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Overweight in childhood and young adulthood increases the risk for adult thromboembolic events

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Background. Approximately one third of thromboembolic (TE) events are related to obesity, but to which extent elevated body mass index (BMI) during the distinct periods of childhood and puberty contributes is not known. We aimed to evaluate the impact of high BMI during childhood and puberty for the risk of adult venous and arterial thromboembolic events (VTE, ATE, respectively) in men.

Methods. We included 37,672 men from the BMI Epidemiology Study (BEST) Gothenburg with data on weight and height in childhood, young adult age, and on pubertal BMI change. Information on outcomes (VTE [$n = 1683$], ATE [$n = 144$], or any first TE event [VTE or ATE; $n = 1780$]) was retrieved from Swedish national registers. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated by Cox regressions.

Results. Both BMI at 8 years of age and the pubertal BMI change were associated with VTE, independently of each other (BMI at 8: HR 1.06 per standard deviation [SD] increase, 95% CI, 1.01;1.11; pubertal BMI change: HR 1.11 per SD increase, 95% CI, 1.06;1.16). Individuals with normal weight during childhood followed by young adult overweight (HR 1.40, 95% CI, 1.15;1.72), and individuals with overweight at both childhood and young adult age (HR 1.48, 95% CI, 1.14;1.92), had a significantly increased risk of VTE in adult life, compared with the normal weight reference group. Individuals with overweight in childhood and in young adult age had increased risk of ATE and TE.

Conclusion. Young adult overweight was a strong determinant, and childhood overweight a moderate determinant, of the risk of VTE in adult men.

Keywords: childhood BMI, cohort study, pubertal BMI change, thromboembolism, young adult BMI

Introduction

Thromboembolic (TE) disorders account for one in four deaths worldwide [1] and are a major contributor to disability-adjusted life years lost in young and middle-aged adults [2]. A recent study found that one third of incident idiopathic venous thromboembolic (VTE) events are attributable to obesity [3].

Arterial thromboembolism (ATE) and VTE have traditionally been seen as distinct conditions separated from each other with different pathology, risk factors, and treatment. However, thrombosis is the common underlying event of myocardial infarction, ischemic stroke, ATE, and VTE. Excessive weight in adulthood is an established risk factor for some of the major conditions underpinning thrombosis, such as arterial hypertension, peripheral artery disease, coronary artery disease, as well as pulmonary embolism and deep venous thrombosis

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[4]. An increased risk of VTE has been observed in adults who had high body mass index (BMI) during childhood [5] or late adolescence [6], and we and others have demonstrated an increased risk of adult cardiovascular mortality and stroke in individuals with excessive BMI increase during puberty, but not in childhood [7].

Elevated BMI in childhood, adolescence, and adulthood is a global challenge, and the rise in the prevalence of obesity has been shown to be steeper among children and youths than in adults [8]. Extended follow-up and large statistical power are needed to evaluate the consequences of overweight and obesity during childhood and adolescence, and such studies have therefore been difficult to perform. In addition, the importance of the timing of overweight or obesity during development, and the relative contribution of high BMI during childhood and puberty, are not known.

In the present study, we hypothesized that excessive weight in childhood and/or adolescence, and pubertal weight gain may affect the risk for TE events (i.e., any first VTE or ATE event) in adult life. We used the population-based BMI Epidemiology Study (BEST) Gothenburg with information on BMI at 8 and 20 years and the pubertal BMI change and aimed to evaluate the association between overweight during childhood, puberty, and young adult age for the risk of adult VTE, ATE, and TE, among men.

Methods

Study population and data collection

The population-based BEST Gothenburg cohort was initiated with the overall aim to study the impact of BMI during childhood and puberty on adult diseases, as previously described [7]. To this end, we collected data on birthweight and developmental height and weight from school healthcare records for all men born 1945–1961 in Gothenburg, Sweden. During this period, school was mandatory from 7 years of age, and the school healthcare included >98.5% of all children in the municipality from calendar year 1952 (corresponding to birth year 1945) [9]. We also retrieved height and weight at young adult age from military conscription tests, mandatory until 2010 for all Swedish men, for the individuals in the cohort. Eligible individuals were those with a school health record in the regional central archive and a 10-digit PIN. Individuals with data available for childhood BMI and young adult BMI were included in this study (n = 37,672). We followed the men in the study from 20 years of age until censoring due to TE, death, migration, or until December 31, 2019 (Fig. S1). This study was approved by the ethics committee of the University of Gothenburg, Sweden (DNR 013-10, with several amendments). Informed consent was not required.

Exposures

Childhood BMI and young adult BMI were calculated using all paired height and weight measurements between 6.5 and 9.5 years of age for childhood BMI, and between 17.5 and 22.0 years of age for young adult BMI. Both BMI variables were age-adjusted using linear regression models to age 8 years for childhood BMI and 20 years for young adult BMI, as previously described [7]. The follow-up started at 20 years of age. Thus, the age-adjusted young adult BMI and start of follow-up was at the same time. Overweight and obesity at young adult age were defined as BMI $\geq$ 25 kg/m^2 and BMI $\geq$ 30 kg/m^2, respectively. Childhood normal weight and overweight were defined according to the cut-offs from the US Centers for Disease Control and Prevention. For individuals with information on height between 21 and 50 years of age in the Passport register (available for 79.9% of the study cohort), we used the mean of available heights for each individual to calculate adult height. For individuals with no information on height after 21 years of age in the Passport register (20.1%), we used height measurements from the School Health Care and/or the Conscription register. Height measurements in the age interval of 17.5–22 years were age-adjusted to 21 years of age. For individuals with several measurements in the interval, the mean of their age-adjusted heights was used.

Linkage with registers

In Sweden, a personal identity number (PIN) is assigned to every citizen at birth or immigration. Using the individuals' PIN, the BEST cohort was linked with the Longitudinal Integration Database for Health Insurance and Labour Market Studies at Statistics Sweden, and country of birth for every study participant and their parents were retrieved. From the same register, the study participants' highest education level was retrieved and categorized as low (= elementary school), middle (= secondary education), or high (= post-secondary education). Linkage to registers held

by the National Board of Health and Welfare was performed to retrieve information on outcomes. Dates for the first appearance of a diagnosis of TE disease was retrieved from high-quality national Swedish registers; the National Patient Register and the Cause of Death register. The National Patient register, including information on diagnoses from inpatient care, was initiated 1964 with full coverage in the Gothenburg region from 1972. The Cause of Death register holds information on causes of deaths since 1961, covering the entire follow-up period of this study [10].

Outcomes

TEs were defined as hospital-based care or death with a code corresponding to this diagnosis (Table S1) according to the International Classification of Diseases system. Individuals who had received a diagnosis of TE in any coding position or had died or emigrated before age 20 were excluded from the analyses. Provoked VTE was defined as cancer death within 2 years after the VTE or lower extremity fracture within 3 months prior to the VTE (Table S1).

Statistical analyses

There were no missing values for the main variables in the included cohort (childhood BMI, young adult BMI, birth year, or outcomes).

We used Cox proportional hazards regression (with follow-up in years starting from age 20) to estimate hazard ratios for the association between exposures and events, with all analyses adjusted for birth year and country of birth. Possible nonlinear associations were evaluated by the inclusion of a quadratic term in the model. The assumption of proportionality in the Cox regression models was fulfilled as assessed both through visual evaluations of Schoenfeld residual plots, and through proportional hazard tests using the 'survival' package in the R statistical software [11]. Possible interactions were evaluated by an addition of an interaction term (the variables of interest multiplied with each other) in the linear Cox regression models, and $p < 0.05$ for an interaction term was interpreted as a statistically significant interaction.

The population attributable fraction (PAF) was estimated using the hazard ratio (HR) for VTE in individuals with overweight in childhood and in young adulthood, respectively. The PAF was calculated using the formula $\text{PAF} = p_e(1 - 1/\text{HR})$, where p_e is the prevalence of exposure to overweight among cases of VTE [12].

We performed sensitivity analyses to account for birthweight, socioeconomic status, and young adult height. We also analyzed the association between childhood BMI and pubertal BMI change and the risk of VTE, ATE and TE in a subpopulation of individuals born in Sweden and with parents born in Sweden.

Kaplan–Meier plots and cumulative incidence plots were performed in R (version 4.2.0) using the 'survival' package [11]. For all other statistical analyses, SPSS version 28, was used (Fig. S2).

Results

Study population and event rates

In this population-based study, men born between 1945 and 1961 with information on childhood BMI at 8 years, young adult BMI at age 20 years, and the pubertal BMI change (BMI at 20 years – BMI at 8 years) were followed until December 31, 2019 ($n = 37{,}672$). Mean follow-up until first VTE event, starting from 20 years of age, was 42.4 years (standard deviation [SD] 10.2 years) with a total of 1597,000 person-years of follow-up. There were 1683 cases of VTE, 144 cases of ATE, and 1780 cases of any first TE event (VTE or ATE together) (Table 1).

Association between BMI during development and risk of thromboembolism

In Cox proportional hazards models adjusted for birth year and country of birth, a linear association was seen for the pubertal BMI change (HR 1.12 per SD increase, 95% confidence interval [CI], 1.06;1.17), and for childhood BMI at 8 years (HR 1.06 per SD increase, 95% CI, 1.02;1.12), with the risk of adult VTE. Similar results were seen in a combined analysis when childhood BMI and pubertal BMI change were included in the same model (Table 2). Inclusion of a quadratic term did not indicate any nonlinear association between childhood BMI and pubertal BMI change ($p > 0.05$ for both pubertal BMI^2 and childhood BMI^2, respectively) and the risk of VTE. No statistically significant interaction between childhood BMI and pubertal BMI change was seen for the association with risk of VTE (childhood BMI × pubertal BMI change, $p = 0.35$). We did not detect any violations of the assumption of proportional hazards

Table 1. *Cohort description.*

Exposures and outcomes	Mean (SD)	Median (IQR)
Birthweight (kg)	3.6 (0.6)	3.6 (3.3–3.9)
Childhood BMI (kg/m^2)	15.7 (1.4)	15.6 (14.8–16.4)
Pubertal BMI change (kg/m^2)	5.6 (2.0)	5.4 (4.3–6.7)
Young adult BMI at age 20 years (kg/m^2)	21.4 (2.5)	21.1 (19.7–22.6)
	***N* (%)**	
Country of birth		
Sweden	31,407 (83.4)	
Other	6265 (16.6)	
Overweight		
Childhood	2,358 (6.3)	
Young adulthood	2,790 (7.4)	
Obesity		
Childhood	504 (1.3)	
Young adulthood	328 (0.9)	
TE	1780 (4.7)	
ATE	144 (0.4)	
VTE	1683 (4.5)	
PE	642 (1.7)	
DVT	1041 (2.8)	
Unprovoked VTE	1431 (3.8)	

Note: 37,672 Swedish men followed for a mean of 42.4 (10.2) years after age 20 years. Unprovoked events: exclusion of individuals who had a provoked VTE (i.e., died of cancer within 2 years of VTE or had a lower extremity fracture within 3 months prior to the VTE).
Abbreviations: ATE, arterial thromboembolism; BMI, body mass index; DVT, deep venous thrombosis; IQR, interquartile range; PE, pulmonary emboli; SD, standard deviation; TE, thromboembolism; VTE, venous thromboembolism.

Table 2. *Adjusted hazard ratios (HRs) for venous thromboembolism (VTE), arterial thromboembolism (ATE), thromboembolism (TE), and unprovoked VTE in relation to childhood body mass index (BMI) and pubertal BMI change in separate and combined analyses among 37,672 Swedish men followed for a mean of 42.4 (10.2) years after age 20 years.*

	Separate analyses		Combined analyses	
	Childhood BMI HR (95% CI) per SD increase	Pubertal BMI change HR (95% CI) per SD increase	Childhood BMI HR (95% CI) per SD increase	Pubertal BMI change HR (95% CI) per SD increase
VTE	1.06 (1.02;1.12)	1.12 (1.06;1.17)	1.06 (1.01;1.11)	1.11 (1.06;1.16)
ATE	1.17 (1.01;1.37)	1.12 (0.96;1.31)	1.17 (1.00;1.36)	1.11 (0.95;1.29)
TE	1.07 (1.02;1.12)	1.11 (1.06;1.16)	1.06 (1.01;1.11)	1.10 (1.05;1.15)
Unprovoked VTE	1.06 (1.01;1.12)	1.11 (1.06;1.17)	1.05 (1.00;1.11)	1.11 (1.06;1.17)

Note: HRs with 95% CI were calculated using Cox proportional hazards regression, including birth year and country of birth as covariates. Unprovoked VTE defined as VTE with the exclusion of men with PE or DVT who died in cancer within 2 years of VTE diagnosis, or who had a lower extremity fracture within 3 months prior to the VTE.
Abbreviations: CI, confidence interval, SD, standard deviation.

for the association between childhood BMI and the pubertal BMI change, and the risk of VTE.

Next, we investigated the association between developmental BMI and the risk of *unprovoked* VTE through the exclusion of men with VTE who died of cancer within 2 years of the VTE diagnosis, or who had a lower extremity fracture within 3 months prior to the VTE. In combined analyses, including both the pubertal BMI change and childhood BMI at 8 years, we found a significant direct association for BMI change during puberty (HR 1.11 per SD increase, 95% CI, 1.06;1.17) and the risk of unprovoked VTE in adulthood, but for childhood BMI, the analysis fell just short of significance (Table 2). In addition, young adult BMI, the sum of childhood BMI, and the pubertal BMI change was significantly associated with VTE (HR 1.12 per SD increase, 95% CI, 1.07;1.18).

In less-powered analyses of the risk of ATE ($n = 144$), we found that childhood BMI at 8 years of age, but not the pubertal BMI change, was significantly associated with the risk of ATE in a combined model, including both childhood BMI and the pubertal BMI change (HR 1.17 per SD increase, 95% CI, 1.00;1.36; Table 2).

In analyses evaluating the risk of TE, defined as the first event of either VTE or ATE, a significant association was seen for both childhood BMI and the pubertal BMI change in separate as well as combined analyses (Table 2).

Risk of thromboembolism in relation to overweight status at childhood and young adult age

To evaluate the impact of overweight status in childhood and young adult age for the risk of adult VTE, ATE and TE, we categorized the study subjects into four groups depending on their overweight status at 8 years (childhood) and at 20 years (young adult age). We used the group with normal weight at both childhood and young adult age as the reference group and compared the three other groups (with different combinations of overweight status in childhood and young adult age) with the reference group. Individuals with normal weight during childhood followed by young adult overweight (HR 1.40, 95% CI, 1.15;1.72), and individuals with overweight at both childhood and young adult age (HR 1.48, 95% CI, 1.14;1.92), had a clearly increased risk of VTE in adult life, compared with the normal weight reference group. For individuals with overweight in childhood and normal weight in young adulthood, the association did not reach statistical significance (Table 3). Kaplan-Meier plots confirmed these findings (Fig S2). Thus, young adult overweight was robustly associated with increased risk of adult VTE, compared with the normal weight reference group.

Next, in less-powered analyses we evaluated the risk for ATE related to developmental overweight status. There was a pronounced excess risk for individuals who were overweight throughout childhood and young adult age (HR 3.45, 95% CI, 1.86;6.40), whereas normal weight at 8 years followed by overweight at 20 years, and overweight at 8 years, and normal weight at 20 years were not associated with a significantly increased risk, compared with the reference group (Table 4).

Men with overweight throughout childhood and young adult age had a clearly increased risk of any TE event, as did individuals who developed overweight during puberty (i.e., normal weight at 8 years and overweight at 20 years), compared with the reference group (Table 5). Subjects with overweight during childhood that normalized during puberty had a remaining significant increase in risk of TE, compared with the reference group.

We also estimated PAF and found that of the VTE cases, 1.3% were attributable to overweight in childhood and 1.7% to overweight in young adulthood.

Additional adjustments and sensitivity analyses

We adjusted the association between overweight status during development and the risk for VTE in adult age for the individuals' adult height. This did not substantially change the results (Table S2). We then included birthweight in the model investigating associations between overweight status at childhood and at young adult age and the risk of adult VTE, ATE, and TE. The observed associations were consistent (Tables S3–S5).

Inclusion of socioeconomic status in the model ($n = 36,572$) did not alter the described associations for overweight status at childhood and at young adult age with the risk of adult VTE, ATE, and TE (Tables S6–S8).

Finally, we analyzed the association between childhood BMI and pubertal BMI change and the

Table 3. *Adjusted hazard ratios (HRs) for venous thromboembolism (VTE) in relation to childhood and young adult weight status among 37,672 Swedish men followed for a mean of 42.4 (10.2) years after age 20 years.*

	Childhood normal weight	Childhood overweight
Young adult normal weight	Reference	1.25 (0.99;1.58)
Young adult overweight	1.40 (1.15;1.72)	1.48 (1.14;1.92)

Note: HRs with 95% confidence intervals (CI) were calculated using Cox proportional hazards regression. All analyses are adjusted for birth year and country of birth. Young adult normal weight was categorized as BMI below 25 kg/m^2, young adult overweight was categorized as BMI above 25 kg/m^2, childhood normal weight and overweight was defined according to the US Centers for Disease Control and Prevention (CDC) cut-off for boys at 8 years of age. Childhood normal weight, young adult normal weight (= reference group) $n = 33{,}514$, cases $n = 1451$; childhood normal weight, young adult overweight $n = 1800$, cases $n = 101$; childhood overweight, young adult normal weight $n = 1368$, cases = 72; childhood overweight, young adult overweight $n = 990$, cases $n = 59$.

Table 4. *Adjusted hazard ratios (HRs) for arterial thromboembolism (ATE) in relation to childhood and young adult weight status among 37,672 Swedish men followed for a mean of 42.1 (10.2) years after age 20 years.*

	Childhood normal weight	Childhood overweight
Young adult normal weight	Reference	1.74 (0.85;3.55)
Young adult overweight	1.56 (0.79;3.08)	3.45 (1.86;6.40)

Note: HRs with 95% confidence intervals (CI) were calculated using Cox proportional hazards regression. All analyses are adjusted for birth year and country of birth. Young adult normal weight was categorized as BMI below 25 kg/m^2, young adult overweight was categorized as BMI above 25 kg/m^2, childhood normal weight and overweight was defined according to the US Centers for Disease Control and Prevention (CDC) cutoff for boys 8 years of age. Childhood normal weight, young adult normal weight (= reference group) $n = 33{,}514$ cases $n = 116$; childhood normal weight, young adult overweight $n = 1800$, cases $n = 9$; childhood overweight, young adult normal weight $n = 1368$, cases = 8; childhood overweight, young adult overweight $n = 990$, cases $n = 11$.

risk of VTE, ATE, and TE in a subpopulation of individuals born in Sweden and with parents born in Sweden ($n = 31{,}407$). The observed associations were mainly unchanged (Tables S9–S11).

Discussion

Excessive weight is a clear risk factor of TE, and obesity is estimated to account for one third of incident VTE [3]. The relative contribution of a high BMI during childhood and puberty is not known, but given the obesity epidemic among children as well as adults, it is a priority to investigate if overweight and obesity in childhood and puberty associate with the risk of thromboembolism. In this population-based cohort, including 37,672 men, the pubertal BMI change was significantly associated with an increased risk of both VTE and unprovoked VTE. Moreover, overweight at young adult age, or at both childhood and young adult age, was strongly associated with an increased risk of adult VTE, compared with individuals with

Table 5. *Adjusted hazard ratios (HRs) for thromboembolism (TE) in relation to childhood and young adult weight status among 37,672 Swedish men followed for a mean of 42.4 (10.2) years after age 20 years.*

	Childhood normal weight	Childhood overweight
Young adult normal weight	Reference	1.30 (1.04;1.63)
Young adult overweight	1.40 (1.15;1.70)	1.55 (1.21;1.99)

Note: HRs with 95% confidence intervals (CI) were calculated using Cox proportional hazards regression. All analyses are adjusted for birth year and country of birth. Young adult normal weight was categorized as BMI below 25 kg/m^2, young adult overweight was categorized as BMI above 25 kg/m^2, childhood normal weight and overweight according to the US Centers for Disease Control and Prevention (CDC) cutoff for boys 8 years of age. Childhood normal weight, young adult normal weight (= reference group) $n = 33{,}514$, cases $n = 1530$; childhood normal weight, young adult overweight $n = 1800$, cases $n = 106$; childhood overweight, young adult normal weight $n = 1368$, cases = 79; childhood overweight, young adult overweight $n = 990$, cases $n = 65$.

normal weight. Men with overweight at any or both time points during development had a significantly increased risk of TE, compared with the reference group. In addition, in less-powered analyses, we observed that individuals with overweight throughout childhood and puberty had a statistically significant increased risk of ATE, compared with the reference group. Thus, a high BMI during puberty is robustly, and high childhood BMI is modestly, associated with the risk of adult VTE and TE in men.

The ongoing obesity epidemic has led to secular changes in BMI during development that may have altered the risk panorama for CVD. With the persistent prevalence of TE and VTE [3], the identification of new risk factors remains a priority. Previous studies have shown that overweight and obesity both in childhood and in young adulthood increase the risk for VTE [5, 6] later in life. Recently, a Danish study examined the association between a high BMI in childhood and subsequent risk of VTE in adulthood and reported that individuals with a high BMI, defined as over the 75 percentile, during childhood (7 years) and early adolescence (13 years) had an increased risk for VTE in adulthood. The study also reported that this excess risk was reversed if overweight at 7 years was followed by normal weight at 13. These findings are in-line with our results. The limitations with the Danish study include that BMI measurements at young adulthood were not available, and the study could therefore not evaluate the association between the pubertal BMI change and the risk of VTE. Moreover, given the profound effect of puberty on body composition, and that some individuals will have completed puberty at the age of 13 while others are still in the pre-pubertal phase, BMI at the age of 13 is an uncertain marker of adiposity without information on pubertal stage. A Swedish study using BMI from the conscription examination evaluated the association between BMI in young adulthood and the risk for subsequent VTE. The results indicate that obesity at young adult age increased the risk for VTE almost threefold [6], but because the study only included one BMI measurement in young adult age, it was not possible to evaluate the relative contribution of BMI during childhood and puberty. In an American study by Hagan et al., self-reported weight status in childhood and young adult age, recalled in mid-life using somatotypes (silhouettes picturing different BMI levels), was not associated with the risk of adult VTE [13]. The relative contribution of a high BMI during childhood and puberty to the risk of VTE is therefore not known. Importantly, childhood BMI and BMI during puberty correlate only marginally and thus have the potential to contribute nonoverlapping information as risk markers for adult disease [7]. In the present study, we demonstrate that the pubertal BMI change is robustly, and childhood BMI moderately, associated with the risk of VTE in adult age. Overweight throughout childhood and puberty, and overweight at young adult age (with onset during puberty) are associated with an increased risk of VTE and with TE in adult men. In less-powered analyses, we also observed that overweight throughout childhood and puberty was significantly associated with the risk for ATE later in life.

Several possible mechanisms may explain the pathophysiology behind the link between excessive weight and the increased TE risk. Data on BMI are readily available and therefore the most widely used measure to define overweight and obesity, although waist circumference provides additional information with respect to fat distribution, which is of importance for morbidity and mortality. Central obesity is linked to the metabolic syndrome that also includes dysglycemia, elevated blood pressure, and dyslipidemia. Individuals with overweight or obesity also have higher levels of white blood cells and platelets and may have elevated acute-phase proteins, indicating low-grade systemic inflammation leading to alterations in the coagulation system with elevated plasma concentrations of clotting factors and impaired fibrinolytic activity. This, in turn, may lead to hypercoagulability and thrombus formation [14, 15]. Furthermore, obesity in childhood and in young adulthood is associated with obesity later in adulthood [16]. Excessive fat mass already, during development, therefore gives long exposure to low-grade inflammation, induced by obesity, which may affect the hemostatic balance and lead to peripheral arterial disease [17]. Venous stasis due to adiposity is another proposed explanation. Previous studies have shown that weight reduction can reverse the risk of developing thromboembolism [5, 18]. Our results indicate that increased BMI during puberty and in young adult age was associated with an elevated risk for VTE. Moreover, in sub-analyses we evaluated the association between developmental overweight and VTE after the 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). We found that

pubertal BMI change, but not childhood BMI, was significantly associated with an increased risk for unprovoked VTE. The components of the metabolic syndrome and its association with VTE is uncertain except for abdominal adiposity, which is a strong risk factor for VTE [19]. We have previously demonstrated that excessive BMI increase during puberty is associated with an increased amount of the metabolically harmful visceral fat [20], supporting a role of abdominal adiposity in the association between pubertal BMI change and VTE. There is also evidence of associations between high BMI during development and adult hypertension [21] and type 2 diabetes [22].

There is a clear association between BMI and peripheral arterial disease, CVD, and stroke (conditions affecting arteries) in adults in observational studies [7, 23, 24] and a causal association is indicated in a recent Mendelian randomization study [4]. The association between a high BMI in childhood and puberty and the risk of ATE later in life has not been examined before. We, herein, demonstrate an association between childhood BMI and ATE, indicating that overweight throughout childhood and puberty is associated with an increased risk of ATE. As the number of ATE cases in the present study is limited, further studies are required.

The strengths with the present study include the well-powered, population-based cohort with information on directly measured developmental and young adult BMI and the near complete follow-up in high-quality Swedish registers. The main limitation is that we only have data on men, as the effects of cardiovascular risk factors may differ between men and women. Further limitations with the present study are that the included individuals are mainly of European ancestry. The generalizability to other ethnicities and to women might therefore be limited. In addition, data on waist circumference were not available. Also, we were not able to control for other important risk factors such as smoking, diabetes, immobilization, physical activity, BMI in middle age, biomarkers or comorbidities during childhood and adolescence.

In conclusion, young adult overweight was a strong determinant, and childhood overweight a moderate determinant, of the risk of VTE in adult men. We evaluated the relative contribution of BMI during the physiologically distinct periods of childhood and puberty for the risk of VTE, ATE, and TE and found that the pubertal BMI change is strongly, and BMI in childhood moderately, associated with the risk of VTE in adult men. Thus, the ongoing childhood obesity epidemic may add to the burden of adult disease through the association with thromboembolism.

Author contributions

Conceptualization-equal; data curation-equal; formal analysis-equal; funding acquisition-equal; investigation-equal; methodology-equal; project administration-equal; validation-equal; visualization-equal; writing—original draft-lead; writing—review and editing-equal: Lina Lilja. *Conceptualization-equal; data curation-equal; formal analysis-supporting; investigation-supporting; methodology-supporting; project administration-supporting; supervision-supporting; writing—review and editing-equal*: Maria Bygdell. *Data curation-equal; formal analysis-equal; software-equal; writing—review and editing-supporting*: Jari Martikainen. *Conceptualization-supporting; formal analysis-supporting; methodology-supporting; writing—review and editing-equal*: Annika Rosengren. *Conceptualization-lead; data curation-equal; formal analysis-equal; funding acquisition-equal; investigation-equal; methodology-equal; project administration-equal; resources-equal; software-equal; supervision-lead; validation-supporting; writing—original draft-supporting; writing—review and editing-lead*: Jenny M. Kindblom. *Conceptualization-lead; data curation-equal; formal analysis-equal; funding acquisition-equal; investigation-equal; methodology-equal; resources-lead; software-supporting; supervision-supporting; validation-equal; writing—review and editing-lead*: Claes Ohlsson.

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Conflict of interest statement

The authors have no conflict of interests.

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