The risk of incident venous thromboembolism attributed to overweight and obesity: The Tromsø Study

Short title: venous thromboembolism, overweight and obesity

Tobias Frischmuth,[1,2] Birgitte G. Tøndel,[1] Sigrid K. Brækkan,[1,2] John-Bjarne Hansen,[1,2] and Vânia M. Morelli[1,2]

[1]Thrombosis Research Center, Department of Clinical Medicine, UiT - The Arctic University of Norway, Tromsø, Norway

[2]Division of Internal Medicine, University Hospital of North Norway, Tromsø, Norway

Corresponding author:

Tobias Frischmuth, MD

Thrombosis Research Center, Department of Clinical Medicine, UiT - The Arctic University of Norway, N-9037 Tromsø, Norway

Phone: +47 77625105; Fax: +47 77625105; E-mail: tobias.frischmuth@uit.no

Text word count: 3379

Abstract word count: 250

Figure/table count: 7 (4 tables / 3 figures)

Reference count: 54

Essentials

- The risk of venous thromboembolism (VTE) attributed to overweight and obesity is unclear
- We investigated the population attributable fraction (PAF) of VTE due to an excess of body fat
- In a population-based cohort study, 25% of VTE events were attributed to overweight and obesity
- Fighting the obesity epidemic may substantially lower the VTE incidence in the general population

Abstract

Background: Obesity is a well-established risk factor for venous thromboembolism (VTE). However, data on the proportion of incident VTEs attributed to overweight and obesity in the general population is limited.

Objective: To investigate the population attributable fraction (PAF) of VTE due to overweight and obesity in a population-based cohort with repeated measurements of body mass index (BMI).

Methods: Participants from the 4-7th surveys of the Tromsø Study (enrolment: 1994-2016) were followed throughout 2020, and all incident VTEs were recorded. In total, 36,341 unique participants were included, and BMI measurements were updated for those attending more than one survey. BMI was categorized as <25 kg/m^2, 25-30 kg/m^2 (overweight) and ≥30 kg/m^2 (obesity). Time-varying Cox regression models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). The PAF was estimated based on age- and sex-adjusted HRs and the prevalence of BMI categories in VTE cases.

Results: During a median follow-up of 13.9 years, 1,051 VTEs occurred. The age-and sex-adjusted HRs of VTE were 1.40 (95% CI:1.21-1.61) for overweight and 1.86 (95% CI:1.58-2.20) for obesity compared with subjects with BMI <25 kg/m^2. The PAF of VTE due to overweight and obesity was 24.6% (95% CI:16.6-32.9), with 12.9% (95% CI:6.6-19.0) being attributed to overweight and 11.7% (95% CI:8.5-14.9) to obesity. Similar PAFs were obtained in analyses stratified by sex and VTE subtypes (provoked/unprovoked events, deep vein thrombosis, pulmonary embolism).

Conclusion: Our findings indicate that almost 25% of all VTE events in the general population can be attributed to overweight and obesity.

Keywords: obesity; overweight; population attributable fraction; venous thrombosis; venous thromboembolism.

Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disease (CVD), annually affecting more than 10 million people worldwide.[1-3] VTE is associated with serious short- and long-term complications, including recurrence, post-thrombotic syndrome, post-PE syndrome, and death.[4,5] The socioeconomic burden of VTE is not only related to the management of the thrombotic event, but also to the detrimental impact on quality of life and increased risk of work-related disability.[2,6-8] In contrast to a declining incidence of arterial CVD (i.e., myocardial infarction and stroke) over the last decades,[9,10] the incidence of VTE has slightly increased during the same time period.[11,12] The incidence of VTE will probably continue to increase due to the rising prevalence of major VTE risk factors,[13] among which obesity is one of the most challenging for public health. The worldwide prevalence of obesity, defined as body mass index (BMI) $\geq$30kg/m^2, nearly tripled between 1975 and 2016, with numbers reaching epidemic proportions in high-income countries, and are currently on the rise in low- and middle-income countries, particularly in urban settings.[14]

Obesity is associated with a two- to three-fold increased risk of VTE and the risk increases linearly with increasing BMI.[15,16] Additionally, weight gain over time is associated with increased VTE risk,[17,18] and several Mendelian randomization (MR) studies have shown that genetically elevated BMI is associated with a higher VTE risk.[19-23] These findings imply that obesity is causally related to VTE and that fighting the obesity epidemic will probably contribute to reduce the VTE incidence. However, to what extent obesity contributes to the incidence of VTE at the population level is not well addressed. Estimation of the population attributable fraction (PAF), which reflects the proportion of cases of a particular disease in a population that is attributable to a specific risk factor,[24,25] may address this question. The concept of PAF has a causal interpretation as it indicates the proportion of which the

incidence of a disease would decrease if a specific risk factor could hypothetically be removed.[24,25]

Data on the proportion of incident VTE cases attributed to overweight and obesity in the general population is scarce, with estimates ranging from 12.4% for overall VTE to 33% for unprovoked events.[13,26] There is a need to provide updated PAF estimates that can reflect the marked increase in the prevalence of overweight and obesity in recent years. Furthermore, since intra-individual BMI may fluctuate over time, the impact of overweight and obesity on VTE risk may be underestimated in cohort studies with a single assessment of BMI and long follow-up because of regression dilution.[27] We therefore set out to estimate the PAF of VTE due to overweight and obesity in a population-based cohort study with repeated measurements of BMI.

Methods

Study population

The Tromsø Study is a prospective population-based cohort study with repeated health surveys of the inhabitants of Tromsø, Norway. A total of 36,627 individuals aged ≥ 25 years, who consented to take part in medical research, were recruited from the fourth (1994/95), fifth (2001/02), sixth (2007/08), and seventh (2015/16) surveys of the Tromsø Study (the attendance rates were high, varying from 79% in Tromsø 5 to 65% in Tromsø 7). Detailed methodology and demographics of the Tromsø Study can be found elsewhere.[28-30] We excluded individuals who were not officially registered as inhabitants of the Tromsø municipality at baseline (n = 27), with a history of VTE (n = 88), and with missing BMI (n = 171). Accordingly, 36,341 unique individuals attending one (n = 16,609), two (n = 10,179), three (n = 6,780) or four (n = 2,773) surveys were included in the present study, as described

in Figure 1. The study was approved by the Regional Committee for Medical and Health Research Ethics, and all participants signed an informed consent form prior to inclusion.

Measurements

Baseline information at survey inclusion was obtained from physical examination, blood samples, and self-administered questionnaires. Height and weight were measured with participants wearing light clothes and no shoes, and BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Information on smoking habits, diabetes mellitus, use of oral contraceptives or hormone replacement therapy, and history of cardiovascular disease (CVD) (angina pectoris, myocardial infarction, and stroke) was collected through validated self-administered questionnaires. Blood pressure measurement and blood sampling were previously described for Tromsø 4-6[28,29] and were conducted in the same way for Tromsø 7. In brief, systolic and diastolic blood pressure were measured three times with an automated device and the average of the two last measures was used. Non-fasting blood samples were used for the assessment of total cholesterol by standard methods at the University Hospital of North Norway (UNN).[28,29]

Identification of VTE during follow-up

Incident VTE events among the study participants were recorded from the date of enrollment through the end of follow-up, 31 December 2020. All first life-time VTE events were identified by searching the hospital discharge registry, the autopsy registry, and the radiology procedure registry at the UNN, which is the only hospital providing diagnostic radiology and treatment for VTE in the region. Trained personnel extensively reviewed the medical records to adjudicate each VTE event, as described previously in detail.[31] In brief, a VTE event was

confirmed if signs and symptoms of DVT or PE were combined with objective confirmation by radiological procedures and treatment initiation (unless contraindications were specified).

All VTEs were classified as DVT or PE. Cases in whom both clinical presentations were present were classified as a PE. The events were also classified as either provoked or unprovoked VTEs. An event was considered provoked if it was closely preceded by one or more of the following provoking factors: major surgery, trauma, or an acute medical condition (acute myocardial infarction, acute ischemic stroke, or major infectious disease) within 8 weeks before the event, immobilization (bed rest > 3 days or confinement to wheelchair within the last 8 weeks, or long-distance travel ≥ 4 h within the last 14 days), active cancer at the time of VTE diagnosis, or other factors specifically described as provoking by a physician in the medical record (e.g., intravascular catheter).

Statistical analysis

Statistical analysis was carried out with Stata (version 16; Stata Corporation, College Station, TX, USA). Means (± standard deviation) and proportions of baseline characteristics were calculated using descriptive statistics. For each participant, person time of follow-up was accrued from inclusion in the first survey with BMI measurement until an incident VTE, migration from Tromsø, death or end of follow-up (31 December 2020), whichever came first. A time-varying analysis was used, where subjects who participated in more than one survey contributed with one observation period per attended survey. Such approach allowed for update of the BMI measurement for those who were re-measured during follow-up (Figure 1). This resulted in 67,957 observation periods with BMI assessment derived from the 36,341 unique participants.

The study participants were divided into three BMI categories according to cut-off values defined by the World Health Organization (WHO): BMI <25 kg/m^2, BMI 25-30 kg/m^2

(overweight) and BMI ≥30 kg/m^2 (obesity).[14] Crude incidence rates (IRs) with 95% confidence intervals (CIs) for incident VTE were calculated by dividing the number of events by the total accrued person-time in each BMI category and expressed as number of events per 1,000 person-years.

Time-varying Cox proportional hazards regression models were used to estimate hazard ratios (HRs) with 95% CIs for incident VTE across categories of BMI, with the BMI <25 kg/m^2 category serving as the reference. Adjustment for age was carried out using age as time scale in the Cox models, with the age at enrollment defined as the entry time, and the age at time of incident VTE, migration, death, or study end defined as the exit time. Analyses were additionally adjusted for sex, except when stratified according to sex. Subgroup analyses were performed according to anatomical location (i.e., DVT and PE ± DVT), the presence of provoking factors (i.e., provoked and unprovoked VTE events), and age (above and below 70 years of age). The proportional hazards assumption was evaluated and verified by Schoenfeld residuals and found not violated.

The PAF calculation was based on a formula that takes the relative risk for the exposure under investigation and the prevalence (p) of the exposure among cases into account (PAF = p[1-1/HR]). With this approach, internally valid PAF estimates are generated when adjusted risk estimates are used.[24,25] An extension of this formula for multicategory exposures was applied in the current analyses: $PAF = \left(1 - \sum_{i=0}^{k} \frac{pd_i}{HR_i}\right)$, where *i* refers to the *i*th exposure level (i.e. *i=0*, BMI <25 kg/m^2; *i=1*, BMI 25-30 kg/m^2; *i=2*, BMI ≥30 kg/m^2), pd_i is the prevalence of *i*th exposure level among the cases, and HR_i corresponds to the hazard ratio comparing *i*th exposure level with unexposed group (*i*=0). In our analyses, the PAF was calculated based on HRs adjusted for age (as a time scale) and sex. The prevalence of each of the three BMI categories among VTE cases was calculated according to the observational periods in order to account for BMI changes over the study period. We used bootstrapping

with 10,000 resamples to calculate the 95% CIs for PAFs. Subgroup analyses stratified by sex, age, and VTE subtypes (i.e., DVT, PE ± DVT, provoked and provoked VTE) were also carried out.

Results

Baseline characteristics of the study population are shown in Table 1. The sex distribution was approximately equal (47.9% men), the mean age at enrollment was 47 years, and the mean BMI was 25.7 kg/m^2. At baseline, 37.9% of the population were overweight and 13.8% were obese, and 2.2% and 5.3% reported a history of diabetes mellitus and arterial CVD, respectively.

There were 1,051 recorded incident VTE events during a total of 595,091 person-years of follow-up, which corresponded to a crude IR of 1.77 (95% CI 1.66-1.88) per 1,000 person-years. Median follow-up time was 13.9 years. The characteristics of the VTE events are described in Table 2. Mean age at the time of VTE occurrence was 69 years, 49.3% were men, and 55.2% of the events were DVTs and 58.4% were provoked VTEs. The most common provoking factors were cancer (24.7%), immobilization (21.1%) and major surgery (14.8%).

IRs and HRs for overall VTE and subgroups stratified according to sex and VTE subtypes are shown in Table 3. The crude IRs of overall VTE increased across categories of BMI, with an IR of 1.13 (95% CI 1.01-1.26) per 1000 person-years for individuals with a BMI <25 kg/m^2, and IRs of 2.04 (95% CI 1.87-2.24) and 3.01 (95% CI 2.67-3.39) per 1000 person-years for overweight (BMI 25-30 kg/m^2) and obese (BMI ≥30 kg/m^2) individuals, respectively. The age- and sex-adjusted HRs were 1.40 (95% CI 1.21-1.61) for overweight and 1.86 (95% CI 1.58-2.20) for obesity compared with the reference category (BMI <25 kg/m^2). The linear relationship between an increasing BMI and risk of VTE (*P* for trend <

0.001) is visualized in Figure 2. Risk estimates according to sex were similar to those of overall VTE, with age-adjusted HRs of 1.99 (95% CI 1.59-2.48) in women and 1.66 (95% CI 1.29-2.13) in men for obesity versus a BMI <25kg/m^2. Analyses stratified by VTE subtypes (Table 3) and age (< 70 years and ≥ 70 years, Supplemental Table 1) yielded essentially similar results to those obtained in overall VTE.

The PAF estimations for overall VTE and subgroups are shown in Table 4. For overall VTE, the age- and sex-adjusted PAF of overweight and obesity was 24.6% (95% CI 16.6-32.9), where 12.9% (95% CI 6.6-19.0) of VTE cases were attributed to overweight and 11.7% (95% CI 8.5-14.9) to obesity (Table 4, Figure 3). In analyses stratified according to sex, VTE subtypes (Table 4) and age (Supplemental Table 1), the PAF estimates did not substantially differ from those observed for overall VTE. The PAF for overweight and obesity was 25.9% (95% CI 15.3-36.7) in women and 21.8% (95% CI 8.9-35.0) in men. Regarding VTE subtypes, it is noteworthy that the thrombosis risk attributed to overweight and obesity was slightly higher for unprovoked VTE as compared with provoked events, with PAFs of 29.1% (95% CI 16.8-41.0) and 21.3% (95% CI 10.3-32.3), respectively.

Discussion

In this population-based cohort study, we investigated the proportion of VTEs that could be attributed to overweight and obesity. We found that overweight and obesity accounted for almost 25% of all incident VTE events in the general adult population. Subgroup analyses yielded essentially similar results to the overall analyses, irrespective of the anatomical location of the thrombus (i.e. DVT or PE), presence of provoking factors, sex and age group (below or above 70 years), with PAF estimates ranging from 21% to 29%. Our results demonstrate that overweight and obesity are major contributors to the VTE burden in the general population. From a public health perspective, our findings suggest that strategies

pursuing an effective mitigation of the obesity epidemic as well as targeted interventions aimed to reduce the thrombosis risk in overweight and obese subjects have the potential to substantially lower the incidence of VTE at the population level.

To date, the contribution of overweight and obesity to incident VTE in the general population has been scarcely investigated.[13,26] The PAF of overweight and obesity for VTE was assessed in a Swedish cohort study, where 12.4% of the VTE cases were attributed to a BMI ≥25 kg/m^2.[26] The estimate is lower compared with ours (~25%) but some reasons might account for such difference. In the Swedish cohort, height and weight used to calculate BMI were self-reported and the diagnosis of VTE was based on the International Classification of Diseases,[26] which could have resulted in some degree of misclassification. Further, estimates were based on a single baseline assessment of anthropometrics in 1997.[26] Given that BMI is a modifiable exposure, intra-individual change of BMI over time among participants of the Swedish cohort could have introduced regression dilution bias, which can lead to an underestimation of the results compared with the true associations.[27] In the present study, we sought to mitigate regression dilution bias by taking repeated measurements of BMI into account. Moreover, because our cohort study was composed of several surveys conducted over time (1994/95-2015/16), we were able to account for the rising prevalence of overweight and obesity in the last two decades when calculating the PAF. Indeed, data from the Tromsø study showed that the age-adjusted prevalence of obesity in men and women increased from 9.8% and 11.8% in 1994/95 to 25.2% and 23% in 2015/16, respectively.[30,32] This is in line with estimates from the WHO which indicate that almost one quarter (23%) of adults in the European Region were obese in 2016.[33]

The proportion of VTE cases attributed to overweight and obesity was substantial in men and women, among those aged below and above 70 years, and across VTE subtypes, with estimates ranging from 21% to 29%. Interestingly, the PAF estimate for provoked VTE

(21%) was slightly lower than the estimate for unprovoked VTE (29%). These findings can be interpreted in light of the thrombosis potential model. In this model, each risk factor contributes to increase the thrombosis potential of an individual, and when sufficient risk factors have been accumulated in a patient, the thrombosis potential exceeds the so-called thrombosis threshold, and an event occurs.[34] In this study, some of the factors used to categorize an event as provoked are strong risk factors for VTE, including major surgery and active cancer,[35] which were present in almost 15% and 25% of the VTE patients in our study, respectively. As these provoking factors could be sufficiently strong to push the thrombosis potential over the threshold in both normal weight and overweight/obese individuals, this could explain why we observed a lower PAF of overweight and obesity for provoked VTE. Our estimate that 29% of the unprovoked VTEs were attributed to overweight and obesity was similar to the estimate of 33% reported in a population-based cohort study from Olmsted County in the USA.[13]

Importantly, our findings indicate that regardless of advancing age, sex or presence of VTE provoking factors, an excess of total body fat seems to contribute to at least 20% of the incident VTE events occurring in the general population. Hence, it is reasonable to assume that the promotion of a healthy lifestyle to fight the obesity epidemic could lower the incidence of VTE in the general population. While population-based strategies to improve lifestyle have contributed in recent decades to an important decline in smoking in several countries,[36-38] current population strategies have not been successful in reversing the obesity epidemic.[14,38] Obesity is recognized to have a chronic, relapsing and multicausal nature.[39] Even though weight loss is achievable by most lifestyle and dietary interventions, long-term maintenance of lost weight is challenging and weight regain is typical.[39,40] For instance, a meta-analysis comprising 29 studies on long-term weight loss showed that more than 50% of the lost weight was regained in an individual within 2 years, and by 5 years, the proportion of

lost weight that was regained was approximately 80%.[41] Further, a recent systematic review evaluating weight regain after lifestyle interventions in the adult population revealed that a continuous weight gain typically becomes apparent around 36 weeks after the end of the interventions.[42]

Interventions that rely on targeting causal pathways involved in the pathophysiology of obesity-related VTE could emerge as promising approaches to reduce the VTE risk among overweight and obese subjects. Still, for these interventions to be effective and safe, it is crucial to unravel the complex mechanisms by which obesity increases thrombosis risk. While venous stasis,[43] chronic low-grade inflammation,[44] hypercoagulability,[45] and attenuated fibrinolysis[46,47] have all been implicated in the mechanisms underlying the association between obesity and VTE, only a few studies have pursued the identification of specific explanatory factors for this association. Chronic inflammation, assessed by C-reactive protein, appears to explain only a small fraction of the VTE risk among obese.[48,49] Recently, we showed that plasminogen activator inhibitor 1 (PAI-1), the main inhibitor of fibrinolysis, displayed a dose-dependent association with VTE risk and mediated approximately 15% of the association between obesity and VTE.[50] These findings underscore the potential use of PAI-1 as a target to reduce the VTE risk in obese subjects. Indeed, drugs that can modulate PAI-1 activity, known as PAI-1 inhibitors, have been extensively characterized in experimental studies and some of them are currently being tested in clinical trials although for conditions other than obesity and VTE.[51,52] Future research dedicated to identify biomarkers with a causal role in the association between overweight/obesity and VTE may facilitate the development of targeted intervention to lower the risk of incident VTE in overweight and obese people.

The main strengths of the present study include a large number of participants recruited from the general population with a wide age distribution, a high participation rate in

the surveys, a prospective design that enables the establishment of a clear relationship between exposure and outcome, a long follow-up time, an objective and validated assessment of the exposure and outcome, and the repeated measurements of BMI for a part of the study population. Several limitations merit attention. Repeated measurements of BMI were not available for 10,291 participants as they attended only one of the Tromsø 4-6 surveys (Figure 1). The lack of repeated BMI measurements for some participants could have led to an underestimation of the PAF estimates due to regression dilution bias.[27] Therefore, the true PAF estimates might be even higher than those reported in the present study. BMI was the only obesity measure that was available in all surveys of the Tromsø study. BMI, which is used to assess total body adiposity, has been the most commonly reported measure of obesity in epidemiological studies, thereby facilitating comparison across studies. However, waist circumference, a measure of abdominal obesity that reflects visceral adiposity, seems to yield the highest risk estimates for VTE and identify most people at risk.[26,53,54] Hence, the assessment of overweight and obesity based on waist circumference could have provided additional information for the present study.

In conclusion, almost 25% of all VTE events could be attributed to overweight and obesity in this population-based cohort study. Our findings suggest that public health efforts dedicated to develop strategies that can effectively fight the obesity epidemic along with targeted interventions aimed to reduce the thrombosis risk in overweight and obese subjects may substantially lower the incidence of VTE in the general population.

Authorship

Conception and design: JBH, VMM, SKB. Data collection: SKB, JBH. Data analysis: TF. Interpretation of results: TF, VMM, JBH, SKB, BGT. Manuscript draft: TF, VMM. Critical

revision of manuscript: JBH, SKB, BGT. All authors read and approved the submitted version of the manuscript.

Acknowledgments

The Thrombosis Research Center has received an independent grant from Stiftelsen Kristian Gerhard Jebsen (2014-2020). T. Frischmuth is supported by the Northern Norway Regional Health Authority.

Conflict-of-interest statements

The authors report no conflict of interest.

References

1. Glynn RJ, Rosner B. Comparison of Risk Factors for the Competing Risks of Coronary Heart Disease, Stroke, and Venous Thromboembolism. American Journal of Epidemiology. 2005;162:975-982
2. Raskob GE, Angchaisuksiri P, Blanco AN, Buller H, Gallus A, Hunt BJ, Hylek EM, Kakkar A, Konstantinides SV, McCumber M, Ozaki Y, Wendelboe A, Weitz JI. Thrombosis: a major contributor to global disease burden. Arterioscler Thromb Vasc Biol. 2014;34:2363-2371
3. Khan F, Tritschler T, Kahn SR, Rodger MA. Venous thromboembolism. Lancet. 2021;398:64-77
4. Schulman S, Lindmarker P, Holmstrom M, Larfars G, Carlsson A, Nicol P, Svensson E, Ljungberg B, Viering S, Nordlander S, Leijd B, Jahed K, Hjorth M, Linder O, Beckman M. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. J Thromb Haemost. 2006;4:734-742
5. Klok FA, van der Hulle T, den Exter PL, Lankeit M, Huisman MV, Konstantinides S. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. Blood Rev. 2014;28:221-226
6. Kahn SR, Shbaklo H, Lamping DL, Holcroft CA, Shrier I, Miron MJ, Roussin A, Desmarais S, Joyal F, Kassis J, Solymoss S, Desjardins L, Johri M, Ginsberg JS. Determinants of health-related quality of life during the 2 years following deep vein thrombosis. J Thromb Haemost. 2008;6:1105-1112
7. Braekkan SK, Grosse SD, Okoroh EM, Tsai J, Cannegieter SC, Naess IA, Krokstad S, Hansen JB, Skjeldestad FE. Venous thromboembolism and subsequent permanent work-related disability. J Thromb Haemost. 2016;14:1978-1987
8. Jørgensen H, Horváth-Puhó E, Laugesen K, Brækkan S, Hansen JB, Sørensen HT. Risk of a permanent work-related disability pension after incident venous

thromboembolism in Denmark: A population-based cohort study. PLoS Med. 2021;18:e1003770
9. Mannsverk J, Wilsgaard T, Mathiesen EB, Løchen ML, Rasmussen K, Thelle DS, Njølstad I, Hopstock LA, Bønaa KH. Trends in Modifiable Risk Factors Are Associated With Declining Incidence of Hospitalized and Nonhospitalized Acute Coronary Heart Disease in a Population. Circulation. 2016;133:74-81
10. Vangen-Lonne AM, Wilsgaard T, Johnsen SH, Lochen ML, Njolstad I, Mathiesen EB. Declining Incidence of Ischemic Stroke: What Is the Impact of Changing Risk Factors? The Tromso Study 1995 to 2012. Stroke. 2017;48:544-550
11. Arshad N, Isaksen T, Hansen JB, Braekkan SK. Time trends in incidence rates of venous thromboembolism in a large cohort recruited from the general population. Eur J Epidemiol. 2017;32:299-305
12. Münster AM, Rasmussen TB, Falstie-Jensen AM, Harboe L, Stynes G, Dybro L, Hansen ML, Brandes A, Grove EL, Johnsen SP. A changing landscape: Temporal trends in incidence and characteristics of patients hospitalized with venous thromboembolism 2006–2015. Thrombosis Research. 2019;176:46-53
13. Heit JA, Ashrani A, Crusan DJ, McBane RD, Petterson TM, Bailey KR. Reasons for the persistent incidence of venous thromboembolism. Thromb Haemost. 2017;117:390-400
14. World Health Organization (WHO). Fact sheet: Obesity and overweight. 2018. Available at: https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight. Accessed February 24, 2020
15. Braekkan SK, Siegerink B, Lijfering WM, Hansen JB, Cannegieter SC, Rosendaal FR. Role of obesity in the etiology of deep vein thrombosis and pulmonary embolism: current epidemiological insights. Semin Thromb Hemost. 2013;39:533-540
16. Rahmani J, Haghighian Roudsari A, Bawadi H, Thompson J, Khalooei Fard R, Clark C, Ryan PM, Ajami M, Rahimi Sakak F, Salehisahlabadi A, Abdulazeem HM, Jamali MR, Mirzay Razaz J. Relationship between body mass index, risk of venous thromboembolism and pulmonary embolism: A systematic review and dose-response meta-analysis of cohort studies among four million participants. Thromb Res. 2020;192:64-72
17. Horvei LD, Braekkan SK, Hansen JB. Weight Change and Risk of Venous Thromboembolism: The Tromso Study. PLoS One. 2016;11:e0168878
18. French SA, Lutsey PL, Rosamond W, Maclehose RF, Cushman M, Folsom AR. Weight change over 9 years and subsequent risk of venous thromboembolism in the ARIC cohort. International Journal of Obesity. 2020
19. Klovaite J, Benn M, Nordestgaard BG. Obesity as a causal risk factor for deep venous thrombosis: a Mendelian randomization study. J Intern Med. 2015;277:573-584
20. Klarin D, Emdin CA, Natarajan P, Conrad MF, Invent Consortium, Kathiresan S. Genetic Analysis of Venous Thromboembolism in UK Biobank Identifies the ZFPM2 Locus and Implicates Obesity as a Causal Risk Factor. Circ Cardiovasc Genet. 2017;10:e001643
21. Lindstrom S, Germain M, Crous-Bou M, Smith EN, Morange PE, van Hylckama Vlieg A, de Haan HG, Chasman D, Ridker P, Brody J, de Andrade M, Heit JA, Tang W, DeVivo I, Grodstein F, Smith NL, Tregouet D, Kabrhel C, Consortium I. Assessing the causal relationship between obesity and venous thromboembolism through a Mendelian Randomization study. Hum Genet. 2017;136:897-902
22. Larsson SC, Back M, Rees JMB, Mason AM, Burgess S. Body mass index and body composition in relation to 14 cardiovascular conditions in UK Biobank: a Mendelian randomization study. Eur Heart J. 2020;41:221-226

23. Kim MS, Kim WJ, Khera AV, Kim JY, Yon DK, Lee SW, Shin JI, Won HH. Association between adiposity and cardiovascular outcomes: an umbrella review and meta-analysis of observational and Mendelian randomization studies. Eur Heart J. 2021;42:3388-3403
24. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. Am J Public Health. 1998;88:15-19
25. Mansournia MA, Altman DG. Population attributable fraction. Bmj. 2018;360:k757
26. Yuan S, Bruzelius M, Xiong Y, Håkansson N, Åkesson A, Larsson SC. Overall and abdominal obesity in relation to venous thromboembolism. J Thromb Haemost. 2021;19:460-469
27. Clarke R, Shipley M, Lewington S, Youngman L, Collins R, Marmot M, Peto R. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. Am J Epidemiol. 1999;150:341-353
28. Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njolstad I. Cohort profile: the Tromso Study. Int J Epidemiol. 2012;41:961-967
29. Eggen AE, Mathiesen EB, Wilsgaard T, Jacobsen BK, Njølstad I. The sixth survey of the Tromso Study (Tromso 6) in 2007-08: collaborative research in the interface between clinical medicine and epidemiology: study objectives, design, data collection procedures, and attendance in a multipurpose population-based health survey. Scand J Public Health. 2013;41:65-80
30. Løvsletten O, Jacobsen BK, Grimsgaard S, Njølstad I, Wilsgaard T, Løchen ML, Eggen AE, Hopstock LA. Prevalence of general and abdominal obesity in 2015-2016 and 8-year longitudinal weight and waist circumference changes in adults and elderly: the Tromsø Study. BMJ Open. 2020;10:e038465
31. Braekkan SK, Borch KH, Mathiesen EB, Njolstad I, Wilsgaard T, Hansen JB. Body height and risk of venous thromboembolism: The Tromso Study. Am J Epidemiol. 2010;171:1109-1115
32. Jacobsen BK, Aars NA. Changes in body mass index and the prevalence of obesity during 1994-2008: repeated cross-sectional surveys and longitudinal analyses. The Tromsø Study. BMJ Open. 2015;5:e007859
33. World Health Organization. Regional Office for E. *WHO European Regional Obesity Report 2022.* Copenhagen: World Health Organization. Regional Office for Europe; 2022
34. Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet. 1999;353:1167-1173
35. Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing GJ, Kyrle PA. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. J Thromb Haemost. 2016;14:1480-1483
36. National Institutes of Health State-of-the-Science conference statement: tobacco use: prevention, cessation, and control. Ann Intern Med. 2006;145:839-844
37. Mozaffarian D, Afshin A, Benowitz NL, Bittner V, Daniels SR, Franch HA, Jacobs DR, Jr., Kraus WE, Kris-Etherton PM, Krummel DA, Popkin BM, Whitsel LP, Zakai NA. Population approaches to improve diet, physical activity, and smoking habits: a scientific statement from the American Heart Association. Circulation. 2012;126:1514-1563
38. Folsom AR, Cushman M. Exploring Opportunities for Primary Prevention of Unprovoked Venous Thromboembolism: Ready for Prime Time? J Am Heart Assoc. 2020;9:e019395

39. Bray GA, Kim KK, Wilding JPH. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. Obes Rev. 2017;18:715-723
40. Hall KD, Kahan S. Maintenance of Lost Weight and Long-Term Management of Obesity. Med Clin North Am. 2018;102:183-197
41. Anderson JW, Konz EC, Frederich RC, Wood CL. Long-term weight-loss maintenance: a meta-analysis of US studies. Am J Clin Nutr. 2001;74:579-584
42. Machado AM, Guimarães NS, Bocardi VB, da Silva TPR, Carmo ASD, Menezes MC, Duarte CK. Understanding weight regain after a nutritional weight loss intervention: Systematic review and meta-analysis. Clin Nutr ESPEN. 2022;49:138-153
43. Willenberg T, Schumacher A, Amann-Vesti B, Jacomella V, Thalhammer C, Diehm N, Baumgartner I, Husmann M. Impact of obesity on venous hemodynamics of the lower limbs. J Vasc Surg. 2010;52:664-668
44. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol. 2011;11:85-97
45. Faber DR, De Groot PG, Visseren FLJ. Role of adipose tissue in haemostasis, coagulation and fibrinolysis. Obesity Reviews. 2009;10:554-563
46. Mertens I, Van Gaal LF. Obesity, haemostasis and the fibrinolytic system. Obes Rev. 2002;3:85-101
47. Skurk T, Hauner H. Obesity and impaired fibrinolysis: role of adipose production of plasminogen activator inhibitor-1. Int J Obes Relat Metab Disord. 2004;28:1357-1364
48. Olson NC, Cushman M, Lutsey PL, McClure LA, Judd S, Tracy RP, Folsom AR, Zakai NA. Inflammation markers and incident venous thromboembolism: the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort. J Thromb Haemost. 2014;12:1993-2001
49. Horvei LD, Grimnes G, Hindberg K, Mathiesen EB, Njolstad I, Wilsgaard T, Brox J, Braekkan SK, Hansen JB. C-reactive protein, obesity, and the risk of arterial and venous thrombosis. J Thromb Haemost. 2016;14:1561-1571
50. Frischmuth T, Hindberg K, Aukrust P, Ueland T, Braekkan SK, Hansen JB, Morelli VM. Elevated plasma levels of plasminogen activator inhibitor-1 are associated with risk of future incident venous thromboembolism. J Thromb Haemost. 2022;20:1618-1626
51. Morrow GB, Whyte CS, Mutch NJ. A Serpin With a Finger in Many PAIs: PAI-1's Central Function in Thromboinflammation and Cardiovascular Disease. Front Cardiovasc Med. 2021;8:653655
52. Sillen M, Declerck PJ. Targeting PAI-1 in Cardiovascular Disease: Structural Insights Into PAI-1 Functionality and Inhibition. Front Cardiovasc Med. 2020;7:622473
53. Borch KH, Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Stormer J, Hansen JB. Anthropometric measures of obesity and risk of venous thromboembolism: the Tromso study. Arterioscler Thromb Vasc Biol. 2010;30:121-127
54. Horvei LD, Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Hansen JB. Obesity measures and risk of venous thromboembolism and myocardial infarction. Eur J Epidemiol. 2014;29:821-830

Tables

Table 1 Baseline characteristics of study participants (n=36,341) from the 4th (1994/95) to the 7th (2015/16) surveys of the Tromsø Study

Characteristics	Value
n	36,341
Sex (men), % (n)	47.9 (17,414)
Age in years, mean ± SD	47 ± 14
BMI in kg/m^2, mean ± SD	25.7 ± 4.2
Overweight, % (n)	37.9 (13,764)
Obese, % (n)	13.8 (5,006)
SBP in mmHg, mean ± SD	132 ± 20
DBP in mmHg, mean ± SD	77 ± 12
Total Cholesterol in mmol L^{-1}, mean ± SD	5.9 ± 1.3
Smoking, % (n)	32.0 (11,624)
OC & HRT, % (n)	17,1 (3,244)
Diabetes mellitus, % (n)	2.2 (794)
Arterial CVD, % (n)	5.3 (1,909)

Abbreviations: BMI, body mass index; CVD cardiovascular disease; DBP, diastolic blood pressure; HRT, hormone replacement therapy; OC, oral contraceptives; SD, standard deviation; SBP, systolic blood pressure.
Overweight defined as BMI 25-30 kg/m^2; obesity defined as BMI ≥ 30 kg/m^2, OC & HRT percentage in women only.

Table 2 Characteristics of venous thromboembolism (VTE) events (n=1,051) in the Tromsø study (1994-2020)

Characteristics	Value
Age at VTE	69 ± 13
Sex (men)	49.3 (518)
Deep vein thrombosis	55.2 (580)
Pulmonary embolism	44.8 (471)
Unprovoked VTE	41.6 (437)
Provoked VTE	58.4 (614)
Major surgery	14.8 (155)
Trauma	9.2 (97)
Acute medical conditions	12.2 (128)
Cancer	24.7 (260)
Immobilization	21.1 (222)
Others	4.0 (42)

Values are % (n) for categorical variables or means ± standard deviation for continuous variables.

Table 3 Crude incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) according to categories of body mass index (BMI) for overall venous thromboembolism (VTE) and subgroups stratified by sex and VTE subtypes

BMI (kg/m^2)	Person-years	VTE events	Crude IR[a] (95% CIs)	HR[b] (95% CIs)
Overall VTE				
<25	273865	309	1.13 (1.01-1.26)	1 (reference)
25-30	232830	476	2.04 (1.87-2.24)	1.40 (1.21-1.61)
≥30	88396	266	3.01 (2.67-3.39)	1.86 (1.58-2.20)
Women				
<25	166807	169	1.01 (0.87-1.18)	1 (reference)
25-30	101565	206	2.03 (1.77-2.33)	1.41 (1.14-1.73)
≥30	47825	158	3.30 (2.83-3.86)	1.99 (1.59-2.48)
Men				
<25	107058	140	1.31 (1.11-1.54)	1 (reference)
25-30	131265	270	2.06 (1.83-2.32)	1.35 (1.10-1.66)
≥30	40571	108	2.66 (2.20-3.21)	1.66 (1.29-2.13)
Deep vein thrombosis				
<25	273865	179	0.65 (0.56-0.76)	1 (reference)
25-30	232830	264	1.13 (1.01-1.28)	1.38 (1.14-1.67)
≥30	88396	137	1.55 (1.31-1.83)	1.69 (1.35-2.12)
Pulmonary embolism				
<25	273865	130	0.47 (0.40-0.56)	1 (reference)
25-30	232830	212	0.91 (0.80-1.04)	1.43 (1.15-1.78)
≥30	88396	129	1.46 (1.23-1.73)	2.09 (1.64-2.68)
Unprovoked VTE				
<25	273865	122	0.45 (0.37-0.53)	1 (reference)
25-30	232830	202	0.87 (0.76-1.00)	1.52 (1.21-1.91)
≥30	88396	113	1.28 (1.06-1.54)	2.05 (1.58-2.66)
Provoked VTE				
<25	273865	187	0.68 (0.59-0.79)	1 (reference)
25-30	232830	274	1.18 (1.05-1.32)	1.32 (1.09-1.59)
≥30	88396	153	1.73 (1.48-2.03)	1.74 (1.40-2.16)

[a] IRs per 1000 person-years

[b] Adjusted for age (time scale) and sex (if applicable)

Table 4 Population attributable fraction (PAF) with 95% confidence intervals (CIs) due to overweight and obesity for overall venous thromboembolism (VTE) and subgroups stratified by sex and VTE subtypes

BMI (kg/m^2)	Prevalence among VTE, %	HR[a] (95% CIs)	PAF (95% CIs), %
Overall VTE			
<25	29.4	1 (reference)	
25-30	45.3	1.40 (1.21-1.61)	12.9 (6.6-19.0)
≥30	25.3	1.86 (1.58-2.20)	11.7 (8.5-14.9)
Overweight and obesity			24.6 (16.6-32.9)
Women			
<25	31.7	1 (reference)	
25-30	38.6	1.41 (1.14-1.73)	11.2 (3.3-18.6)
≥30	29.6	1.99 (1.59-2.48)	14.7 (9.8-19.6)
Overweight and obesity			25.9 (15.3-36.7)
Men			
<25	27.0	1 (reference)	
25-30	52.1	1.35 (1.10-1.66)	13.5 (2.7-23.6)
≥30	20.8	1.66 (1.29-2.13)	8.3 (3.7-12.5)
Overweight and obesity			21.8 (8.9-35.0)
Deep vein thrombosis			
<25	30.9	1 (reference)	
25-30	45.5	1.38 (1.14-1.67)	12.4 (3.5-20.5)
≥30	23.6	1.69 (1.35-2.12)	9.7 (5.1-13.9)
Overweight and obesity			22.1 (10.8-33.1)
Pulmonary embolism			
<25	27.6	1 (reference)	
25-30	45.0	1.43 (1.15-1.78)	13.5 (3.5-22.2)
≥30	27.4	2.09 (1.64-2.68)	14.3 (9.5-19.0)
Overweight and obesity			27.8 (15.6-39.9)
Unprovoked VTE			
<25	27.9	1 (reference)	
25-30	46.2	1.52 (1.21-1.91)	15.8 (5.9-24.5)
≥30	25.9	2.05 (1.58-2.66)	13.3 (8.4-18.0)
			29.1 (16.8-41.0)
Provoked VTE			
<25	30.5	1 (reference)	
25-30	44.6	1.32 (1.09-1.59)	10.7 (2.0-19.0)
≥30	24.9	1.74 (1.40-2.16)	10.6 (6.1-14.8)
Overweight and obesity			21.3 (10.3-32.3)

Abbreviations: HR, hazard ratio.

[a] Adjusted for age (time scale) and sex (if applicable)

Overweight defined as BMI 25-30 kg/m^2; obesity defined as BMI ≥ 30 kg/m^2

Figures

Figure 1 Overview of included participants. Dots represent participation at the survey, and arrows between dots represent observation periods. A total of 36,341 unique individuals were included in the study.

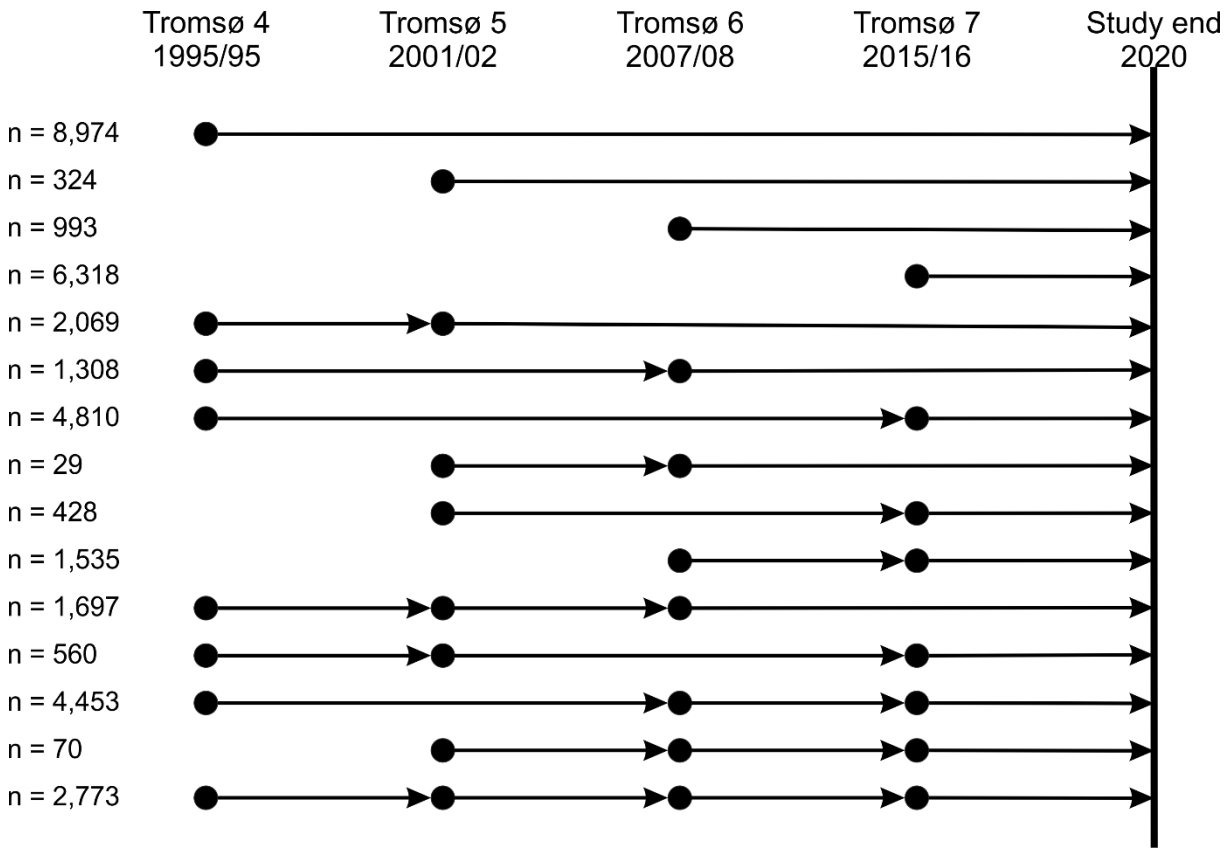


Figure 2 Age- and sex-adjusted hazard ratios with 95% confidence intervals for overall venous thromboembolism according to categories of body mass index

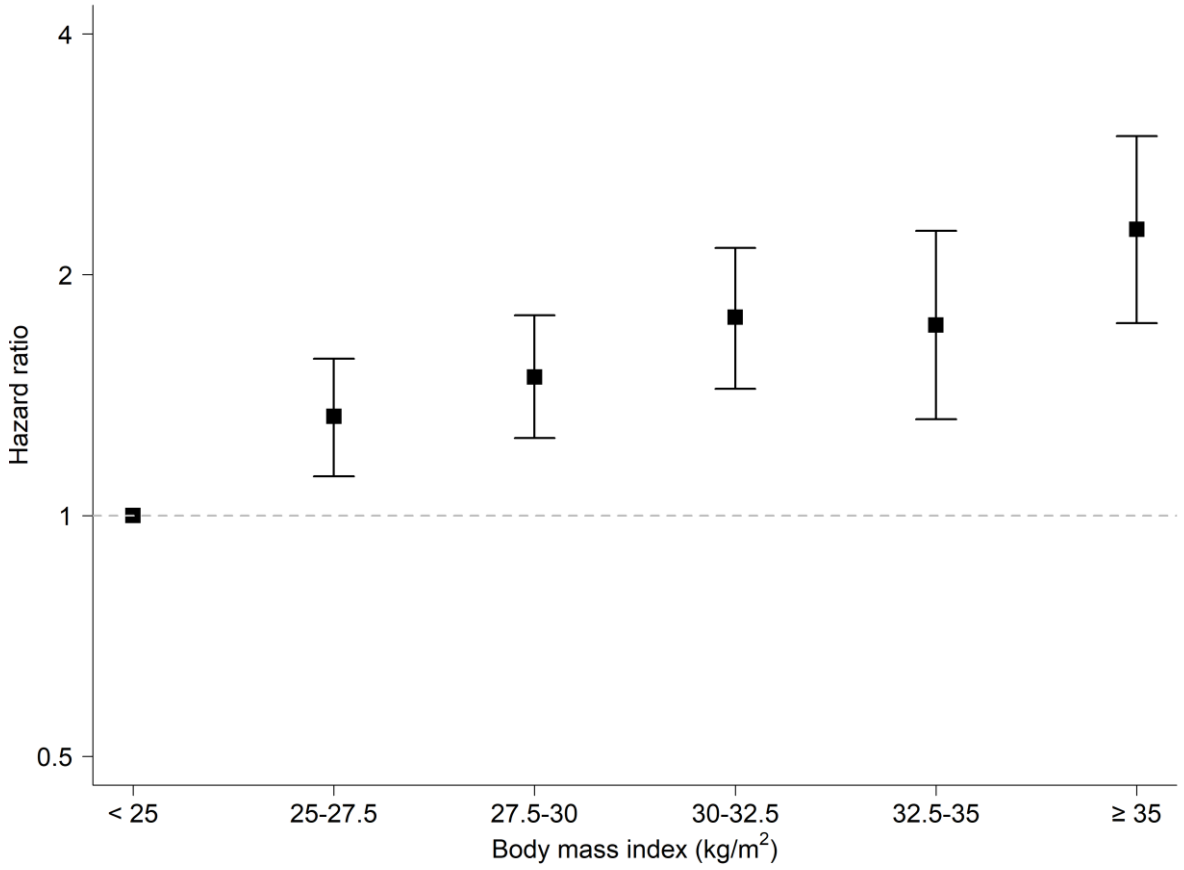
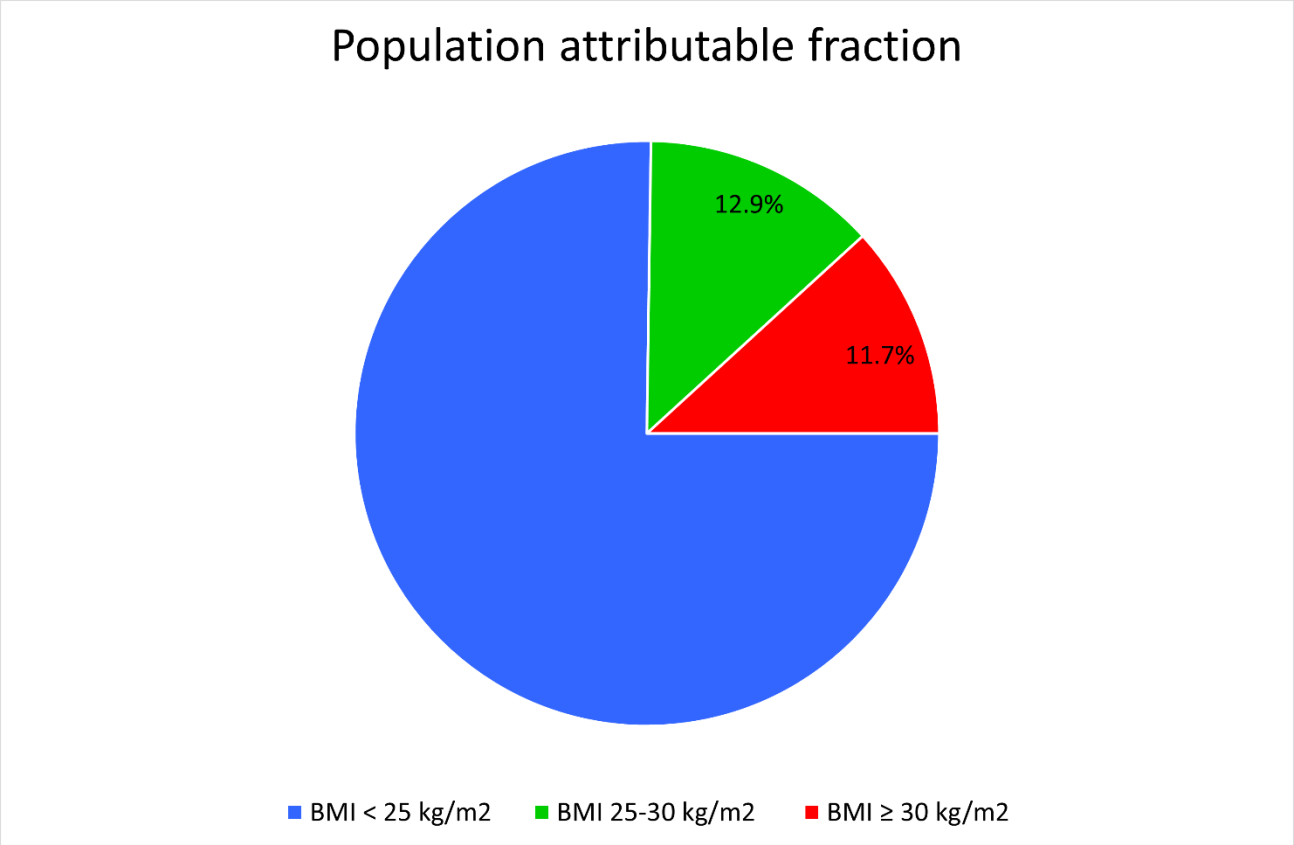


Figure 3 Population attributable fraction of overall venous thromboembolism according to categories of body mass index



Supplementary material

Supplementary Table 1 Crude incidence rates (IRs), hazard ratios (HRs) and population attributable fraction (PAF) with 95% confidence intervals (CIs) for overall venous thromboembolism in analyses stratified by age

BMI (kg/m^2)	Person-years	VTE events	Prevalence among VTE, %	Crude IR[a] (95% CIs)	HR[b] (95% CIs)	PAF (95% CIs), %
Age < 70 years						
<25	238257	173	33.1	0.73 (0.63-0.84)	1 (reference)	
25-30	187193	216	41.3	1.15 (1.01-1.32)	1.27 (1.03-1.55)	8.7 (-0.7-17.3)
≥30	66793	134	25.6	2.01 (1.69-2.38)	2.11 (1.68-2.65)	13.5 (9.3-17.8)
Overweight and obesity						22.2 (10.8-33.5)
Age ≥ 70 years						
<25	35608	136	25.8	3.82 (3.23-4.52)	1 (reference)	
25-30	45637	260	49.2	5.70 (5.05-6.43)	1.51 (1.23-1.86)	16.7 (7.0-25.1)
≥30	21603	132	25.0	6.11 (5.15-7.25)	1.64 (1.29-2.09)	9.8 (4.1-14.6)
Overweight and obesity						26.5 (13.2-38.4)

a IRs per 1000 person-years

b Adjusted for age (time scale) and sex

Overweight defined as BMI 25-30 kg/m^2; obesity defined as BMI ≥ 30 kg/m^2