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ORIGINAL ARTICLE

Obesity and risk of bleeding: the SMART study.

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Essentials

- Whether obesity protects against clinically relevant bleeding is unclear.
- We investigated the risk of bleeding according to various measures of obesity in a cohort of 9736 patients.
- Obesity was not associated with a lower risk of bleeding.
- The procoagulant profile in obese subjects may not be enough to protect against clinically relevant bleeding.

Summary. *Background:* Obesity is associated with increased levels of procoagulant factors and decreased fibrinolytic activity. Whether this hemostatic profile protects against clinically relevant bleeding has been scarcely investigated. *Objectives:* To assess the impact of measures of obesity on the risk of bleeding in a large cohort of patients at increased atherothrombotic risk. *Methods:* The Second Manifestation of ARTerial disease (SMART) study included 9736 patients aged 18–79 years, followed for a median of 5.9 years. Body mass index (BMI), waist circumference and hip circumference were measured at inclusion. All incident fatal or non-fatal hemorrhagic events were recorded. *Results:* During follow-up, 359 first bleeding events occurred. In quintile-based analyses, the risk of bleeding was highest in the lowest quintile (Q) of BMI (age and sex-adjusted HR Q2 vs. Q1, 0.68; 95% CI, 0.50–0.94), but there was a threshold effect at low BMI levels (men, < 23.84 kg m^{-2}; women, < 22.49 kg m^{-2}), and the risk estimates for bleeding did not further change across the remaining quintiles (HR Q3 0.81 and Q5 0.75). For waist circumference the relationship appeared to be U-shaped, with the lowest risk of bleeding in quintile 3 (HR Q3 vs. Q1, 0.69; 95% CI, 0.46–1.04). Adjustments for hypertension, hemoglobin level, renal failure, diabetes and use of oral anticoagulants or platelet inhibitors did not affect the results. *Conclusion:* Obesity was not associated with lower risk of bleeding. Our findings suggest that presumed protection against bleeding due to an apparently efficient hemostatic system may be counterbalanced by other factors in obese subjects.

Keywords: anthropometry; bleeding; hemorrhage; obesity; risk factors.

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Introduction

Although obesity is a well-established risk factor for thrombosis [1–3], the pathophysiological mechanism behind the association has not been fully explained. Obesity is associated with low-grade inflammation, atherosclerosis, immobility and stasis, which may all potentially lead to thrombosis [4,5]. Additionally, support for a biological link between obesity and coagulation arises from observational studies showing higher levels of procoagulant factors with increasing body weight. Obesity is associated with higher levels of coagulation factors VII, VIII, IX and XII and von Willebrand factor (VWF), higher levels of fibrinogen and plasminogen activator inhibitor-1 (PAI-1) activity, and inversely associated with tissue plasminogen activator (t-PA) activity and the activated protein C (APC) ratio [6–10].

If obesity is causally associated with thrombosis through mechanisms of coagulation or fibrinolysis, it would be assumed that obese patients are less prone to bleeding. Thus far, the impact of obesity on the incidence of bleeding has been scarcely investigated. In a recent observational study of 15 532 patients at risk of atherothrombosis, originally enrolled in a clinical trial of clopidogrel, subjects

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with a low body mass index (BMI) were at higher risk of bleeding complications compared with those with a high and normal BMI [11]. In a study of patients undergoing percutaneous coronary intervention (PCI), obese subjects (BMI 30–34.5 kg m^{-2}) had significantly lower risk of bleeding compared with normal-weight (BMI 18.5–24.9 kg m^{-2}) subjects [12].

To our knowledge, no study has extensively assessed the risk of bleeding using measures of obesity such as waist circumference, hip circumference and waist-to-hip ratio. As the majority of the measures of obesity have been associated with thrombosis, though with varying impact [2,13,14], we hypothesized that they would display an inverse association with the risk of bleeding. Therefore, the aim of the present study was to assess the impact of different measures of obesity on the risk of bleeding in a large cohort study of patients at increased atherothrombotic risk regardless of antiplatelet or anticoagulant therapy use.

Methods

Study population

The Second Manifestation of ARTerial disease (SMART) study, a large single-center prospective cohort study, included 9736 patients aged 18–79 years, newly referred to the University Medical Center Utrecht, the Netherlands, with classical risk factors for arterial disease (hypertension, hyperlipidemia and diabetes mellitus) or with symptomatic arterial disease (coronary artery disease, cerebrovascular disease, peripheral arterial obstructive disease or abdominal aortic aneurysm) [15]. Patients underwent a standardized vascular screening program, including a health questionnaire, laboratory assessment and ultrasonography to investigate the prevalence of additional vascular disease. Measures of obesity, including body mass index (BMI), waist circumference (WC), hip circumference (HC) and waist-to-hip ratio (WHR), were measured at inclusion. Patients were included during the period September 1996 to February 2012, and then followed until 1 March 2012. Measurements of waist circumference and hip circumference were not standardized in subjects included before 1 January 1999 and therefore 8395 subjects had complete data on all measures of obesity.

Outcome

In the current study, the primary outcome was defined as the first occurrence of a fatal or non-fatal hemorrhagic event. This included any intracranial bleeding, fatal bleeding and any bleeding complication requiring hospitalization. In the SMART study, potential outcome events reported by the patient were confirmed by evaluation of hospital discharge records and results of relevant laboratory and radiology examinations. Three members of the SMART committee independently audited all events on the basis of available information, and in the case of disagreement consensus was reached by consulting other members of the outcome committee.

Statistical analysis

Baseline measures of obesity were divided into sex-specific quintiles and into categories based on predefined cut-off levels for men and women recommended by the World Health Organization (WHO) or National Cholesterol Education Program - Adult Treatment Panel III (NCEP-ATPIII) guidelines [16,17]. Person-years of follow-up were counted from the date of inclusion to the date of a first bleeding event, death or the end of the study period (March 2012), whichever came first. Patients with incomplete follow-up were censored from the date of the last observation.

Cox proportional hazards regression models were used to estimate crude and multivariable hazard ratios (HRs) with 95% confidence intervals (CIs) for bleeding events by categories of measures of obesity and by a continuous approach. In quintile-based analyses the lowest quintile was used as a reference, and in analyses of predefined BMI categories the normal-weight category (18.5–24.9 kg m^{-2}) was used as a reference. The multivariable model included age, sex, baseline hemoglobin, hypertension, renal failure, diabetes mellitus and antithrombotic treatment (vitamin K antagonists and platelet inhibitors). The number of subjects included in the adjustment model varied slightly due to missing values on covariates (< 10% missing). Additionally, analyses were conducted for subtypes of bleeding (i.e. cerebral hemorrhages and bleedings at other sites).

Age and sex-adjusted associations between BMI and bleeding were visualized by a generalized additive regression plot using R version 2.15.1. In this plot, BMI was modeled with a smoothing spline fit in a Cox proportional hazards model.

The proportional hazards assumption was evaluated by a log-log plot and formally tested using Schoenfeld residuals. Statistical interactions with age and sex were tested. Moreover, we tested for interaction with antithrombotic (i.e. antiplatelet or anticoagulant) treatment. For sensitivity purposes, we also repeated the analyses after exclusion of subjects with clinically manifest cardio- or cerebrovascular disease at baseline. In order to investigate whether severe underlying illness could explain the increased risk of bleeding in subjects with low BMI, we performed a separate sensitivity analysis where those who died during the first year were excluded. Moreover, since BMI was measured in more subjects than WC and HC, we did complete-case analyses (i.e. included those who had complete measures on all obesity variables) to investigate

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whether discrepancies in risk of bleeding between the different obesity measures could be explained by missing data.

Results

Baseline characteristics across quintiles of BMI are shown in Table 1. The age and sex distribution did not differ notably across quintiles. As expected, the proportion of subjects with hypertension, prior myocardial infarction and diabetes increased across quintiles, and the highest quintile contained the highest proportion of people treated with statins and vitamin K antagonists. Hemoglobin and hematocrit levels did not differ across quintiles (Table 1). Quintile ranges of BMI, WC, HC and WHR in men and women are provided in Table S1.

In total, there were 359 bleeding events during a median of 5.9 years of follow-up (25–75th percentile range, 3.0–9.2 years). In quintile-based analyses, the risk of bleeding was highest in the lowest quintile of BMI (HR second vs. first quintile, 0.68; 95% CI, 0.50–0.94) (Table 2). Apparently, there was a threshold effect at low BMI levels (<23.84 kg m^{-2} in men and < 22.49 kg m^{-2} in women), as the risk estimates for bleeding did not further change across the remaining quintiles (HR Q3, 0.81; Q4, 0.70; Q5, 0.75). For waist circumference the relationship appeared to be U-shaped, with the lowest risk of bleeding in quintile 3 (HR, 0.69; 95% CI, 0.46–1.04); however, all the CIs were overlapping. Measures of hip circumference showed essentially the same pattern as BMI, whereas for the waist-to-hip ratio the risks of bleeding were apparently 30% higher in the two upper quintiles compared with the lowest quintile (Table 2). Further adjustments for hypertension, hemoglobin level, renal failure, diabetes and use of oral anticoagulants or platelet inhibitors did not affect the risk estimates.

Analyses of BMI as a continuous variable confirmed that the risk of bleeding was high in subjects with low BMI, and that there was no further decline in risk of bleeding for subjects with BMI levels above 26.3 (50th percentile) (Fig. 1). When measures of obesity were analyzed according to predefined cut-off levels based on WHO/NCEP-ATPIII guidelines, no significant differences in risk of bleeding were observed across categories (Table 3).

Risk estimates of cerebral hemorrhages and bleedings at other sites showed the same pattern as the risk estimates of overall bleeding across quintiles of BMI and waist circumference (Table 4). In analyses of intervention-related bleedings at other sites (i.e. non cerebral hemorrhages), the high risk of bleeding in the lowest quintile of BMI was even more pronounced than in analyses of overall bleeding, but still there was no further decrease in bleeding risk across the remaining quintiles (Table 4).

The results were essentially similar when analyses were restricted to those without clinically manifest cardio- or cerebrovascular disease at baseline and those who survived the first year, and in analyses of subjects with complete data on BMI, WC and HC (data not shown).

Table 1 Baseline characteristics across sex-specific quintiles of body mass index presented as means with standard deviations, or as numbers with percentages in brackets. The SMART study.

	BMI quintiles				
	Q1	Q2	Q3	Q4	Q5
*n**	1946	1936	1948	1943	1948
BMI range men	15.90–23.84	23.85–25.60	25.61–27.25	27.26–29.63	29.64–50.10
BMI range women	14.27–22.48	22.49–24.74	24.77–27.10	27.11–30.47	30.48–58.82
Age, years	54.7 (14.3)	57.4 (12.5)	57.6 (11.9)	57.8 (11.4)	55.5 (11.5)
Sex (women)	633 (32.5)	632 (32.6)	637 (32.7)	629 (32.4)	639 (32.8)
Hypertension	836 (43.4)	1007 (52.0)	1063 (54.6)	1186 (61.0)	1303 (66.9)
History of stroke	242 (12.4)	222 (11.5)	222 (11.4)	236 (12.1)	192 (9.9)
History of MI	285 (14.6)	395 (20.4)	449 (23.1)	428 (22.0)	484 (24.8)
Diabetes	235 (12.1)	302 (15.6)	318 (16.3)	387 (19.9)	641 (32.9)
Renal failure	162 (8.3)	163 (8.4)	164 (8.4)	171 (8.8)	185 (9.5)
VKA treatment	153 (7.9)	148 (7.6)	158 (8.9)	171 (8.8)	178 (9.1)
Platelet inhibitors	922 (47.4)	1080 (55.8)	1156 (59.3)	1132 (58.3)	1085 (55.7)
Statins†	689 (35.4)	807 (41.7)	930 (47.7)	919 (47.3)	1004 (51.5)
Creatinine clearance mL min^{-1} 1.73 m^{-2}	80 (20)	77 (18)	77 (18)	76 (18)	79 (20)
Hemoglobin (mmol L^{-1})	8.78 (0.8)	8.83 (0.8)	8.90 (0.8)	8.89 (0.8)	8.94 (0.8)
Hematocrit (%)	41.6 (3.8)	41.7 (3.8)	42.0 (3.7)	41.8 (3.7)	42.1 (3.6)
Cholesterol (mmol L^{-})	5.2 (1.4)	5.2 (1.4)	5.2 (1.4)	5.2 (1.4)	5.1 (1.4)
HDL cholesterol (mmol L^{-})	1.40 (0.46)	1.31 (0.40)	1.24 (0.37)	1.20 (0.35)	1.12 (0.31)
CRP (mg L^{-})	4.2 (10.8)	3.6 (6.7)	4.0 (9.0)	4.3 (7.9)	5.4 (9.9)

BMI, body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein; MI, myocardial infarction; VKA, vitamin K antagonist. Renal failure was defined as a creatinine level > 120 μmol L− or a urine albumin /creatinine ratio >20 mg mmol−1. *BMI data were missing in 15 subjects. †Not registered in subjects included before 1 July 2001.

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Table 2 Incidence rates (IRs) per 1000 person-years and hazard ratios (HRs) with 95% confidence intervals (CI) of bleeding events across quintiles (Q) of obesity measures

	Person-years	Events	IR (95% CI)	HR (95% CI)*	HR (95% CI)†
Body mass index					
Q1	12072	86	7.1 (5.8–8.8)	1 (reference)	1 (reference)
Q2	12308	66	5.4 (4.2–6.8)	0.68 (0.50–0.94)	0.72 (0.51–1.00)
Q3	12453	79	6.3 (5.1–7.9)	0.81 (0.60–1.10)	0.80 (0.58–1.11)
Q4	12543	67	5.3 (4.2–6.8)	0.70 (0.51–0.96)	0.72 (0.52–1.01)
Q5	11987	61	5.1 (4.0–6.5)	0.75 (0.54–1.04)	0.83 (0.58–1.17)
Waist circumference					
Q1	9636	48	5.0 (3.8–6.6)	1 (reference)	1 (reference)
Q2	9822	50	5.1 (3.9–6.7)	0.85 (0.57–1.26)	0.92 (0.60–1.39)
Q3	10003	45	4.5 (3.4–6.0)	0.69 (0.46–1.04)	0.77 (0.50–1.18)
Q4	10163	69	6.8 (5.4–8.6)	1.01 (0.69–1.46)	1.06 (0.71–1.57)
Q5	8859	50	5.6 (4.3–7.4)	0.90 (0.61–1.34)	1.04 (0.68–1.58)
Hip circumference					
Q1	9868	62	6.3 (4.9–8.1)	1 (reference)	1 (reference)
Q2	10067	59	5.9 (4.5–7.6)	0.85 (0.60–1.22)	0.85 (0.58–1.23)
Q3	9513	50	5.3 (4.0–6.9)	0.82 (0.56–1.19)	0.87 (0.59–1.28)
Q4	9518	48	5.0 (3.8–6.7)	0.74 (0.51–1.09)	0.76 (0.51–1.13)
Q5	9503	43	4.5 (3.4–6.1)	0.74 (0.50–1.09)	0.77 (0.51–1.17)
Waist-to-hip ratio					
Q1	10473	40	3.8 (2.8–5.2)	1 (reference)	1 (reference)
Q2	8465	44	5.2 (3.9–7.0)	1.10 (0.72–1.70)	1.16 (0.74–1.82)
Q3	12498	59	4.7 (3.7–6.1)	0.92 (0.61–1.37)	0.99 (0.65–1.51)
Q4	8765	62	7.1 (5.5–9.1)	1.30 (0.87–1.94)	1.30 (0.85–1.99)
Q5	8300	59	7.1 (5.5–9.2)	1.27 (0.85–1.91)	1.39 (0.91–2.14)

Waist circumference and hip circumference were not measured in subjects included before 1 January 1999. *Adjusted for age and sex. †Adjusted for age, sex, hypertension, hemoglobin level, renal failure, diabetes, use of oral anticoagulants and use of platelet inhibitors.

Overall, 61% of the study subjects used antithrombotic therapy at baseline (52.5% used platelet inhibitors, 5.5% used oral anticoagulant therapy and 3.0% used both in combination). There was no statistical interaction between the various measures of obesity and antithrombotic therapy with regard to risk of bleeding (*P*-values for test of interaction, BMI, $P = 0.2$; WC, $P = 0.7$; HC, $P = 0.4$; WHR, $P = 0.2$), and analyses stratified on use of antithrombotic therapy (yes/no) showed basically similar results (data not shown).

Discussion

In the present study, we found no consistent evidence for an association between obesity and lower risk of bleeding. When BMI was used as a measure of obesity, subjects in the lowest quintile had the highest risk of bleeding. The relationship exhibited a threshold pattern, and no further changes in bleeding risk were observed across quintiles two to five of BMI. There was no association between the other measures of obesity and risk of bleeding. All estimates remained essentially similar in analyses restricted to those without clinically manifest cardio- or cerebrovascular disease at baseline.

Our results concur with those of Mak and co-workers [11]. In a cohort of 15 532 patients originally assigned to clopidogrel or placebo and followed for a median of 28 months, they showed that subjects in the lower quartile of BMI (< 25.08 kg m^{-2}) had the highest risk of severe bleeding (HR 0.66 for second vs. first quartile), whereas no further change in risk of bleeding was observed across the remaining quartiles [11]. In a study of 16 783 patients who underwent PCI, underweight patients (BMI < 18.5 kg m^{-2}) had increased risk of bleeding, but this association disappeared after adjustment for potential confounders related to co-morbidities and clinical presentation [12]. Moreover, obese patients (BMI 30–34.9 kg m^{-2}) had a 32% lower risk of bleeding than normal-weight patients, and the risk estimate remained unchanged upon adjustment [12]. Partly in contrast, we found an increased risk of intervention-related bleedings in the lowest BMI category, which persisted after adjustments without further decline in risk across the remaining quintiles of BMI.

Based on the current knowledge that obesity enhances the risk of both arterial and venous thrombosis, and the procoagulant profile observed in obese individuals, we hypothesized that there was an inverse relationship between measures of obesity and risk of bleeding. Contrary to our hypothesis, there was no decrease in risk of clinically relevant bleeding in either overweight or obese subjects compared with normal-weight subjects according to any of the anthropometric measures of obesity. The risk of venous thrombosis has been shown to increase in a dose-dependent manner within population ranges of all common anthropometric measures of obesity [13,14], and

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obesity is associated with higher coagulation activity and decreased fibrinolytic activity [6–10]. If an imbalance in the procoagulant/fibrinolytic activity due to obesity in itself is sufficient to cause thrombosis, then one would also expect a reduced risk of bleeding in obese subjects. Thus, our findings suggest that presumed protection against bleeding due to an apparently efficient hemostatic system may be counterbalanced by other factors in obese subjects.

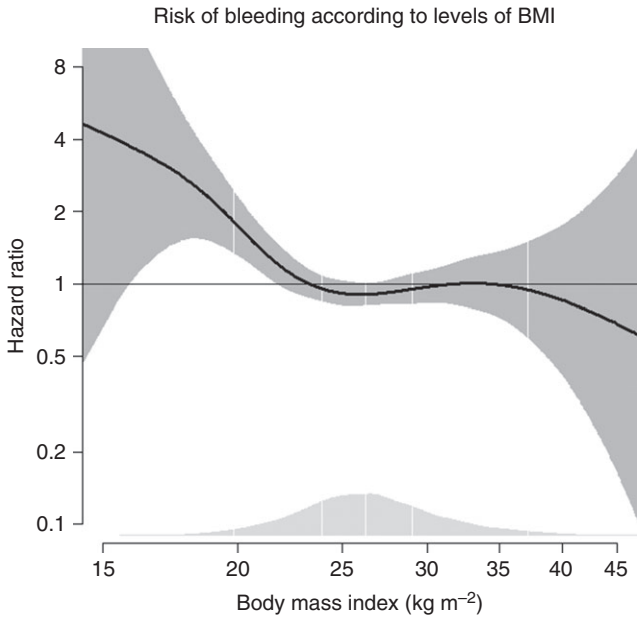

Fig. 1. Association between body mass index (BMI) and risk of bleeding obtained by generalized additive regression. BMI was modeled with a smoothing spline fit in a Cox proportional hazards model adjusted for age and sex. The solid line shows the hazard ratio and the shaded areas show 95% confidence interval. The density plot shows the distribution of BMI and white vertical lines indicate 2.5th, 25th, 50th, 75th and 97.5th percentiles.

Several factors may facilitate thrombus formation and a procoagulant profile alone may not be sufficient to cause thrombosis in obese individuals. While obesity-related vessel wall changes or stasis may act as component causes of thrombosis, the reverse effect of these factors would not necessarily be related to bleeding. Moreover, several obesity-related factors may increase the risk of bleeding and thereby counteract the effect of the procoagulant hemostatic profile in obese subjects. High age, hypertension, diabetes, renal and liver abnormalities, low hemoglobin levels, high alcohol intake and use of antithrombotic drugs are all associated with increased risk of bleeding [18,19]. Hypertension and type 2 diabetes are frequent complications of obesity [20] and obesity is associated with renal abnormalities [21]. Although adjustments for potential confounders including age, sex, hypertension, hemoglobin level, renal failure and use of antithrombotic drugs did not affect our results, residual confounding could still be present.

When we analyzed the risk of bleeding according to BMI quintiles, the highest risk was found in those with the lowest BMI. This relationship could potentially be attributed to the presence of other severe co-morbid conditions (e.g. cancer) that we were unable to adjust for, an assumption supported by the higher all-cause and cancer-related mortality rate in the lowest BMI group (Table S2). However, this finding was not consistent across the various obesity measures, and a low BMI may reflect low muscle mass in these individuals rather than a low proportion of body fat. Moreover, in sensitivity analyses excluding those who died

Table 3 Incidence rates (IRs) per 1000 person-years and hazard ratios (HRs) with 95% confidence intervals (CIs) of bleeding events across predefined WHO/NCEP-ATPIII criteria of obesity.

	Person-years	Events	IR (95% CI)	HR (95% CI)*	HR (95% CI) †
Body mass index (kg m^{-2})					
Underweight (<18.5)	360	3	8.3 (2.7–25.8)	1.94 (0.61–6.14)	1.79 (0.56–5.68)
Normal weight (18.5–24.9)	21483	134	6.2 (5.3–7.4)	1 (reference)	1 (reference)
Overweight (25–29.9)	27973	162	5.8 (5.0–6.8)	0.86 (0.68–1.08)	0.85 (0.67–1.09)
Obese (> 30)	11547	60	5.2 (4.0–6.7)	0.92 (0.68–1.25)	1.00 (0.73–1.38)
Waist circumference (cm)					
Low Women, < 80; men, < 94	16928	82	4.8 (3.9–6.0)	1 (reference)	1 (reference)
Intermediate Women, 80–87.9; men, 94–101.9	15122	78	5.2 (4.1–6.4)	1.12 (0.82–1.53)	1.07 (0.77–1.48)
High Women, ≥ 88; men, ≥ 102	16433	102	6.2 (5.1–7.5)	1.22 (0.91–1.65)	1.24 (0.91–1.69)
Waist-to-hip ratio					
Low Women, < 0.85; men, < 0.95	28561	134	4.7 (4.0–5.6)	1 (reference)	1 (reference)
High Women, ≥ 0.85; men, ≥ 0.95	19940	130	6.5 (5.5–7.7)	0.89 (0.70–1.13)	0.90 (0.70–1.16)

*Adjusted for age and sex. †Adjusted for age, sex, hypertension, hemoglobin level, renal failure, diabetes, use of oral anticoagulants and use of platelet inhibitors.

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Table 4 Incidence rates (IRs) per 1000 person-years and hazard ratios (HRs) with 95% confidence intervals (CIs) for intracranial and extracranial bleedings across quintiles (Q) of body mass index and waist circumference

	Person-years	Events	IR (95% CI)	HR (95% CI)*	HR (95% CI)†
Cerebral hemorrhages					
Body mass index					
Q1	12072	14	1.2 (0.7–2.0)	1 (reference)	1 (reference)
Q2	12308	12	1.0 (0.6–1.7)	0.75 (0.35–1.63)	0.82 (0.37–1.79)
Q3	12453	17	1.4 (0.8–2.2)	1.06 (0.52–2.15)	0.92 (0.42–2.00)
Q4	12543	12	1.0 (0.5–1.7)	0.76 (0.35–1.64)	0.77 (0.34–1.74)
Q5	11987	9	0.8 (0.4–1.4)	0.68 (0.29–1.57)	0.84 (0.35–1.99)
Waist circumference					
Q1	9636	7	0.7 (0.3–1.5)	1 (reference)	1 (reference)
Q2	9822	9	0.9 (0.5–1.8)	1.03 (0.38–2.76)	0.78 (0.27–2.25)
Q3	10003	6	0.6 (0.3–1.3)	0.63 (0.21–1.88)	0.66 (0.22–1.98)
Q4	10163	16	1.6 (1.0–2.6)	1.58 (0.65–3.87)	1.34 (0.53–3.40)
Q5	8859	7	0.8 (0.4–1.7)	0.88 (0.31–2.51)	1.01 (0.35–2.92)
Bleedings at other sites‡ (Admission)					
Body mass index					
Q1	12072	38	3.1 (2.3–4.3)	1 (reference)	1 (reference)
Q2	12308	35	2.8 (2.0–4.0)	0.82 (0.52–1.31)	0.84 (0.53–1.35)
Q3	12453	42	3.4 (2.5–4.6)	0.98 (0.63–1.53)	0.91 (0.57–1.46)
Q4	12543	37	2.9 (2.1–4.1)	0.88 (0.56–1.38)	0.93 (0.58–1.48)
Q5	11987	34	2.8 (2.0–4.0)	0.94 (0.59–1.50)	1.01 (0.62–1.64)
Waist circumference					
Q1	9636	22	2.3 (1.5–3.5)	1 (reference)	1 (reference)
Q2	9822	26	2.6 (1.8–3.9)	0.97 (0.55–1.71)	1.03 (0.57–1.86)
Q3	10003	27	2.7 (1.9–3.9)	0.92 (0.52–1.61)	0.94 (0.53–1.71)
Q4	10163	31	3.1 (2.1–4.3)	1.00 (0.58–1.73)	1.11 (0.63–1.97)
Q5	8859	30	3.4 (2.4–4.8)	1.20 (0.69–2.08)	1.38 (0.78–2.47)
Bleedings at other sites (intervention related)					
Body mass index					
Q1	12072	29	2.4 (1.7–2.5)	1 (reference)	1 (reference)
Q2	12308	14	1.1 (0.7–1.9)	0.43 (0.23–0.82)	0.50 (0.26–0.96)
Q3	12453	20	1.6 (1.0–2.5)	0.61 (0.34–1.07)	0.73 (0.40–1.31)
Q4	12543	15	1.2 (0.7–2.0)	0.46 (0.24–0.85)	0.46 (0.23–0.91)
Q5	11987	14	1.2 (0.7–2.0)	0.49 (0.26–0.93)	0.52 (0.26–1.05)
Waist circumference					
Q1	9636	16	1.7 (1.0–2.7)	1 (reference)	1 (reference)
Q2	9822	12	1.2 (0.7–2.2)	0.62 (0.29–1.31)	0.78 (0.36–1.72)
Q3	10003	12	1.2 (0.7–2.1)	0.55 (0.26–1.17)	0.69 (0.31–1.53)
Q4	10163	19	1.9 (1.2–2.9)	0.84 (0.43–1.65)	0.99 (0.48–2.05)
Q5	8859	12	1.4 (0.8–2.4)	0.64 (0.30–1.36)	0.69 (0.30–1.58)

Intervention-related bleedings were bleedings that occurred in relation to percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG) surgery, valve replacement, other endovascular procedures or vascular operations. *Adjusted for age and sex. †Adjusted for age, sex, hypertension, hemoglobin level, renal failure, diabetes, use of oral anticoagulants and use of platelet inhibitors. ‡Mostly bleedings in the gastrointestinal tract.

during the first year of follow-up ($n = 156$), the results remained unchanged. Previous studies reporting an association between low body weight and risk of bleeding were mainly conducted in patients who received potent antiplatelet agents [11]. As these drugs are normally given in a fixed-dose regimen, it is plausible that a higher plasma concentration in lean subjects could contribute to the increased risk of bleeding. In our study, a large proportion (61%) of subjects used conventional antithrombotic therapy at baseline. However, because the results were essentially similar in those who did not use antithrombotic therapy in our cohort, the observed increased bleeding risk among the leanest subjects was not likely to be explained by the use of fixed-dose antiplatelet drugs.

The major strengths of the present study are the large number of participants closely followed for a median of 5.9 years with well-validated outcome assessment. Some limitations merit consideration. The study population comprised patients with or at high risk of cardio- and cerebrovascular diseases and is therefore not representative of the general population. Although these patients are likely to have a more prothrombotic profile than subjects without cardiovascular disease, we believe that the comparison between BMI categories with respect to bleeding events has not been distorted by this selection. The latter assumption is supported by the results of analyses restricted to subjects without clinically manifest cardio- or cerebrovascular disease at baseline, which

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remained essentially the same. Information on use of anticoagulant and antiplatelet drugs was assessed at baseline only, and changes in the drug regime during follow-up could potentially have influenced the results of our adjusted model. Due to the single-center design of our study, we assumed that all patients received treatment according to local protocol, and that changes in treatment regimens during follow-up would not differ between groups. In our study, we only recorded major bleedings and their corresponding sites. Potentially, if obese subjects are procoagulant they could have a smaller total blood loss during a major bleed than lean subjects. Moreover, the frequency of minor bleeding could be lower among the obese. Unfortunately, we did not have any information on minor bleeds or the quantity of bleeding among those with major bleeds. Bleeding events were identified by patient reports, and we did not systematically review medical charts to detect bleeding complications that fulfilled our definitions. It is therefore possible that we have underestimated the overall incidence of major bleeds. We do not consider this a large problem because the patients participating in SMART generally were very compliant in responding to the 6-month questionnaire on hospital admissions. Moreover, missed bleeding events would presumably not be BMI dependent and therefore not influence our comparisons between the BMI groups.

In conclusion, obesity was not associated with lower risk of bleeding in our study. Our findings suggest that the procoagulant hemostatic profile in obese individuals may not be sufficient to protect against clinically relevant bleeding.

Addendum

S. K. Braekkan and A. Algra designed the research, analyzed the data and drafted the manuscript. Y. van der Graaf and F. L. J. Visseren contributed to the collection and interpretation of the data and critical revision of the manuscript.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Quintile ranges of body mass index (BMI), waist circumference (WC), hip circumference (HC) and waist-to-hip ratio (WHR) in men and women.
Table S2. Mortality rate (MR) per 1000 person-years with 95% confidence interval (CI) according to death from all causes and cancer-related death.

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