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ORIGINAL ARTICLE

Joint effect of myocardial infarction and obesity on the risk of venous thromboembolism: The Tromsø Study

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Abstract

Background: Myocardial infarction (MI) is associated with an increased risk of venous thromboembolism (VTE). Obesity is a recognized risk factor for both MI and VTE. Whether obesity further increases the risk of VTE in MI patients is scarcely investigated.

Aim: To study the joint effect of MI and obesity on the risk of VTE.

Methods: Study participants (n = 29 410) were recruited from three surveys of the Tromsø Study (conducted in 1994–1995, 2001, and 2007–2008) and followed up through 2014. All incident MI and VTE cases during follow-up were recorded. Cox regression models with MI as a time-dependent variable were used to estimate hazard ratios (HRs) of VTE (adjusted for age and sex) by combinations of MI exposure and obesity status. Joint effects were assessed by calculating relative excess risk and attributable proportion (AP) due to interaction.

Results: During a median of 19.6 years of follow-up, 2090 study participants experienced an MI and 784 experienced a VTE. Among those with MI, 55 developed a subsequent VTE, yielding an overall incidence rate (IR) of VTE of 5.3 per 1000 person-years (95% confidence interval [CI]: 4.1–6.9). In the combined exposure group (MI+/Obesity+), the IR was 11.3 per 1000 person-years, and the adjusted HR indicated a 3-fold increased risk of VTE (HR 3.16, 95% CI: 1.99–4.99) compared to the reference group (MI−/Obesity−). The corresponding AP was 0.46 (95% CI: 0.17–0.74).

Conclusions: The combination of MI and obesity yielded a supra-additive effect on VTE risk of which 46% of the VTE events were attributed to the interaction.

KEYWORDS
epidemiology, myocardial infarction, obesity, risk factor, venous thromboembolism

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1 | INTRODUCTION

Several large cohort studies have reported a link between myocardial infarction (MI) and venous thromboembolism (VTE; i.e., deep vein thrombosis [DVT] and pulmonary embolism [PE]).[1–4] MI is associated with a short-term increased risk of VTE that appears to be particularly pronounced for PE, with an approximately 8-fold increased risk of PE during the first 6 months after the acute MI event.[1,5] The mechanism for this relationship is not well established. However, neither atherosclerosis nor traditional cardiometabolic risk factors such as hypertension, dyslipidemia, or diabetes mellitus are associated with risk of VTE,[6,7] and are therefore not likely shared risk factors for the two conditions.[8,9] The American College of Chest Physicians guidelines recommend thromboprophylaxis with anticoagulants for high-risk hospitalized medical patients,[10] but currently, no risk assessment model exists for identifying MI patients at particularly high risk of VTE. Therefore, there is a need to identify risk factors that are associated with VTE in MI patients.

Obesity is recognized as a risk factor for both MI and VTE[11] and a large proportion (13%) of the world's adult population is obese according to the World Health Organization (WHO) definition.[12] The risk of VTE increases with increasing body mass index (BMI), and obesity (BMI ≥ 30 kg/m^2) is associated with a 2-fold increased risk of VTE in the general population.[13,14] In addition, obesity is shown to interact with other risk factors, such as oral contraceptives,[15] body height,[16] and some prothrombotic genotypes,[15,17] yielding a more than additive effect on VTE risk. Even though obesity is a common feature in patients with MI, the role of obesity on VTE risk in MI patients has not been specifically explored, and it has not been investigated whether obesity yields a more than additive effect on risk of VTE in combination with MI. The aim of the present study was therefore to explore the joint effects of MI and obesity on VTE risk in a large population-based cohort.

Essentials

- Myocardial infarction (MI) is associated with an increased risk of venous thromboembolism (VTE).
- Obesity is a shared risk factor for MI and VTE.
- We investigated the joint effect of MI and obesity on VTE risk.
- Obesity resulted in an excess risk of VTE in subjects with MI.

2 | MATERIALS AND METHODS

2.1 | Study population

The Tromsø Study is a Norwegian single-center prospective follow-up study with consecutive health surveys of the inhabitants of the Tromsø municipality, and has been described thoroughly elsewhere.[18] The fourth survey (T4) was initiated in 1994–1995, during which all inhabitants ≥25 years were invited to the study. The participation was high (77%), and 27 158 individuals participated. Further surveys were conducted in 2001 (T5) and 2007–2008 (T6) with participation of 78% and 66%, respectively. In sum, 30 288 participants aged 25 to 97 years took part in ≥1 of the surveys. Participants not officially registered as inhabitants of the municipality of Tromsø at the date of study enrollment (n = 21) and participants with a VTE or an MI before the enrollment date (n = 82 and n = 732, respectively) and missing data on BMI (n = 43) were excluded. Hence, 29 410 study subjects were enrolled and followed from study inclusion to end of follow-up (December 31, 2014) or to the date of VTE, migration, or death, whichever came first (Figure 1). The regional committee for medical and health research ethics in Northern Norway approved the study, and all participants provided informed written consent to participation.

2.2 | Baseline measurements

At baseline inclusion in each survey, information was obtained by questionnaires, physical examination, and blood samples. Blood samples were collected from an antecubital vein in a non-fasting state. From the self-administered questionnaires, data on diabetes mellitus and smoking status (never/former/current) was collected. Blood pressure was measured as previously described,[1] and hypertension was defined as mean systolic blood pressure ≥140 mm Hg or mean diastolic blood pressure ≥90 mm Hg or current use of antihypertensive medication. Hypercholesterolemia was defined as serum total cholesterol ≥6.5 mmol/L or current use of anticholesteremic medication. Further information regarding baseline variables in the Tromsø Study can be found elsewhere.[18]

2.3 | Assessment of obesity

Body height and weight were measured with subjects wearing light clothing and no shoes. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). The WHO defines a BMI ≥ 30 kg/m^2 as obesity, and this definition was applied in the present study. No obesity was defined as a BMI of <30 kg/m^2.

2.4 | Assessment of MI

The national Norwegian identification number consisting of 11 digits allowed linkage to national and local diagnosis registries. All incident MI events were identified by linkage to the hospital discharge diagnosis registry at the University Hospital of Northern Norway (UNN) and the Norwegian Cause of Death registry at Norwegian Institute of Public Health. The UNN is the only hospital in the region, and all in-hospital and outpatient care of MI and VTE is provided solely

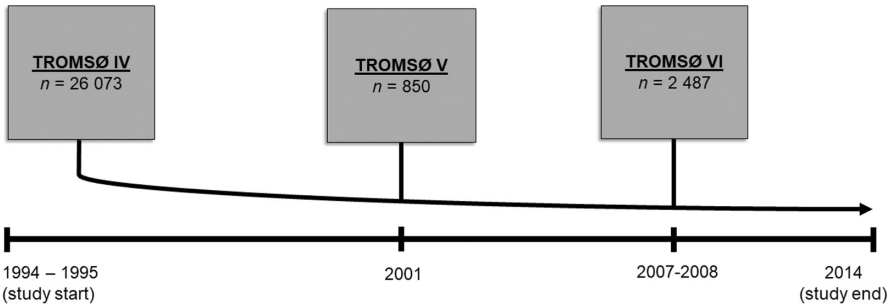

FIGURE 1 Inclusion of study participants from the fourth (1994–1995), fifth (2001), and sixth (2007–2008) surveys of the Tromsø Study.

by this hospital. Events of possible incident MI were identified by a broad search for the International Classification of Diseases (ICD) 9th revision codes 410–414, 427, 428, 430–438, and 798–799 in the period 1994–1998, and for the ICD 10th edition codes I20-I25, I46–I48, I50, I60–I69, and R96, R98, R99 thereafter.

The hospital medical records were thoroughly reviewed for case validation according to the WHO MONICA/MORGAM criteria, which include clinical symptoms and findings of MI, ischemic changes in electrocardiograms (ECG), values of cardiac enzymes, and findings from autopsy records, when applicable.[19]

2.5 | Outcome ascertainment: venous thromboembolism

All incident VTE cases were identified from the date of inclusion in one of the three surveys (T4–6) until end of follow-up (December 31, 2014) by an extensive search in registries (radiology registry, discharge diagnosis registry, and autopsy registry) at the UNN. Each VTE event was adjudicated after review of medical records, as described previously.[20] The criteria for adjudication were presence of symptoms and findings of DVT or PE combined with objective confirmation by a radiological procedure, which resulted in treatment initiation unless contraindications were specified. The VTE events from the autopsy registry were included when the death certificate indicated VTE as the cause of death or a significant condition associated with death. Further, a VTE was classified as either a DVT or PE, and if DVT and PE occurred at the same time, the VTE was classified as a PE. The VTE cases were classified as provoked or unprovoked according to the presence of provoking factors at the time of diagnosis. Provoking risk factors were immobilization (i.e., bed rest for >3 days, wheelchair use, or long-distance travel exceeding 4 h within the 14 days prior to the event), recent surgery or trauma within the previous 8 weeks, active cancer, or any other potentially VTE-provoking factor described by a physician in the medical record (e.g., central venous catheterization).

2.6 | Statistical analysis

Statistical analysis was performed using the STATA software version 16.0 (StataCorp). Cox proportional hazards regression models were applied to estimate hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) for VTE by combinations of MI exposure and obesity status in a multivariable model. Subjects without MI and with no obesity were implemented as reference group. Further, age was used as time scale in the regression model,[21] and MI was included as a time-dependent covariate. Accordingly, those who developed MI during follow-up contributed with unexposed person-time from baseline to the date of MI, and exposed person-time from MI to the end of follow-up. Subgroup analyses were conducted according to the localization of the thrombotic event (PE or DVT), and the presence of provoking factors at the time of diagnosis. All analyses were adjusted for age (as time scale) and sex, and the proportional hazards assumption was tested using Schoenfeld residuals and found not violated. Cancer is a risk factor for obesity, MI, and VTE, and could serve as a potential confounder. For sensitivity purposes, we therefore additionally performed the analysis after exclusion of those with cancer-related VTE.

To investigate whether the effect of MI and obesity on VTE risk is larger than the sum of the separate risk factors combined, the presence of interaction on an additive scale was evaluated with the relative excess risk due to interaction (RERI) and attributable proportion (AP). These measures of interaction with their corresponding 95% CIs were calculated according to Andersson et al,[22] using an Excel sheet (epinet.se/res/xls/epinetcalculation.xls). In short, RERI is calculated as $HR_{AB}-HR_A-HR_B+1$, where HR_A is the hazard ratio for the first risk factor (i.e., MI) in the absence of the second risk factor (i.e., obesity), HR_B is the hazard ratio for the second risk factor in the absence of the first risk factor, and HR_{AB} is the hazard ratio when both risk factors are present. AP corresponds to $RERI/HR_{AB}$, and should be interpreted as the proportion of cases in the combined exposure group that is due to interaction between the two exposures. RERI and AP > 0 indicates positive interaction, that is, that the effect of the combined exposure is greater than the sum of the individual effects.[22,23]

3 | RESULTS

In total, 26 073 participants were recruited from T4, and 850 and 2487 new participants were recruited from T5 and T6, respectively (Figure 1). During a median of 19.6 years of follow-up, 2090 (7.1%) study participants experienced a first-time MI, and 784 (2.7%) participants had a first-time VTE. Among those with MI, 55 developed a subsequent VTE, yielding an overall incidence

rate (IR) of VTE of 5.3 per 1000 person-years (95% CI: 4.1–6.9) after MI. The baseline characteristics of participants with and without incident MI during follow-up are presented in Table 1. Those who experienced an MI were on average older and had higher BMI, and included a higher proportion of men, subjects with hypertension and hypercholesterolemia, and smokers than those without MI (Table 1).

Clinical characteristics of the 784 VTE events are shown in Table 2. There were 451 DVTs (57.5%) and 333 PEs (42.5%). Additionally, 423 events (54.0%) were classified as provoked VTE, and 361 events (46.0%) were classified as unprovoked VTE. Active cancer, immobilization, and surgery within 8 weeks prior to the VTE event were the most frequent provoking factors (Table 2).

IRs and HRs of VTE and subtypes of VTE according to MI exposure and obesity status are shown in Table 3. Among study subjects without MI and with no obesity the IR of VTE was 1.5 per 1000 person-years. In obese participants with no MI, the IR was 3.1 per 1000 person-years and the corresponding HR indicated a 57% increased risk after adjustment for age and sex (HR 1.57, 95% CI: 1.30–1.89). In subjects with MI and no obesity the IR was 4.1 per 1000 person-years and the adjusted HR was 1.15 (95% CI: 0.81–1.61). In the combined exposure group, the IR was 11.3 per 1000 person-years, and the HR indicated a 3-fold increased risk (HR 3.16, 95% CI: 1.99–4.99) compared with the reference group after adjustment for age and sex. Subgroup analyses indicated that in non-obese subjects, MI was associated with PE (HR 1.54, 95% CI: 0.98–2.43), but not with DVT (HR 0.84, 95% CI: 0.50–1.43). However, in the joint exposure group the HR was 3.49 (95% CI: 1.78–6.81) for PE and 2.91 (95% CI: 1.55–5.49) for DVT, respectively, compared to the reference category. Sensitivity analyses with exclusion of patients with cancer-related VTE showed similar results (Table S1 in supporting information).

In analyses stratified by the presence of provoking factors, MI without obesity was associated with a 1.5-fold increased risk (HR 1.48, 95% CI: 0.98–2.24) while the combination of MI and obesity was associated with a 2.8-fold higher risk (HR 2.78, 95% CI: 1.43–5.41) of provoked VTE compared to the reference category (Table 4). In the absence of obesity, MI was not associated with increased risk of unprovoked VTE (HR 0.76, 95% CI: 0.41–1.39), whereas the combination of MI and obesity was associated with a 3.6-fold increased risk of unprovoked VTE compared to the reference category (HR 3.59, 95% CI: 1.90–6.79).

As shown in Table 5, measures quantifying interaction on an additive scale (i.e., RERI and AP) suggested a supra-additive effect of the combination of MI and obesity on the risk of VTE (Figure 2). The AP measure revealed that 46% of the VTE events in participants with both MI and obesity were attributable to interaction between the two exposures. In subgroup analysis, 34% of PEs and 56% of DVTs in participants with both MI and obesity, respectively, were attributable to interaction between the two exposures. Similar numbers as for PE and DVT were observed for provoked VTE and unprovoked VTE.

TABLE 1 Baseline characteristics of study subjects without and with incident myocardial infarction (MI) during follow-up ($n = 29\,410$): The Tromsø Study

	No MI ($n = 27\,320$)	MI ($n = 2090$)
Age (years), mean ± SD	45 ± 14	61 ± 13
Sex (male), % (*n*)	45.8 (12503)	61.3 (1282)
BMI (kg/m^2), mean ± SD	25.2 ± 3.9	26.5 ± 4.0
Obesity (BMI ≥ 30 kg/m^2), % (*n*)	11.0 (2998)	16.1 (336)
Hypertension,[a] % (*n*)	31.3 (8562)	68.2 (1425)
Hypercholesterolemia,[b] % (*n*)	29.8 (8151)	61.4 (1283)
Smoking,[c] % (*n*)	35.5 (9682)	41.9 (875)
Self-reported diabetes mellitus, % (*n*)	1.4 (393)	6.0 (126)

Abbreviations: BMI, body mass index; SD, standard deviation.

[a]Mean systolic/diastolic blood pressure of ≥140 mm Hg/≥90 mm Hg, use of antihypertensives, or self-reported hypertension.

[b]Total cholesterol level of ≥6.5 mmol/L, use of lipid-lowering drugs, or self-reported hypercholesterolemia.

[c]Self-reported daily smoking; yes/no.

TABLE 2 Characteristics of venous thromboembolism events ($n = 784$): The Tromsø Study

	% (*n*)
Clinical characteristics	
Deep vein thrombosis	57.5 (451)
Pulmonary embolism	42.5 (333)
Provoked	54.0 (423)
Unprovoked	46.0 (361)
Provoking factors	
Surgery	15.9 (124)
Trauma	9.1 (71)
Cancer	24.1 (189)
Immobility[a]	21.1 (165)
Others[b]	4.5 (35)

[a]Bed rest for >3 days, journeys >4 h by car, boat, train, or air within the last 14 days, or other types of immobilization.

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

4 | DISCUSSION

In the present cohort of participants recruited from the general population, we found that the joint exposure of MI and obesity yielded a supra-additive effect on the risk of VTE. Individuals exposed to both MI and obesity had a 3-fold higher risk of VTE compared to individuals exposed to neither risk factor, and the combined effect of the two exposures exceeded the sum of the separate effects. Accordingly, 46% of the VTE events occurring among study participants jointly exposed to MI and obesity were estimated to be

TABLE 3 Incidence rates (IRs) and hazard ratios (HRs) of venous thromboembolism (VTE), deep vein thrombosis (DVT), and pulmonary embolism (PE) according to myocardial infarction (MI) and obesity exposure: The Tromsø Study

		Person-years	VTE	IR (95% CI)[a]	HR (95% CI)[b]
Overall VTE					
MI−	Obesity−	392 287	589	1.5 (1.4–1.6)	Reference
MI−	Obesity+	45 290	140	3.1 (2.6–3.6)	1.57 (1.30–1.89)
MI+	Obesity−	8707	36	4.1 (3.0–5.7)	1.15 (0.81–1.61)
MI+	Obesity+	1688	19	11.3 (7.2–17.7)	3.16 (1.99–4.99)
PE					
MI−	Obesity−	392 287	239	0.6 (0.5–0.7)	Reference
MI−	Obesity+	45 290	64	1.4 (1.1–1.8)	1.75 (1.33–2.32)
MI+	Obesity−	8707	21	2.4 (1.6–3.7)	1.54 (0.98–2.43)
MI+	Obesity+	1688	9	5.3 (2.8–10.2)	3.49 (1.78–6.81)
DVT					
MI−	Obesity−	392 287	350	0.9 (0.8–1.0)	Reference
MI−	Obesity+	45 290	76	1.7 (1.3–2.1)	1.44 (1.12–1.85)
MI+	Obesity−	8707	15	1.7 (1.0–2.9)	0.84 (0.50–1.43)
MI+	Obesity+	1688	10	5.9 (3.2–11.0)	2.91 (1.55–5.49)

Abbreviations: CI, confidence interval; MI+/−, incident MI/no incident MI during follow-up, respectively; Obesity+/−, body mass index ≥/<30 kg/m^2 at baseline.

[a]Per 1000 person-years.

[b]Age as time scale, adjusted for sex.

TABLE 4 Incidence rates (IRs) and hazard ratios (HRs) of provoked and unprovoked venous thromboembolism (VTE) according to myocardial infarction (MI) and obesity exposure: The Tromsø Study

		Person-years	VTE	IR (95% CI)[a]	HR (95% CI)[b]
Provoked VTE					
MI−	Obesity−	392 287	314	0.8 (0.7–0.9)	Reference
MI−	Obesity+	45 290	75	1.7 (1.3–2.1)	1.56 (1.21–2.01)
MI+	Obesity−	8707	25	2.9 (1.9–4.2)	1.48 (0.98–2.24)
MI+	Obesity+	1688	9	5.3 (2.8–10.2)	2.78 (1.43–5.41)
Unprovoked VTE					
MI−	Obesity−	392 287	275	0.7 (0.6–0.8)	Reference
MI−	Obesity+	45 290	65	1.4 (1.1–1.8)	1.57 (1.20–2.06)
MI+	Obesity−	8707	11	1.3 (0.7–2.3)	0.76 (0.41–1.39)
MI+	Obesity+	1688	10	5.9 (3.2–11.0)	3.59 (1.90–6.79)

Abbreviations: CI, confidence interval; MI+/−, incident MI/no incident MI during follow-up, respectively; Obesity+/−, body mass index ≥/< 30 kg/m^2 at baseline.

[a]Per 1000 person-years.

[b]Age as time scale, adjusted for sex.

attributable to interaction between the two risk factors. Subgroup analyses indicated that the effect of the interaction was more pronounced for the risk of DVT and unprovoked VTE, and obesity was apparently a prerequisite for increased risk of these outcomes in MI patients.

Obesity is recognized as a causal risk factor for VTE,[24,25] associated with a 2-fold increased risk (compared to normal weight) in population-based studies. Obesity is associated with both provoked and unprovoked VTE[13,26] and has been shown to interact with environmental (e.g., oral contraceptive use) and genetic factors (e.g., factor V Leiden) to yield synergistic effects on VTE risk.[13,15,16] Obesity is also a risk factor for MI,[27] and as expected,

TABLE 5 Measures of interaction on an additive scale between previous myocardial infarction (MI) and obesity exposure: The Tromsø Study

	RERI (95% CI)	AP (95% CI)
Overall VTE	1.44 (−0.05 to 2.94)	0.46 (0.17 to 0.74)
PE	1.19 (−1.22 to 3.61)	0.34 (−0.15 to 0.83)
DVT	1.63 (−0.26 to 3.52)	0.56 (0.23 to 0.89)
Provoked VTE	0.74 (−1.20 to 2.67)	0.27 (−0.27 to 0.81)
Unprovoked VTE	2.26 (−0.05 to 4.58)	0.63 (0.35 to 0.91)

Abbreviations: AP, proportion attributable to interaction; CI, confidence interval; PE, pulmonary embolism; RERI, relative excess risk attributable to interaction; VTE, venous thromboembolism.

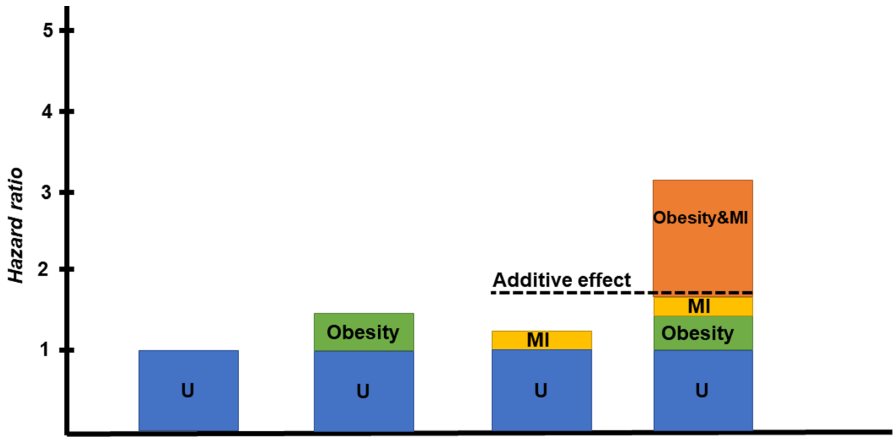

FIGURE 2 Hazard ratio of overall venous thromboembolism with contributions from different exposure categories marked green (obesity), yellow (myocardial infarction [MI]) and orange (obesity & MI). U, common reference category; dotted line, additive effect Obesity & MI.

the prevalence of obesity was higher among those who developed MI than those who did not in our study. In analyses of overall VTE, the effect of MI on VTE risk in the non-obese was small (15% increased), while the combined effect of MI and obesity exceeded the sum of the expected individual effects, yielding a >3-fold increased risk. Subgroup analyses revealed that in non-obese subjects, MI was associated with provoked, but not unprovoked, VTE. Thus, it appears that in the absence of obesity, presence of other provoking factors is required to increase the risk of VTE in MI patients. These findings fit well with those of a previous case-crossover study,[28] in which we showed that infection and immobilization, which are known provoking factors for VTE, mediated the VTE risk within the 3-month period after an MI by approximately 60%.[28]

Our findings further suggest that the increased risk of unprovoked VTE and DVT is dependent on the presence of obesity in MI patients, as the thrombosis risk among non-obese participants with MI was not increased in these subgroups. Our results indicate that 63% and 56% of the events in the joint exposure group could be attributed to an interaction between the two exposures. The potential mechanism behind such interaction is unknown. However, as both obesity and MI are associated with an inflammatory state,[29,30] one might speculate that the observed excess VTE risk could be related to thromboinflammation.[31] Moreover, obesity is associated with both hypercoagulability and hypofibrinolysis,[13] which could add to the hypercoagulable state induced by an MI,[32] and resulting in an excess risk of VTE. MI is associated with subsequent heart failure,[33] which is a risk factor for VTE,[34] and potentially, heart failure induced stasis may be further enhanced in obese patients, leading to increased risk of DVT. We are not aware of studies investigating the combined effect of heart failure and obesity on VTE risk. Unfortunately, we did not have information on heart failure in our study, and thus, we could not assess the potential role of heart failure as a mediator for the observed excess risk.

Development of a risk prediction model to recognize MI patients with a particularly high risk of VTE is pivotal, and future studies should aim at identifying predictors of VTE following MI. The findings from the present study of a supra-additive effect of MI and obesity on VTE risk suggest that obesity could be an important factor for risk assessment of VTE in MI patients. Designated prediction studies in large cohorts of MI patients are warranted to explore the predictive capability of obesity and assess to what extent obesity would facilitate risk stratification of VTE and aid clinical decisions regarding thromboprophylaxis.

Strengths of our study include the prospective design with participants recruited from a general Caucasian population, the well-validated events of both MI and VTE, and the long follow-up period. The high participation rate in the Tromsø Study and the broad age range minimized the risk of self-selection bias. A limitation of our study is that despite the large cohort size, the number of events were small in some subgroups and our findings need to be interpreted with caution. Additionally, because interaction is defined in numerical terms, we cannot draw any conclusions about the underlying mechanisms for the excess combined effect of MI and obesity on risk of venous thrombosis.[35] Unfortunately, we did not have information on use of anticoagulant medications for prevention of VTE during the entire follow-up for all participants, and therefore we did not have the possibility to adjust for it. If MI patients to a larger extent received thromboprophylaxis than patients without MI, our risk estimates could be somewhat underestimated. Finally, we cannot exclude the potential presence of unrecognized residual confounding, which may influence the impact of MI and obesity on VTE risk.

In conclusion, the combination of MI and obesity resulted in an excess risk of VTE, suggesting an interaction between MI and obesity on VTE risk. Future studies are warranted to explore the predictive capability of obesity in MI patients, and to discover to what extent obesity would improve the risk stratification of VTE.

AUTHOR CONTRIBUTIONS

JKS analyzed the data, interpreted results, and drafted the manuscript. BGT and VMM were involved in analyses, interpretation of the results, and critical revision of the manuscript. MLL, IN, TW, and EBM were responsible for data collection, interpretation of results, and revision of the manuscript. SKB and JBH designed the study, and were involved in data collection, interpretation of results, and critical revision of the manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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