Obesity in adolescent men increases the risk of venous thromboembolism in adult life

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Abstract. Glise Sandblad K, Jern S, Åberg M, Robertson J, Torén K, Lindgren M, Adiels M, Hansson PO, Rosengren A (Sahlgrenska University Hospital/Östra; Sahlgrenska Academy, University of Gothenburg; University of Gothenburg, Gothenburg, Sweden). Obesity in adolescent men increases the risk of venous thromboembolism in adult life. J Intern Med 2020; 287: 734–745.

Background. As the population of obese and severely obese young adults grows, it is becoming increasingly important to recognize the long-term risks associated with adolescent obesity.

Objectives. This study aimed to determine the association between body mass index (BMI) in young men at enlistment for military service and later risk of venous thromboembolism (VTE).

Methods. Nationwide register-based prospective cohort study of men enlisting 1969 to 2005, followed through the Swedish National Patient and Cause of Death registries. We identified 1 639 838 men (mean age, 18.3 years) free of prior venous thromboembolism, of whom 29 342 were obese (BMI 30 to <35 kg m⁻²) and 7236 severely obese (BMI ≥35 kg m⁻²). The participants were followed until a first registered diagnosis of VTE.

Results. During a median follow-up of 28 years (interquartile interval, 20 to 36 years), 11 395 cases of deep vein thrombosis and 7270 cases of pulmonary embolism were recorded. Compared with men with a BMI of 18.5 to <20 kg m⁻², men with higher BMI in young adulthood showed an incrementally increasing risk of VTE that was moderately but significantly increased already at normal BMI levels. Adolescent obese men with a BMI of 30 to 35 kg m⁻² had an adjusted hazard ratio of 2.93 (95% confidence interval, 2.65 to 3.24) for VTE. Severely obese men with a BMI of ≥35 kg m⁻² had a hazard ratio of 4.95 (95% confidence interval, 4.16 to 5.90).

Conclusions. Men who were obese or severely obese in young adulthood had a marked increase in risk of VTE.

Keywords: obesity, venous thromboembolism.

Introduction

The global burden of obesity (BMI ≥30 kg m⁻²) is increasing, particularly of severe obesity (BMI ≥35 kg m⁻²), where 2.3% of the men and 5.0% of the women were estimated to be severely obese in 2014 [1]. The global prevalence of obesity in children aged 5–19 years increased between 1975 and 2016, reaching 5.6% in girls and 7.8% in boys, with a childhood obesity prevalence of over 20% in many countries [2]. Obesity is an important contributor to morbidity and mortality in cardiovascular disease, type 2 diabetes and cancer [3].

Data on risk of venous thromboembolism (VTE) in relation to overweight and obesity mostly acknowledge obesity as an important risk factor [4, 5]. However, the 2019 European Society of Cardiology (ESC) Guidelines on pulmonary embolism state that obesity is a weak risk factor for PE, with an odds ratio below 2 [6], based on a review article from 2003 [7]. The conclusions on obesity from this
review were based on only three studies, including two small perioperative studies from the 1970s [8, 9], with one of the three a small case–control study reporting no association between BMI and VTE [10]. In contrast, a large Danish Mendelian randomization study of middle-aged individuals followed for up to 35 years showed high hazard ratios (HR) of 5.1 for DVT complicated by PE for severely obese individuals (BMI $\geq 35$ kg m$^{-2}$) compared to normal weight; however, patients with pulmonary embolism (PE) without a documented deep vein thrombosis (DVT) were excluded [11]. Other, more recent, studies in middle-aged persons have also shown a relationship between obesity and VTE [12–15]. So far, there have been no studies investigating the effect of severe obesity in late adolescence on subsequent VTE risk, which is important, given that this is a rapidly growing segment of the population, affecting large groups of young men and women.

The sharp increase of obesity in young individuals indicates that there is a need for more information on the relationship between obesity in young individuals and the development of health problems such as VTE later in life. A few studies have explored this topic. However, it is difficult to draw any conclusions from these studies as they feature a low proportion of obese individuals in the high BMI group (and therefore underestimate the true risk), [16–18] are based on recalled weight and somatotype rather than measures [19], or few events [20, 21]. Given the limitation of previous studies, there is a need for further research on obesity in young individuals and VTE. The present study aim was therefore to explore the relationship between BMI levels in young adulthood and later development of VTE using a long-term follow-up of a large population of men from the Swedish Military Service Conscription Register.

Methods

Study population and design

This was a prospective cohort study. The study population was derived from a cohort of all men enlisting for military service in Sweden between 1969 and 2005 ($n = 1\:885\:924$). Exemption from mandatory enlistment was granted only for men who were incarcerated or had severe chronic medical or mental conditions (approximately 2% to 3%). Enlistment took place at one of six conscription centres and included standardized physical and cognitive examinations; [22] the results of which were recorded in the Swedish Military Service Conscription Register. We excluded men enlisting early or late (aged $\leq 16$ years or $\geq 25$ years), women, men whose Swedish personal identification number was reused after their death or emigration, and men with missing BMI values. Additionally, men diagnosed with VTE or stroke prior to enlistment or who had a lower extremity fracture within 1 year prior to enlistment were excluded (Figure S1).

The regional ethical review board in Gothenburg approved the study (Dnr 567-15).

Swedish military service conscription register data

The 2-day examination involved measurement of weight and height. Height (m) was measured using a wall-mounted stadiometer, and weight (kg) was measured using analogue or digital scales. BMI was calculated as weight/height$^2$. Blood pressure was measured in the supine position after 5–10 min of rest. Standardized cognitive evaluations were performed, providing a global intelligence score as a measure of general cognitive performance (intelligence quotient, IQ). These test results were standardized and transformed into STAndard NINE (stanine) scores (1 to 9), as previously described [23, 24]. Muscle strength was assessed using a combination of knee extension, elbow flexion and hand-grip tests. The results were weighted and transformed into a stanine score (1 to 9) [24]. The stanine scores were divided into three groups: low (1 to 3), medium (4 to 6) and high (7 to 9) for IQ and muscle strength. Cardiorespiratory fitness was assessed by bicycle ergometer testing [24]. The maximum work capacity ($W_{\text{max}}$) was divided by weight and transformed into scores of 0 to 9. These were categorized into three groups: low (0 to 4), medium (5 to 6) and high (7 to 9).

Information about highest achieved parental education was collected from the longitudinal integration database for health insurance and labour market services (LISA registry). This registry was established in 1990 and includes all registered inhabitants from the age of 16 years. Education is divided into seven levels ranging from $<$9 years of school to postgraduate research training. We organized these levels into three groups: low, medium and high parental education. For conscripts enlisting before LISA was established, the highest parental level achieved in 1990 was used.
Follow-up procedures

Sweden has a universal healthcare system that provides low-cost outpatient and hospital care to all citizens. The National Patient Registry includes the Swedish inpatient registry, which has a coverage that increased gradually from 1968 and has been complete since 1987, and the outpatient registry, which has existed since 2001. The Swedish Cause of Death Registry includes all deaths of persons registered in Sweden, including deaths abroad. The Prescribed Drug Registry includes all prescriptions that have been retrieved from any Swedish pharmacy since July 2005. Data from these registries were linked through the Swedish personal identification number.

Subjects were followed until (i) a first diagnosis of PE or DVT or (ii) death or (iii) emigration or (iv) the end of the follow-up period on 31 December 2014.

For men diagnosed with VTE before January 2006, we required one inpatient diagnosis of PE or DVT. Outpatient diagnoses were not included. For men diagnosed with VTE after January 2006, we required one inpatient or outpatient diagnosis of PE or DVT in combination with the retrieval of at least one prescription of anticoagulant medication within 6 months after discharge, a method previously suggested to increase accuracy of VTE diagnoses [26]. When the first VTE diagnosis was retrieved from the Cause of Death Registry, meeting of the prescription criterion was not required. Only the first registered diagnosis of VTE, PE or DVT was included (see Figures S2 and S3).

Definitions

PE and DVT were defined as follows: a hospital discharge diagnosis or a cause of death according to the International Classification of Diseases (ICD)-8: PE (450), DVT (451); ICD-9: PE (415B, 416W), DVT (451 except 451 A); or ICD-10: PE (I26), DVT (I80 except I80.0). Diagnoses were accepted regardless of whether they were considered primary or secondary causes of hospitalization or death.

Statistical analysis

Incidence rates and their corresponding 95% confidence intervals (CI) were calculated using Poisson regression. We used Cox proportional hazards regression to estimate associations between BMI at conscription and risk of VTE during follow-up, adding potential confounders to the models.

If a first DVT and PE were diagnosed on the same date, both diagnoses were included and counted separately for PE and DVT, but only counted as one VTE. Patients with inpatient diagnosis and death certificate diagnosis on the same date were registered as an inpatient diagnosis. In a separate analysis, subjects who died of cancer were censored 2 years before death, as we considered it likely that VTE in these cases could have been caused by the cancer. Similarly, patients who had a lower extremity fracture within 3 months prior to VTE diagnosis were excluded, as lower extremity fracture is likely to have been an aggravating factor in these instances.

The following covariates were included and grouped as follows: Model 1: Age at conscription, centre and year of conscription, and baseline comorbidities comprising hypertension, diabetes and congenital heart disease. Model 2: Model 1 + blood pressure. Model 3: Model 2 + parental education (as a measure of socio-economic status). Model 4: Model 1 + IQ, muscular strength, cardiovascular fitness. Model 5: Model 4 + parental education. Individuals with missing data in BMI were excluded. When data were missing in other variables, the individuals were excluded when that variable was included in the model.

Owing to the large number of observations, the p-values were very small and are not therefore reported. For example, for analyses in which the 95% CI did not overlap, most P-values were <0.001. All statistical analyses were performed using R, version 3.5.2.

Results

Study population

Of the 1 639 838 men included, 79.8% were normal weight (BMI 18.5 to <25 kg m⁻²), 9.9% were overweight (BMI 25 to <30 kg m⁻²), and 2.2% were obese (BMI ≥30 kg m⁻²). Baseline information on anthropometrics, cardiovascular fitness, muscular strength, IQ, parental education and medical conditions at baseline are shown in Table 1. The median follow-up time was 28 years for the entire group (interquartile range, 20–36 years).
| Variable                                      | All  | 15 ≤ BMI < 18.5 | 18.5 ≤ BMI < 20 | 20 ≤ BMI < 22.5 | 22.5 ≤ BMI < 25 | 25 ≤ BMI < 27.5 | 27.5 ≤ BMI < 30 | 30 ≤ BMI < 35 | 35 ≤ BMI < 60 |
|-----------------------------------------------|------|-----------------|-----------------|-----------------|-----------------|-----------------|----------------|----------------|----------------|
| n (%)                                         | 1639 838 (100.00) | 133 985 (8.12)  | 296 531 (18.08) | 662 641 (40.41) | 349 546 (21.32) | 118 975 (7.26) | 42 482 (2.59)  | 29 342 (1.79)  | 7236 (0.44)   |
| Follow-up time, median [IQR]                  | 28 [20,36] | 31 [22,40] | 30 [22,39] | 28 [20,37] | 26 [19,35] | 25 [16,33] | 24 [16,32] | 22 [15,30] | 19 [13,27] |
| Age, years (SD)                               | 18.3 (0.61) | 18.3 (0.673) | 18.3 (0.574) | 18.3 (0.594) | 18.3 (0.564) | 18.3 (0.564) | 18.3 (0.564) | 18.3 (0.564) | 18.3 (0.564) |
| Height, cm (SD)                               | 179 (6.58) | 180 (6.86) | 179 (6.59) | 179 (6.50) | 179 (6.56) | 179 (6.56) | 179 (6.56) | 179 (6.56) | 179 (6.56) |
| Weight, kg (SD)                               | 70.4 (11) | 57.1 (4.87) | 62.3 (4.76) | 68.3 (5.43) | 75.6 (5.96) | 83.6 (6.61) | 91.9 (7.38) | 102.5 (9.11) | 122.1 (12.89) |
| BMI, kg m⁻¹ m⁻¹ (SD)                          | 21.9 (3.04) | 17.7 (0.688) | 19.3 (0.422) | 21.2 (0.711) | 23.6 (0.699) | 26.1 (0.725) | 28.6 (0.678) | 31.9 (1.362) | 37.9 (2.962) |
| SBP, mmHg (SD)                                | 129 (11) | 126 (10.8) | 127 (10.8) | 128 (10.8) | 130 (10.8) | 131 (10.8) | 133 (10.8) | 134 (11.1) | 136 (11.5) |
| DBP, mmHg (SD)                                | 67.6 (9.81) | 67.4 (9.59) | 67.2 (9.64) | 67.3 (9.73) | 67.7 (9.87) | 68.4 (10.04) | 69.3 (10.31) | 70.5 (10.55) | 72.7 (11.14) |
| Wmax, (Watt) (SD)                             | 279 (52.5) | 235 (41.1) | 258 (44.5) | 281 (49.2) | 297 (54.2) | 292 (53.1) | 288 (53.3) | 281 (56.9) | 281 (56.9) |
| Wmax/kg bw, (Watt/kg) (SD)                    | 4 (0.721) | 4.12 (0.669) | 4.14 (0.673) | 4.12 (0.681) | 3.94 (0.682) | 3.57 (0.646) | 3.20 (0.581) | 2.83 (0.538) | 2.34 (0.514) |
| Cardiorespiratory fitness                      |       |               |               |               |               |               |               |               |               |
| Low                                           |       |               |               |               |               |               |               |               |               |
| Medium                                        |       |               |               |               |               |               |               |               |               |
| High                                          |       |               |               |               |               |               |               |               |               |
| Data missing                                  | 43 595 (2.66) | 5488 (4.12) | 6044 (2.04) | 13 347 (2.01) | 8524 (2.44) | 3871 (3.25) | 1719 (4.05) | 2527 (8.61) | 2075 (28.68) |
| Muscle strength                               |       |               |               |               |               |               |               |               |               |
| Low                                           |       |               |               |               |               |               |               |               |               |
| Medium                                        |       |               |               |               |               |               |               |               |               |
| High                                          |       |               |               |               |               |               |               |               |               |
| Data missing                                  | 12 785 (0.78) | 2663 (2.00) | 1517 (0.51) | 3097 (0.47) | 1901 (0.54) | 846 (0.71) | 413 (0.97) | 1025 (3.49) | 1323 (18.28) |
| IQ                                            |       |               |               |               |               |               |               |               |               |
| Low                                           |       |               |               |               |               |               |               |               |               |
| Medium                                        |       |               |               |               |               |               |               |               |               |
| High                                          |       |               |               |               |               |               |               |               |               |
| Data missing                                  | 54 554 (3.33) | 11 074 (3.73) | 5651 (4.25) | 21 613 (2.26) | 10 398 (3.00) | 1241 (2.92) | 843 (2.87) | 166 (2.29)  |               |
During follow-up, 17,805 cases of first VTE events were recorded (Table 2). In 860 individuals, a first DVT and PE were diagnosed on the same date. The event rate for VTE per 100,000 years was 73.7 in men with BMI 30 to <35 kg m$^{-2}$ at enlistment and 112.1 in men with BMI $\geq 35$ kg m$^{-2}$ at enlistment, compared with 32.8 in men with BMI 18.5 to $<$20 kg m$^{-2}$ at enlistment. Obese men were markedly younger than lean men at the time of diagnosis: 39.3 years in men with BMI $\geq 35$ kg m$^{-2}$ at enlistment compared with 47.7 years in men with BMI 18.5 to $<$20 kg m$^{-2}$ at enlistment.

Cumulative incidence of VTE

As shown in the survival plot in Figure 1, the cumulative incidence of VTE after 40 years’ follow-up was 5.1% in men with BMI 30 to $<$35 kg m$^{-2}$ at enlistment and 8.4% in men with BMI $\geq 35$ kg m$^{-2}$ at enlistment, compared with 1.8% in men with BMI 18.5 to $<$20 kg m$^{-2}$. There was a gradual increase in cumulative incidence of VTE with increasing BMI, starting already at normal BMI levels ($P < 0.0001$). Survival plots for DVT and PE, respectively, are found in Figures S4 and S5.

Hazard ratios

After adjustment for age at conscription, centre of conscription, year of conscription, baseline conditions (congenital heart disease, hypertension and diabetes), baseline blood pressure, IQ, cardiorespiratory fitness and muscle strength, a BMI of 30 to $<$35 kg m$^{-2}$ was associated with a HR of 2.93 (95% CI, 2.65 to 3.24) for VTE. The corresponding HR for BMI $\geq 35$ kg m$^{-2}$ was 4.95 (95% CI, 4.16 to 5.90) for VTE compared with men with BMI 18.5 to $<$20 kg m$^{-2}$ (Table 3). For PE, the HR for BMI 30 to $<$35 kg m$^{-2}$ was 3.12 (95% CI, 2.68 to 3.64) and for $\geq 35$ kg m$^{-2}$ was 5.18 (95% CI, 3.97 to 6.77). Further adjustments affected the results only marginally (Table S2). In a separate analysis of PE and DVT, respectively, we excluded 1,250 men with PE and 1,782 men with DVT who died of cancer within 2 years of diagnosis or who had a lower extremity fracture within 3 months prior to the PE. This only affected the HRs marginally (Table 3).

A separate analysis of influence of individual covariates was made, please see Figure S6.
Table 2.  *Events, event rates and age at diagnosis by BMI group*

| Variable                        | All             | 15 ≤ BMI < 18.5 | 18.5 ≤ BMI < 20 | 20 ≤ BMI < 22.5 | 22.5 ≤ BMI < 25 | 25 ≤ BMI < 27.5 | 27.5 ≤ BMI < 30 | 30 ≤ BMI < 35 | 35 ≤ BMI < 60 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|----------------|----------------|
| Venous thromboembolism, VTE, total |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| Crude Events                    | 17 805 (1.09)   | 1309 (0.98)     | 2838 (0.96)     | 6668 (1.04)     | 3941 (1.13)     | 1560 (1.31)     | 624 (1.47)      | 498 (1.70)     | 167 (2.31)     |
| Event rate per 100 000 years (95% CI) | 39.4 (38.9–40.0) | 33.0 (31.2–34.8) | 32.8 (31.6–34.1) | 37.2 (36.3–38.1) | 42.8 (41.5–44.2) | 52.1 (49.5–54.7) | 60.4 (55.7–65.3) | 73.7 (67.4–80.5) | 112.1 (95.7–130.4) |
| Age at diagnosis, years (SD)    | 46.2 (10.3)     | 48.8 (10.0)     | 47.7 (10.2)     | 46.6 (10.2)     | 45.3 (10.3)     | 44.3 (10.2)     | 43.4 (10.5)     | 42.3 (10.6)    | 39.3 (11.1)    |
| Pulmonary Embolism, PE          |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| Crude Events                    | 7270 (0.44)     | 572 (0.43)      | 1192 (0.40)     | 2780 (0.42)     | 1546 (0.44)     | 630 (0.53)      | 256 (0.53)      | 221 (0.75)     | 73 (1.01)      |
| Event rate per 100 000 years (95% CI) | 16.1 (15.7–16.5) | 14.4 (13.3–15.6) | 13.8 (13.0–14.6) | 15.0 (14.5–15.6) | 16.8 (16.0–17.7) | 21.0 (19.4–22.7) | 24.8 (21.8–28.0) | 32.7 (28.5–37.3) | 49.0 (38.4–61.6) |
| Deep vein thrombosis, DVT       |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| Crude Events                    | 11395 (0.69)    | 789 (0.59)      | 1777 (0.66)     | 4427 (0.67)     | 2584 (0.74)     | 1003 (0.84)     | 404 (0.95)      | 311 (1.06)     | 100 (1.38)     |
| Event rate per 100 000 years (95% CI) | 25.2 (24.8–25.7) | 19.9 (18.5–21.3) | 20.6 (19.6–21.5) | 24.0 (23.3–24.7) | 28.1 (27.0–29.2) | 33.5 (31.5–35.6) | 39.1 (35.4–43.1) | 46.0 (41.1–51.5) | 67.1 (54.6–81.6) |
| PE excluding cancer death and fracture |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| Crude Events                    | 6020 (0.37)     | 444 (0.33)      | 995 (0.34)      | 2291 (0.35)     | 1294 (0.37)     | 525 (0.44)      | 220 (0.52)      | 190 (0.65)     | 61 (0.84)      |
| Event rate per 100 000 years (95% CI) | 13.8 (13.4–14.1) | 11.5 (10.5–12.7) | 11.9 (11.2–12.6) | 12.8 (12.3–13.3) | 14.5 (13.8–15.4) | 18.2 (16.7–19.8) | 22.1 (19.3–25.2) | 29.3 (25.3–33.7) | 42.6 (32.6–54.7) |
| DVT excluding cancer death and fracture |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| Crude Events                    | 9613 (0.59)     | 652 (0.49)      | 1481 (0.56)     | 3715 (0.56)     | 2202 (0.63)     | 876 (0.74)      | 338 (0.80)      | 266 (0.91)     | 83 (1.15)      |
| Event rate per 100 000 years (95% CI) | 22.0 (21.6–22.4) | 16.9 (15.7–18.3) | 17.7 (16.8–18.6) | 20.8 (20.1–21.4) | 24.8 (23.7–25.8) | 30.3 (28.3–32.4) | 34.0 (30.4–37.8) | 41.0 (36.2–46.2) | 57.9 (46.1–71.8) |

BMI, body mass index (kg m⁻²).
Discussion

In this large prospective cohort study, we found that compared with lean young men, young men with even mildly elevated body weight had a greater risk of VTE later in life, and severe obesity (BMI $\geq 35$ kg m$^{-2}$) was associated with a substantial overall VTE risk of 8.4% before the age of 65. These findings confirm the previously described relationship between obesity and VTE [5, 6, 14], and indicate that the risk increase may be larger than previously thought, especially for severely obese individuals, for which there is little information.

Although the risk reported in this study is high, the true risk may have been underestimated. VTE incidence rates increase markedly with age [28]. Most men in the highest BMI groups in our study enlisted during the last years of the inclusion period, reflected by their short follow-up time of 19 years (interquartile range, 13–27) for BMI $\geq 35$ kg m$^{-2}$, compared with 30 years (interquartile range, 22–39) for BMI 18.5 to <20 kg m$^{-2}$ (Table 1). The survival curve showed an exponential VTE risk increase with longer follow-up (Figure 1), which was not fully reflected in event numbers or even event rates for the highest BMI groups, as the event rates for obese individuals are based on fewer, and therefore healthier, years per individual than for lower BMI groups. However, the opposite is also possible. As the diagnostic tools and the accessibility to diagnostic measures have improved over the last decade, the increase in VTE in younger ages of the high BMI group may be due to better diagnostic possibilities [29]. It is also possible that individuals in the high BMI group have more contact with healthcare providers than lean individuals, as they develop metabolic diseases, and thereby might be examined for other diseases, such as VTE.

The event rate per year increased during follow-up, and especially amongst DVT patients after inclusion of outpatient diagnoses (Figures S2 and S3). This is to be expected, since the study population increased in age and since DVT patients had begun to be treated as outpatients before 2006.

Our results on obesity in young adulthood and later VTE risk are comparable to findings from the
Table 3. Hazard ratios and event rates for VTE, DVT and PE by BMI group. The total number of VTEs is 17 805 whereas the combined number of DVT + PE is 18 665. This is due to the 860 patients who were diagnosed with DVT and PE on the same date. PE and DVT are adjusted for cancer death within 2 years of VTE and lower extremity fracture within 3 months prior to VTE. Associations adjusted for groups of covariates called Model 1, 2 and 4. Additional adjustments, see Table S2

| Pulmonary Embolism, PE | Model 1 | Model 2 | Model 4 |
|------------------------|---------|---------|---------|
| (events/population)    | 7270/1 639 838 | 7187/1 556 318 | 7129/1 527 163 |
| 15 ≤ BMI < 18.5        | 1.00 (0.90–1.10) | 1.00 (0.91–1.11) | 1.00 (0.90–1.10) |
| 18.5 ≤ BMI < 20        | 1 (reference) | 1 (reference) | 1 (reference) |
| 20 ≤ BMI < 22.5        | 1.16 (1.08–1.24) | 1.17 (1.09–1.25) | 1.16 (1.08–1.24) |
| 22.5 ≤ BMI < 25        | 1.38 (1.28–1.49) | 1.42 (1.31–1.53) | 1.39 (1.28–1.51) |
| 25 ≤ BMI < 27.5        | 1.82 (1.65–2.00) | 1.87 (1.70–2.06) | 1.83 (1.65–2.02) |
| 27.5 ≤ BMI < 30        | 2.23 (1.95–2.55) | 2.28 (1.98–2.61) | 2.20 (1.91–2.53) |
| 30 ≤ BMI < 35          | 3.15 (2.72–3.64) | 3.29 (2.84–3.82) | 3.12 (2.68–3.64) |
| 35 ≤ BMI < 60          | 5.42 (4.27–6.87) | 5.57 (4.32–7.18) | 5.18 (3.97–6.77) |

| Deep Vein Thrombosis, DVT | Model 1 | Model 2 | Model 4 |
|---------------------------|---------|---------|---------|
| (events/population)       | 11 395/1 639 838 | 11 229/1 556 318 | 11 143/1 527 163 |
| 15 ≤ BMI < 18.5           | 0.94 (0.86–1.02) | 0.94 (0.86–1.02) | 0.95 (0.87–1.04) |
| 18.5 ≤ BMI < 20           | 1 (reference) | 1 (reference) | 1 (reference) |
| 20 ≤ BMI < 22.5           | 1.22 (1.15–1.29) | 1.24 (1.17–1.31) | 1.21 (1.15–1.29) |
| 22.5 ≤ BMI < 25           | 1.51 (1.42–1.60) | 1.55 (1.45–1.64) | 1.49 (1.40–1.59) |
| 25 ≤ BMI < 27.5           | 1.88 (1.74–2.03) | 1.95 (1.80–2.11) | 1.89 (1.74–2.05) |
| 27.5 ≤ BMI < 30           | 2.26 (2.03–2.52) | 2.39 (2.14–2.67) | 2.33 (2.09–2.61) |
| 30 ≤ BMI < 35             | 2.81 (2.49–3.17) | 2.96 (2.61–3.35) | 2.95 (2.60–3.36) |
| 35 ≤ BMI < 60             | 4.55 (3.72–5.58) | 4.96 (4.00–6.15) | 4.84 (3.87–6.06) |

| PE excluding cancer death and fracture | Model 1 | Model 2 | Model 4 |
|---------------------------------------|---------|---------|---------|
| (events/population)                   | 6020/1 639 838 | 5947/1 556 318 | 5899/1 527 163 |
| 15 ≤ BMI < 18.5                       | 0.93 (0.83–1.04) | 0.93 (0.83–1.04) | 0.93 (0.83–1.04) |
| 18.5 ≤ BMI < 20                       | 1 (reference) | 1 (reference) | 1 (reference) |
| 20 ≤ BMI < 22.5                       | 1.14 (1.06–1.23) | 1.15 (1.07–1.24) | 1.14 (1.05–1.23) |
| 22.5 ≤ BMI < 25                       | 1.38 (1.27–1.50) | 1.41 (1.30–1.54) | 1.39 (1.28–1.52) |
| 25 ≤ BMI < 27.5                       | 1.81 (1.63–2.01) | 1.86 (1.67–2.07) | 1.82 (1.63–2.04) |
| 27.5 ≤ BMI < 30                       | 2.29 (1.98–2.65) | 2.33 (2.01–2.71) | 2.27 (1.94–2.64) |
| 30 ≤ BMI < 35                         | 3.24 (2.77–3.79) | 3.38 (2.88–3.97) | 3.20 (2.71–3.78) |
| 35 ≤ BMI < 60                         | 5.35 (4.13–6.94) | 5.35 (4.04–7.10) | 5.12 (3.82–6.86) |

| DVT excluding cancer death and fracture | Model 1 | Model 2 | Model 4 |
|-----------------------------------------|---------|---------|---------|
| (events/population)                     | 9613/1 639 838 | 9467/1 556 318 | 9396/1 527 163 |
| 15 ≤ BMI < 18.5                         | 0.93 (0.85–1.02) | 0.93 (0.85–1.02) | 0.94 (0.86–1.04) |
| 18.5 ≤ BMI < 20                         | 1 (reference) | 1 (reference) | 1 (reference) |
| 20 ≤ BMI < 22.5                         | 1.23 (1.16–1.30) | 1.24 (1.17–1.32) | 1.22 (1.15–1.30) |
| 22.5 ≤ BMI < 25                         | 1.54 (1.45–1.65) | 1.58 (1.48–1.69) | 1.53 (1.42–1.64) |
| 25 ≤ BMI < 27.5                         | 1.97 (1.81–2.15) | 2.04 (1.88–2.23) | 2.00 (1.83–2.18) |
| 27.5 ≤ BMI < 30                         | 2.28 (2.03–2.57) | 2.41 (2.14–2.72) | 2.36 (2.08–2.67) |
smaller conscript registry study from Denmark [20]. It is difficult to compare our results to an earlier Israeli conscript study, as that study only included 70 fatal cases of PE, of which 3 occurred in the highest BMI group ($\geq 30 \text{ kg m}^{-2}$). The most severely obese population (BMI $\geq 35 \text{ kg m}^{-2}$) was not identified [21]. The results differ from studies by Sundbøll et al. [16] and Hagan et al. [19]. However, the latter study included only recall of somatotype and weight, not measures [19]. Sundbøll defined the high BMI group as individuals with a childhood BMI persistently over the 75th percentile [16]. Given the rarity of childhood overweight and obesity in Denmark at the time of the study,[17, 18] most children with BMI above the 75th percentile were actually of normal weight.

Compared with the results of previous reports on adult cohorts, our findings show a higher risk increase in obese individuals [5, 10, 14, 15, 30]. There are several potential explanations for this. One is that low weight in young adults is rarely the result of underlying diseases that increase the risk of VTE, such as cancer, whereas this is more common in older individuals. Another explanation is that in older adults, obesity may have caused diseases controlled for in the multivariate analyses and therefore led to underestimation or even oversight of the true risk. Additionally, many previous studies are limited in size, which affects the reliability of their risk estimates.

The relationship between obesity and VTE has been investigated in two Mendelian randomization studies to clarify if the observed associations between high BMI and VTE are causal or a result of confounding factors or reverse causation. Interestingly, both studies showed a significant association between genetically predisposed high BMI and VTE, indicating a causal relationship [11, 31].

The pathophysiological mechanism behind the increased VTE risk in obesity is unclear. Tilting of the hemostatic balance due to inflammatory substances from adipose tissue and venous stasis due to adiposity are two proposed explanations [30, 32, 33]. Importantly, earlier studies have shown that the increased risk of VTE mediated by obesity early in life can be reverted by weight reduction to normal weight [16, 19].

We explored the effects of exclusion of strongly provoked PE and DVT cases (cancer death within 2 years following the VTE or lower extremity fracture within 3 months prior to the VTE). The exclusions did not alter the results. Many other provoking factors have been identified that we could have included in our analysis, but

| Venous Thromboembolism | (events/population) | Model 1 | Model 2 | Model 4 |
|------------------------|---------------------|--------|--------|--------|
| $30 \leq \text{BMI} < 35$ | 17805/1 639 838 | 2.90 (2.55–3.31) | 3.06 (2.67–3.50) | 3.07 (2.67–3.53) |
| $35 \leq \text{BMI} < 60$ | 17563/1 556 318 | 4.52 (3.62–5.65) | 4.96 (3.92–6.28) | 4.88 (3.81–6.24) |

BMI, body mass index ($\text{kg m}^{-2}$).

Model 1: Adjusted for age at conscription, centre of conscription, year of conscription, baseline comorbidities hypertension, diabetes and congenital heart disease.

Model 2: Model 1 + blood pressure.

Model 4: Model 2 + IQ+ cardiorespiratory fitness + muscle strength.
differentiating the effect of obesity on provoked versus unprovoked VTE was not the main focus of the study.

Strengths and limitations

Strengths of this study include the large sample size, categorization of BMI using measured, not recalled, data and the coverage of our national registries.

Potential limitations of this study include the lack of external validation of the VTE diagnoses. The validity of VTE diagnoses has been questioned, in particular DVT diagnoses, outpatient diagnoses and recurrent VTE [16, 25–27]. We have sought to improve the validity of the VTE diagnoses by only including inpatient diagnoses before 2006 and by requiring prescription of anticoagulants in addition to VTE diagnoses after 2006. Another limitation is that the study lacks information on subsequent weight development after enlistment. However, overweight at a young age correlates strongly with overweight/obesity later in life; [34, 35] therefore, obesity (and severe obesity in youth) is a marker both of probable adult obesity and of high VTE risk. This may be reversible with weight loss, but this could not be determined in the present study. Another limitation is the inclusion only of men (of mainly European ancestry); whether the identified associations can be generalized to other ethnicities or to women is unknown. The number of previous VTE, stroke and fracture may have been underestimated. The Swedish national inpatient register has a gradual increase of coverage since 1964 with complete coverage from 1987 [36]. Therefore, some VTE events, strokes or fractures that occurred before 1987 might not have been registered. However, the incidence of VTE and stroke is quite low in the young, and this is unlikely to have had any major impact on the results. The Swedish cause of death registry is virtually complete since 1952 [37].

Conclusions

In this study, men who in young adulthood were overweight or obese showed a substantial risk increase for development of VTE later in life compared with lean men. The underlying mechanisms for this association remain to be elucidated. A clinical implication of our findings is that overweight and obesity in young adulthood is an important risk factor for later development of VTE later in life. Given the current global obesity epidemic [2], this will lead to great suffering and large costs for society. Action should be taken to reduce overweight and obesity early in life.

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Conflict of interest

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Contributor statement

AR conceived the idea for the study. All authors made important contributions to the design of the study. MA did the data management and analysis. KGS wrote the first draft of the manuscript. KGS and POH provided clinical input at all stages of the project. All authors were involved in the interpretation of the data, contributed in critical revision of the manuscript and approved the final draft. KGS had final responsibility for the submission of the article.

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

Figure S1. Reasons for exclusion from the study.
Figure S2. Included cases of pulmonary embolism.
Figure S3. Included cases of deep vein thrombosis.

Figure S4. Survival plot for PE related to BMI. Due to low numbers of remaining study persons in high BMI-groups, numbers are only reliable until 40 years follow up.

Figure S5. Survival plot for DVT related to BMI. Due to low numbers of remaining study persons in high BMI-groups, numbers are only reliable until 40 years follow up.

Figure S6. Hazard ratio for covariates included in our adjustment models.

Table S1. Anticoagulants for verification of VTE-diagnosis.
Table S2. Hazard ratios for DVT and PE by BMI group.