal	Increased	Substantially increased
Normal	1 (reference)	1.22 (1.10-1.36)	1.53 (1.28-1.81)
Overweight	0.96 (0.82-1.13)	1.31 (1.18-1.45)	1.58 (1.43-1.74)
Obesity	1.46 (0.73-2.94)	1.29 (0.90-1.83)	1.83 (1.63-2.05)

Number of events/individuals			
Body mass index	Waist circumference		
	Normal	Increased	Substantially increased
Normal	797/20 062	466/9042	126/2048
Overweight	151/4117	553/10 351	677/10 103
Obesity	7/116	29/545	390/5404

for those with a large WC. Most but not all studies acknowledged that using aspirin after anticoagulation treatment could reduce the overall risk of recurrence of VTE.³⁰ However, whether aspirin can be used in the primary prevention for VTE remains unknown and needs more investigation. In addition, a review article also indicated that central obesity might increase ectopic fat, thereby facilitating venous thrombosis.³¹

Population-attributable risk for elevated BMI and WC for VTE indicated between approximately 12.4% and 23.7% VTE cases could be prevented if the whole population could maintain a healthy body weight status with a healthy fat mass distribution through primordial prevention. This information informs the importance of reducing the incidence and prevalence of obesity by promoting a healthy lifestyle and diet in the general population and obesity surgery for extremely obese individual for the prevention of VTE. We also noticed that the population-attributable risk of VTE for abnormal-high WC doubled that for abnormal-high BMI. For the angle of this large difference in the estimate of population-attributable risk of VTE caused by elevated BMI and WC, the effectiveness and the input-output ratio of obesity intervention for VTE were assumed to be underestimated in the system using BMI as indicator of obesity. This inaccurate estimation would further tend to bias the policies and resource allocation in public health and clinical settings.

There are several strengths of the present study. Compared to most previous prospective studies, our study was based on a

larger sample size and included more incident VTE cases. In addition, the associations of BMI and WC with VTE risk observed in our cohort study were confirmed in a two-sample MR framework. Furthermore, ascertainment of VTE cases was based on nationwide population-based registers rather than self-reports. This study also has limitations. In the cohort study, body size was self-reported at baseline. This likely introduced measurement error in the exposure assessment as overweight and obese individuals tend to underestimate their BMI and WC to a greater extent than lean individuals, whereas shorter individuals tend to overestimate their height. This reporting bias may have attenuated the risk estimates of the association of BMI and WC with risk of VTE. Thus, the associations might be even stronger in the absence of measurement error. With regard to WC, approximately 17% of individuals with BMI information did not report their WC. We assumed that missing data on WC was randomly distributed in individuals with different WC status given that BMI information was available for these participants. Moreover, mean BMI is similar in those with missing WC and those with WC information (mean BMI 26.0 ± 3.4 and 25.7 ± 3.3 kg/m², respectively, in men and 25.5 ± 4.1 and 25.0 ± 3.8 kg/m², respectively, in women). Thus, this part of missing data would slightly compromise the power of the present analysis but not the accuracy of the estimation. However, the high consistency of estimates across groups did not hinder our observation and misinterpret the findings. With regard to cancer, different types, stages, and grade of the cancer

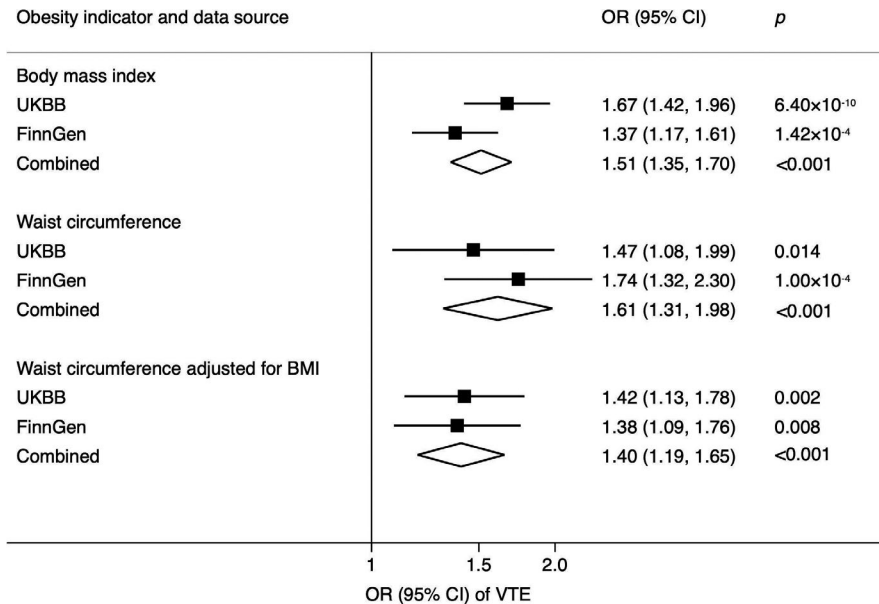


FIGURE 3 Genetic causal associations of body mass index and waist circumference with venous thromboembolism in Mendelian randomization analyses using data from the UK Biobank study and FinnGen consortium. BMI, body mass index; CI, confidence interval; IVW, inverse-variance weighted; OR, odds ratio; VTE, venous thromboembolism; UKBB, UK Biobank. ORs of VTE were scaled to one standard deviation increase in genetically predicted body mass index in kg/m² and waist circumference in cm

likely have different effects on VTE risk.^{32,33} In the present study, all malignant cancers were combined due to insufficient statistical power to take into account specific cancers at different stages. Thus, the possibility that the associations of BMI and WC with VTE risk might be different in cancer patients with certain types of cancers and at a specific stage cannot be ruled out and warrants investigation in future large-scale studies. The diagnostic information of VTE was derived from the National Patient Register, which might cause some misclassification of outcome.³⁴ Nevertheless, previous studies revealed an overall good validity of VTE diagnosis with a positive predictive value of 84% in the UK's primary care data and 99% in the Danish patient register.^{12,34} The specificity of VTE diagnosis in Swedish National Patient Register was approximately 94% and 88% for PE and DVT, respectively, from 1980 onward.³⁴ Therefore, the dilution effect of VTE misclassification is expected to be small.

5 | CONCLUSIONS

The present study confirmed the role of overall and abdominal obesity in VTE and indicated WC might be a preferable anthropometric measure of obesity to discriminate the risk of VTE. Given a high population-attributable risk caused by obesity, we suggest maintaining both healthy BMI and WC to lower the incidence of VTE.

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CONFLICTS OF INTEREST

All authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

SY and SCL conceived and designed the study. SY undertook the statistical analyses. SY wrote the first draft of the manuscript. SY, MB, YX, NH, A.Å., and SCL provided important comments to the manuscript.

DATA AVAILABILITY STATEMENT

De-identified SIMPLER data are available for researchers upon application (www.simpler4health.se). Data used in the Mendelian randomization study were all publicly available.


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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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