# Gestational Age and Risk of Venous Thromboembolism From Birth Through Young Adulthood

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**KEY WORDS**

preterm birth, venous thromboembolism, venous thrombosis, pulmonary embolism, epidemiology

**ABBREVIATIONS**

aHR—adjusted hazard ratio
CI—confidence intervals
DVT—deep venous thrombosis
HR—hazard ratio
ICD—*International Classification of Diseases*
OVTE—other specific types of venous thromboembolism
PE—pulmonary embolism
VTE—venous thromboembolism

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**WHAT'S KNOWN ON THIS SUBJECT:** Preterm birth has been associated with increased risk of venous thromboembolism (VTE) in infancy, but the longer-term risk is unknown.

**WHAT THIS STUDY ADDS:** In a large national cohort, low gestational age at birth was associated with increased risk of VTE in infancy, early childhood, and young adulthood. These findings call for better awareness of the long-term risk of VTE among preterm birth survivors.

## abstract

**BACKGROUND:** Preterm birth has been associated with increased risk of venous thromboembolism (VTE) in infancy, but the longer-term risk is unknown. Our aim was to examine this association from birth through young adulthood.

**METHODS:** National cohort study of 3 571 574 individuals who were live-born in Sweden from 1973 through 2008, including 206 844 born preterm (gestational age <37 weeks), and followed up to 2010 (ages 0–38 years). The main outcome was VTE.

**RESULTS:** A total of 7 519 (0.2%) individuals were diagnosed with VTE in 70.8 million person-years of follow-up. Low gestational age at birth was associated with VTE in infancy (ages <1 year: adjusted hazard ratio 47.16 [95% confidence interval 21.30–104.42] for 22 to 27 weeks, 5.54 [2.53–12.12] for 28 to 33 weeks, 3.54 [2.07–6.06] for 34 to 36 weeks, 1.00 for 37 to 41 weeks [reference]), early childhood (ages 1–5 years), and young adulthood (ages 18–38 years: adjusted hazard ratio 2.76 [1.43–5.31] for 22 to 27 weeks, 1.53 [1.24–1.89] for 28 to 33 weeks, 1.24 [1.10–1.40] for 34 to 36 weeks, and 1.00 for 37 to 41 weeks [reference]), but not in late childhood (ages 6–12 years). Very preterm (<34 weeks) but not late preterm birth (34–36 weeks) was also associated with VTE in adolescence (ages 13–17 years). After further adjustment for comorbidities, these associations were attenuated, but most remained significantly elevated.

**CONCLUSIONS:** In this large national cohort, low gestational age at birth was associated with increased risk of VTE in infancy, early childhood, and young adulthood. *Pediatrics* 2014;134:e473–e480

Preterm birth, defined as birth that occurs before 37 completed weeks of gestation, is a leading cause of morbidity and mortality in developed countries.[1] The prevalence of preterm birth has increased over the past 3 decades and is currently 12% in the United States and 5% to 9% in many other developed countries.[1] Survival of preterm infants has improved dramatically due to advances in neonatal care.[2] A large numbers of individuals who were born preterm are now surviving to adulthood. Although the early effects of preterm birth are well documented, less is known about the long-term outcomes in adulthood.[3,4] A comprehensive understanding of these outcomes is needed to enable earlier prevention, detection, and treatment of the long-term health sequelae.[3,4]

Venous thromboembolism (VTE) is a major medical health problem that affects ~1 per 1 000 individuals per year.[5] Like many common human diseases, VTE is considered to be a complex disorder influenced by several genetic and environmental factors.[5] Inherited deficiencies of the natural anticoagulant inhibitors antithrombin, protein C, and protein S, as well as activated protein C resistance (APC resistance) due to the FV Leiden variant (rs6025) and the prothrombin 20210A variant (rs1799963), have been associated with familial thrombophilia.[5] Acquired risk factors for thrombosis include age, immobilization, surgery, trauma, pregnancy, puerperium, lupus anticoagulant, malignant disease, and female hormones.[5] In childhood, VTE is a rare but severe disease with an incidence of 0.7 per 100 000 aged 1 month to 18 years in Canadian registry data.[6] VTE incidence among US children, calculated from the National Hospital Discharge Survey (1979–2001), is 4.9 per 100 000 children per year.[7] Two US studies reported an increasing incidence of VTE among children.[8,9] Increases in venous catheter procedures were associated with and may have contributed to the observed trends.[9] The highest incidence of childhood thrombosis is in the neonatal period, followed by another peak in adolescence.[6–8,10,11] In children, VTE more often involves venous sites other than the lower limbs, such as upper limb, renal, cerebral, and splanchnic veins. It has been reported to be more common among boys in infancy[12] and among girls in adolescence.[7,12] Several acquired and/or genetic risk factors are usually present simultaneously.[6,8,10] Patients in NICUs and PICUs and oncology patients are at increased risk, and the presence of central venous catheter is an important causal factor.[10,11] An increased risk of VTE in preterm infants has also been previously suggested.[13] However, the risk for VTE associated with preterm birth beyond infancy and into adulthood has not been determined.

We conducted a national cohort study in Sweden to examine the association among gestational age at birth, independent of fetal growth, and VTE. A national cohort of infants born from 1973 through 2008 was followed up until 2010 for VET. We hypothesized that low gestational age at birth would be independently associated with an increased risk of VTE.

## METHODS

### Study Population

We identified 3 595 055 individuals in the Swedish Birth Registry who were live-born from 1973 through 2008. We excluded 8113 (0.2%) persons who had missing information for gestational age at birth, and 10 029 (0.3%) others who had missing information for birth weight. To remove possible coding errors, we also excluded 5339 (0.1%) who had a reported birth weight >4 SD above or below the mean birth weight for gestational age and gender based on a Swedish reference growth curve[14]; 3 571 574 individuals (99.3% of the original cohort) remained for inclusion in the study. This study was approved by the Regional Ethics Committee of Lund University in Sweden.

### VET Ascertainment

The study cohort was followed for the earliest incidence of VTE from birth through December 31, 2010 (maximum attained age was 38 years). VTE was identified by using primary and secondary diagnosis codes from the *International Classification of Diseases, Seventh, Eighth, Ninth,* and *10th* Revisions (*ICD-7*, *-8*, *-9*, and *-10*) in the Swedish Hospital Registry and Outpatient Registry. The Swedish Hospital Registry contains all primary and secondary hospital discharge diagnoses for 6 populous counties in southern Sweden starting in 1964 and with nationwide coverage since 1987; the registry has contained all outpatient diagnoses nationwide starting in 2001. Specifically, VTE included pulmonary embolism (PE, codes 465 in *ICD-7*; 450 in *ICD-8*; 415B and 416W in *ICD-9*; I26 in *ICD-10*), deep vein thrombosis (DVT, codes 463 in *ICD-7*; 451 in *ICD-8*; 451 [excluding 451A, ie, superficial thrombophlebitis] in *ICD-9*; I80 [excluding I800, ie, superficial thrombophlebitis] in *ICD-10*), and other specific types of VTE (OVTE, codes 334.40, 334.50, 464, 466 [excluding 466.10, ie, migrating superficial thrombophlebitis], 583.00 in *ICD-7*; 321, 452, 453 [excluding 453.00, ie, migrating superficial thrombophlebitis] in *ICD-8*; 437G, 452, 453 [excluding 453B, ie, migrating superficial thrombophlebitis] in *ICD-9*; I63.6, I67.6, I81, I82 in *ICD-10*). Pregnancy- or abortion-related VTE events were not included in these outcomes. PE, DVT, and OVTE were also examined separately in secondary analyses. The validity in the Hospital Discharge Register is generally 85% to 95%.[15] The validity of VTE diagnosis has

been reported to be 95%,[16] which is similar to other cardiovascular disorders such as myocardial infarction and stroke.[15]

### Gestational Age at Birth Ascertainment

The main predictor of interest was gestational age at birth, which was identified from the Swedish Birth Registry and linked to VTE diagnosis data using an anonymous personal identification number.[17] Gestational age at birth was based mainly on maternal report of last menstrual period in the 1970s, at which time ultrasound estimation was gradually introduced until it was used exclusively starting in the 1990s. For analysis, gestational age at birth was categorized into 5 groups (extremely preterm, 22–27 weeks; very preterm, 28–33 weeks; late preterm, 34–36 weeks; term, 37–41 weeks; postterm, ≥42 weeks) to allow for a nonlinear effect.

### Other Perinatal and Familial Variables

Other perinatal and familial characteristics that may be associated with gestational age at birth and VTE were identified from the Swedish Birth Registry and national census data and were linked using an anonymous identification number. The following were examined as adjustment variables or predictors: age (used as the Cox model time scale); gender (female or male); birth cohort (1973–1979, 1980–1989, 1990–1999, 2000–2008); fetal growth (measured as the number of SDs from the mean birth weight for gestational age and gender from a Swedish reference growth curve,[14] and categorized into 6 groups [less than −2, −2 to less than −1, −1 to <0, 0 to <1, 1 to <2, ≥2 SD] to allow for a nonlinear effect); multiple birth status (singleton or multiple birth); birth order (1, 2, 3, ≥4); maternal age at delivery (<20, 20–24, 25–29, 30–34, 35–39, ≥40 years; paternal age was also examined but not retained in the final model because of its collinearity with maternal age); maternal marital status (married/cohabiting, never married, divorced/widowed), maternal and paternal education level (compulsory high school or less: ≤9 years; practical or some theoretical high school: 10–11 years; theoretical high school and/or some college: 12–14 years; college and/or postgraduate study: ≥15 years; entered into the model separately for mothers and fathers); family history of VTE in a parent or sibling (yes or no; identified from the Swedish hospital and outpatient registries from 1964 through 2010, not self-reported, thus enabling unbiased ascertainment during this time period, and entered into the model separately for parents and siblings).[18]

### Statistical Analysis

Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between gestational age at birth or other perinatal or familial variables and the earliest diagnosis of VTE. Individuals were censored at death ($n$ = 32 566; 0.9%) or at emigration as determined by the absence of a Swedish residential address in census data ($n$ = 102 217; 2.9%). The association between gestational age at birth and VTE was examined in different intervals of attained age (<1, 1–5, 6–12, 13–17, 18–38 years) among persons who were still at risk at the beginning of the respective period (ie, still living in Sweden and no previous VTE). All HRs were adjusted for age (used as the Cox model time scale) and other perinatal and familial variables (as noted earlier). These were estimated in 2 models, first for the entire cohort and then after excluding individuals with significant congenital malformations (ie, other than undescended testicle, preauricular appendage, congenital nevus, or hip dislocation; $n$ = 59 857; 1.7%) or cerebral palsy ($n$ = 8 295; 0.2%). The second model was further adjusted for diabetes, heart failure, asthma, pneumonia, cancer, and fracture as time-dependent variables using the following codes: diabetes (ICD-8/9 250, ICD-10 E10-E14), heart failure (ICD-8 427.0–427.1, ICD-9 428, ICD-10 I50), asthma (ICD-8/9 493, ICD-10 J45–J46), pneumonia (ICD-8/9 480–486, ICD-10 J12–J18), cancer (ICD-8/9 140–209, ICD-10 all C codes), and fracture (ICD-8/9 800–829, ICD-10 S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12). Congenital malformations (ICD-8/9 codes 740–759 and ICD-10 codes Q) and cerebral palsy (ICD-8/9 343 and ICD-10 G80) were identified from birth records, the Swedish Hospital Registry and Outpatient Registry, or as a cause of death. First-order interactions between gestational age at birth and other variables were explored using a likelihood ratio test. The proportional hazards assumption was evaluated by visual inspection of log-log plots and was met in each of the models.[19] All statistical tests were 2-sided and used an $\alpha$-level of .05. All analyses were conducted by using Stata statistical software, version 12.1.

## RESULTS

### Subject Characteristics

Among the 3 571 574 individuals in this cohort, 7519 (0.2%) were diagnosed with VTE in 70.8 million person-years of follow-up (Table 1). The overall incidence rate was 10.62 per 100 000 person-years (13.59 for females and 7.81 for males). The mean duration of follow-up was 19.8 ± 10.4 years (median 19.8), and the mean age at VTE diagnosis was 23.6 ± 7.5 years (median 24.2). Of the total cohort, 206 844

(5.8%) individuals were born preterm (gestational age <37 weeks). In Table 1, the individual characteristics by VTE are presented. In total, 515 (6.8%) VTE events occurred in individuals born preterm. The VTE incidence rate per 100 000 person-years was 13.57 among those born preterm (<37 weeks) and 10.46 among those not born preterm (≥37 weeks).

## Main Analysis

Adjusted HRs (aHRs) for the association between gestational age at birth and VTE are presented in Table 2. Among individuals still at risk in each time period, low gestational age at birth was strongly associated with increased risk of VTE in infancy (ages <1 year: aHR was 47.16 for 22–27 weeks, 5.54 for 28–33 weeks, and 3.54 for 34–36 weeks) and in early childhood (ages 1–5 years: aHR was not estimable for 22–27 weeks, 3.32 for 28–33 weeks, and 2.53 for 34–36 weeks). No association was observed in late childhood (ages 6–12 years; Table 2). In adolescence (ages 13–17 years), a significant association was found only for gestational age at birth of 28 to 33 weeks (aHR = 2.06). In young adulthood (ages 18–38 years), significant associations reappeared across the full range of preterm gestational ages: aHR 2.76 for 22 to 27 weeks, 1.53 for 28 to 33 weeks, and 1.24 for 34 to 36 weeks (Table 2). Individuals with congenital malformations or cerebral palsies had 340 (4.5%) of the total 7 519 VTE events for the cohort. Exclusion of these individuals and adjustment for several comorbidities in model 2 resulted in attenuation of risk estimates, although several remained significantly elevated (Table 2). Specifically, late preterm birth (34–36 weeks) remained significantly associated with VTE in young adulthood but not in infancy or early childhood (based on only 6 and 9 VTE events, respectively). Extreme preterm

**TABLE 1** Individual Characteristics by VTE Diagnosis (1973–2010)

| | VTE (*n* = 7519), n (%) | No VTE (*n* = 3 564 055), n (%) |
|---|---|---|
| Age at diagnosis (y) | | |
| 0–9 | 411 (5.5) | — |
| 10–19 | 1699 (22.6) | — |
| 20–29 | 3888 (51.7) | — |
| ≥30 | 1521 (20.2) | — |
| Mean ± SD. | 23.6±7.5 | — |
| Gestational age at birth (wk) | | — |
| 22–27 | 16 (0.2) | 7736 (0.2) |
| 28–33 | 125 (1.7) | 45 671 (1.3) |
| 34–36 | 374 (5.0) | 152 922 (4.3) |
| 37–41 | 6181 (82.2) | 3 060 109 (85.9) |
| ≥42 | 823 (10.9) | 297 617 (8.3) |
| Gender | | |
| Female | 4679 (62.2) | 1 731 307 (48.6) |
| Male | 2840 (37.8) | 1 832 748 (51.4) |
| Birth cohort | | |
| 1973–1979 | 4134 (55.0) | 688 720 (19.3) |
| 1980–1989 | 2690 (35.8) | 973 754 (27.3) |
| 1990–1999 | 586 (7.8) | 1 029 085 (28.9) |
| 2000–2008 | 109 (1.4) | 872 496 (24.5) |
| Fetal growth (SD) | | |
| Less than −2 | 415 (5.5) | 112 024 (3.1) |
| −2 to less than −1 | 1286 (17.1) | 534 522 (15.0) |
| −1 to <0 | 2701 (35.9) | 1 264 088 (35.5) |
| 0 to <1 | 2113 (28.1) | 1 116 680 (31.3) |
| 1 to <2 | 795 (10.6) | 427 958 (12.0) |
| ≥2 | 209 (2.8) | 108 752 (3.1) |
| Multiple birth status | | |
| Singleton | 7387 (98.2) | 3 479 713 (97.6) |
| Multiple birth | 132 (1.8) | 84 342 (2.4) |
| Birth order | | |
| 1 | 3198 (42.5) | 1 408 237 (39.5) |
| 2 | 2723 (36.2) | 1 221 530 (34.3) |
| 3 | 1092 (14.5) | 508 667 (14.3) |
| ≥4 | 493 (6.6) | 215 453 (6.0) |
| Unknown | 13 (0.2) | 210 168 (5.9) |
| Maternal age at delivery (y) | | |
| <20 | 370 (4.9) | 83 638 (2.3) |
| 20–24 | 1990 (26.5) | 676 219 (19.0) |
| 25–29 | 2758 (36.7) | 1 249 024 (35.1) |
| 30–34 | 1674 (22.3) | 1 032 783 (29.0) |
| 35–40 | 616 (8.2) | 431 809 (12.1) |
| ≥40 | 111 (1.5) | 86 464 (2.4) |
| Unknown | 0 (0.0) | 4118 (0.1) |
| Maternal marital status | | |
| Married/cohabiting | 4906 (65.2) | 2 867 096 (80.4) |
| Never married | 1691 (22.5) | 348 717 (9.8) |
| Divorced/widowed | 922 (12.3) | 348 242 (9.8) |
| Maternal education (y) | | |
| ≤9 | 2222 (29.6) | 672 977 (18.9) |
| 10–11 | 2875 (38.2) | 1 147 506 (32.2) |
| 12–14 | 1431 (19.0) | 1 044 058 (29.3) |
| ≥15 | 658 (8.8) | 554 237 (15.6) |
| Unknown | 333 (4.4) | 145 277 (4.1) |
| Paternal education (y) | | |
| ≤9 | 2400 (31.9) | 765 333 (21.5) |
| 10–11 | 2289 (30.4) | 1 126 980 (31.6) |
| 12–14 | 1553 (20.7) | 958 766 (26.9) |
| ≥15 | 814 (10.8) | 537 323 (15.1) |
| Unknown | 463 (6.2) | 175 653 (4.9) |
| VTE in a parent | 855 (11.4) | 110 838 (3.1) |
| VTE in a sibling | 110 (1.5) | 9647 (0.3) |

**TABLE 1** Continued

| | VTE ($n$ = 7519), n (%) | No VTE ($n$ = 3 564 055), n (%) |
|---|---|---|
| Inpatient or outpatient diagnoses | | |
| Significant congenital anomalies[a] | 257 (3.4) | 59 600 (1.7) |
| Cerebral palsy | 100 (1.3) | 9099 (0.3) |
| Diabetes | 195 (2.6) | 23 536 (0.7) |
| Heart failure | 126 (1.7) | 4989 (0.1) |
| Asthma | 565 (7.5) | 230 845 (6.5) |
| Pneumonia | 944 (12.6) | 133 079 (3.7) |
| Cancer | 515 (6.9) | 19 607 (0.6) |
| Fracture | 1562 (20.8) | 478 641 (13.4) |

[a] Other than undescended testicle, preauricular appendage, congenital nevus, or hip dislocation.

birth (22–27 weeks) remained significantly associated with VTE in infancy but not in young adulthood. Beyond adjusting for age (which was used as the time scale) and comorbidities, adjustment for any other covariates had a negligible effect on any of the risk estimates. We also found no significant first-order interactions between gestational age at birth and other perinatal or familial variables with respect to VTE risk ($P > .05$ for each), including no interactions between gestational age at birth and gender or birth cohort. Low gestational age at birth was strongly associated with VTE in all birth cohorts (not shown in the tables).

## Secondary Analysis

Postterm birth (≥42 weeks) was associated with VTE in infancy (<1 year; aHR 1.99), and this association remained significant after further adjustment for comorbidities (Table 2). However, there was no association between postterm birth and VTE in early childhood, late childhood, adolescence, or young adulthood.

Risk estimates for the association between model covariates and VTE from birth to maximum follow-up (1973–2010) are presented in Table 3. After

**TABLE 2** aHRs for Association Between Gestational Age at Birth and VTE in Different Intervals of Attained Age (1973–2010)

| | VTE Events | Person-Years | Rate[a] | Model 1[b] | | Model 2[c] | |
|---|---|---|---|---|---|---|---|
| | | | | HR (95% CI) | $P$ | HR (95% CI) | $P$ |
| Ages <1 y | | | | | | | |
| 22–27 wk | 7 | 4692 | 149.19 | 47.16 (21.30–104.42) | <.001 | 42.12 (17.13–103.61) | <.001 |
| 28–33 wk | 7 | 42 444 | 16.49 | 5.54 (2.53–12.12) | <.001 | 3.61 (1.29–10.12) | .02 |
| 34–36 wk | 16 | 112 094 | 10.58 | 3.54 (2.07–6.06) | <.001 | 1.54 (0.67–3.58) | .31 |
| 37–41 wk | 95 | 3 057 884 | 3.11 | 1.00 | | 1.00 | |
| ≥42 wk | 19 | 297 504 | 6.39 | 1.99 (1.21–3.28) | .007 | 1.83 (1.03–3.28) | .04 |
| Ages 1–5 y | | | | | | | |
| 22–27 wk | 0 | 20 937 | 0.00 | NE | NE | NE | NE |
| 28–33 wk | 6 | 199 903 | 3.00 | 3.32 (1.44–7.64) | .005 | 3.18 (1.27–7.98) | .01 |
| 34–36 wk | 17 | 719 115 | 2.36 | 2.53 (1.51–4.22) | <.001 | 1.65 (0.83–3.29) | .15 |
| 37–41 wk | 141 | 14 552 802 | 0.97 | 1.00 | | 1.00 | |
| ≥42 wk | 20 | 1 431 880 | 1.40 | 1.39 (0.86–2.23) | .18 | 1.42 (0.82–2.46) | .21 |
| Ages 6–12 y | | | | | | | |
| 22–27 wk | 0 | 20 847 | 0.00 | NE | NE | NE | NE |
| 28–33 wk | 4 | 225 864 | 1.77 | 1.92 (0.70–5.25) | .21 | 1.32 (0.41–4.21) | .64 |
| 34–36 wk | 10 | 833 369 | 1.20 | 1.29 (0.67–2.46) | .44 | 1.36 (0.71–2.60) | .36 |
| 37–41 wk | 162 | 16 892 326 | 0.96 | 1.00 | | 1.00 | |
| ≥42 wk | 16 | 1 720 492 | 0.93 | 0.99 (0.59–1.66) | .96 | 0.93 (0.52–1.66) | .81 |
| Ages 13–17 y | | | | | | | |
| 22–27 wk | 0 | 9988 | 0.00 | NE | NE | NE | NE |
| 28–33 wk | 20 | 125 085 | 15.99 | 2.06 (1.31–3.24) | .002 | 1.82 (1.13–2.94) | .01 |
| 34–36 wk | 39 | 477 323 | 8.17 | 1.09 (0.78–1.51) | .61 | 0.87 (0.60–1.25) | .45 |
| 37–41 wk | 725 | 9 710 678 | 7.47 | 1.00 | | 1.00 | |
| ≥42 wk | 76 | 1 032 982 | 7.36 | 1.00 (0.79–1.28) | .98 | 1.03 (0.81–1.32) | .78 |
| Ages 18–38 y | | | | | | | |
| 22–27 wk | 9 | 10 571 | 85.14 | 2.76 (1.43–5.31) | .002 | 1.79 (0.85–3.77) | .13 |
| 28–33 wk | 88 | 187 506 | 46.93 | 1.53 (1.24–1.89) | <.001 | 1.36 (1.08–1.70) | .008 |
| 34–36 wk | 292 | 766 648 | 38.09 | 1.24 (1.10–1.40) | <.001 | 1.17 (1.04–1.33) | .01 |
| 37–41 wk | 5058 | 16 168 492 | 31.28 | 1.00 | | 1.00 | |
| ≥42 wk | 692 | 2 115 402 | 32.71 | 0.98 (0.91–1.07) | .68 | 0.99 (0.92–1.08) | .90 |

NE, not estimable.

[a] Incidence rate for first episode of VTE per 100 000 person-years.

[b] Adjusted for age, gender, birth cohort, fetal growth, multiple birth, birth order, maternal age, maternal marital status, maternal and paternal education, and family history of VTE in a parent or sibling.

[c] Excluding individuals with significant congenital anomalies or cerebral palsy, and adjusted for the same variables as above, as well as diabetes, heart failure, asthma, pneumonia, cancer, and fracture.

**TABLE 3** HRs for Associations Between other Perinatal and Familial Factors and VTE From Birth to Maximum Follow-up (1973–2010)

| | Model 1[a] | Model 2[b] | *P* |
|---|---|---|---|
| | HR (95% CI) | HR (95% CI) | |
| Gender | | | |
| Male | 1.00 | 1.00 | — |
| Female | 1.74 (1.66–1.82) | 1.90 (1.81–2.00) | <.001 |
| Birth cohort | | | |
| 1973–1979 | 1.00 | 1.00 | |
| 1980–1989 | 1.23 (1.16–1.30) | 1.26 (1.19–1.34) | <.001 |
| 1990–1999 | 1.64 (1.47–1.82) | 1.64 (1.47–1.83) | <.001 |
| 2000–2008 | 2.29 (1.80–2.91) | 2.52 (1.92–3.31) | <.001 |
| Fetal growth (SD) | | | |
| Less than −2 | 1.31 (1.18–1.46) | 1.21 (1.08–1.35) | .001 |
| −2 to less than −1 | 1.01 (0.94–1.08) | 0.99 (0.92–1.06) | .72 |
| −1 to <0 | 1.03 (0.97–1.09) | 1.02 (0.97–1.09) | .43 |
| 0 to <1 | 1.00 | 1.00 | |
| 1 to <2 | 1.04 (0.96–1.13) | 1.03 (0.95–1.12) | .51 |
| ≥2 | 1.09 (0.95–1.26) | 1.03 (0.88–1.19) | .74 |
| Multiple birth status | | | |
| Singleton | 1.00 | 1.00 | — |
| Multiple birth | 0.82 (0.68–0.97) | 0.82 (0.68–0.99) | .04 |
| Birth order | | | |
| 1 | 1.00 | 1.00 | — |
| 2 | 1.02 (0.97–1.08) | 1.00 (0.95–1.06) | .98 |
| 3 | 1.02 (0.94–1.10) | 0.98 (0.90–1.06) | .58 |
| ≥4 | 1.15 (1.04–1.28) | 1.11 (1.00–1.24) | .06 |
| Maternal age at delivery (y) | | | |
| <20 | 1.30 (1.15–1.46) | 1.28 (1.14–1.45) | <.001 |
| 20–24 | 1.06 (1.00–1.12) | 1.05 (0.99–1.12) | .12 |
| 25–29 | 1.00 | 1.00 | — |
| 30–34 | 0.96 (0.90–1.02) | 0.96 (0.90–1.03) | .26 |
| 35–40 | 0.98 (0.89–1.08) | 0.97 (0.88–1.07) | .56 |
| ≥40 | 0.95 (0.78–1.15) | 0.91 (0.74–1.12) | .39 |
| Maternal marital status | | | |
| Married/cohabiting | 1.00 | 1.00 | |
| Never married | 1.04 (0.98–1.11) | 1.03 (0.97–1.10) | .38 |
| Divorced/widowed | 1.19 (1.11–1.28) | 1.17 (1.08–1.25) | <.001 |
| Maternal education (y) | | | |
| ≤9 | 1.00 | 1.00 | — |
| 10–11 | 0.98 (0.93–1.04) | 0.98 (0.92–1.04) | .46 |
| 12–14 | 0.89 (0.83–0.96) | 0.90 (0.84–0.97) | .008 |
| ≥15 | 0.81 (0.73–0.89) | 0.81 (0.73–0.89) | <.001 |
| Paternal education (y) | | | |
| ≤9 | 1.00 | 1.00 | — |
| 10–11 | 1.01 (0.95–1.07) | 0.99 (0.94–1.05) | .83 |
| 12–14 | 0.93 (0.87–0.99) | 0.94 (0.87–1.00) | .06 |
| ≥15 | 0.89 (0.81–0.98) | 0.91 (0.83–1.00) | .06 |
| VTE in a parent | | | |
| No | 1.00 | 1.00 | — |
| Yes | 2.50 (2.32–2.68) | 2.46 (2.29–2.65) | <.001 |
| VTE in a sibling | | | |
| No | 1.00 | 1.00 | — |
| Yes | 3.06 (2.53–3.69) | 2.84 (2.33–3.45) | <.001 |

—, reference group.

[a] Adjusted for age, gender, birth cohort, fetal growth, multiple birth, birth order, maternal age, maternal marital status, maternal and paternal education, and family history of VTE in a parent or sibling.

[b] Excluding individuals with significant congenital anomalies or cerebral palsy and adjusted for the same variables as model 1, as well as diabetes, heart failure, asthma, pneumonia, cancer, and fracture.

adjusting for the other variables included in model 1, VTE was positively associated with female gender, birth cohort, fetal growth less than –2 SD, birth order of ≥4, maternal age at delivery <20 years, having a divorced/widowed mother, and family history of VTE in a parent or in a sibling (Table 3). VTE was inversely associated with higher maternal and paternal education levels and multiple birth. Results were only slightly attenuated with adjustment of comorbidities and exclusion of congenital malformations and cerebral palsy in model 2. When shorter intervals of attained age were examined, females had decreased risk of VTE relative to males in infancy (aHR, 0.54; 95% CI, 0.38–0.76), similar risk in early and late childhood, and increased risk in adolescence (aHR, 2.12; 95% CI, 1.84–2.45) and young adulthood (aHR, 1.83; 95% CI, 1.74–1.93; not shown in the tables).

### Subanalysis Association of Gestational Age and Subtypes of VTE

Supplementary Tables 4, 5, and 6 present HRs for the association between gestational age at birth and PE (Supplementary Table 4), DVT (Supplementary Table 5), and thrombosis at other venous sites (OVTE; Supplementary Table 6). Low gestational age at birth was associated with pulmonary embolism in infancy and young adulthood, and OVTE in infancy, early childhood, and young adulthood (Supplementary Tables 4, 5, and 6). Low gestational age at birth was associated with DVT in infancy and early childhood, whereas in young adulthood, only late preterm birth (gestational age 34–36 weeks) was significantly associated with DVT. Exclusion of individuals with congenital malformations or cerebral palsy and adjustment for comorbidities in model 2 resulted in attenuation of risk estimates and precision was limited because of small numbers (Supplementary Tables 4, 5, and 6).

## DISCUSSION

We found that low gestational age at birth was associated with an increased

risk of VTE in infancy, early childhood, and young adulthood among individuals born in Sweden in from 1973 through 2008. These associations were consistent across birth cohorts and were independent of fetal growth and other perinatal and socioeconomic factors. They were attenuated after adjusting for comorbidities and excluding congenital malformations and cerebral palsies, which are more common with preterm birth. Thus, common comorbidities associated with preterm birth explain at least part of its association with VTE. Although preterm birth has previously been associated with VTE in infancy,[13] this is the first study to examine this association beyond infancy and into adulthood. Our findings suggest that preterm birth is an important risk factor for VTE not only in early childhood but also in young adulthood, even among those born late preterm (34–36 weeks). The associations we found between preterm birth and long-term risk of VTE are novel and may contribute to the reported increasing incidence of VTE in the United States.[8,9]

We also found that postterm birth (≥42 weeks) was associated with an increased risk of VTE in infancy. The cause is unclear and the association remained after exclusion of congenital malformations and cerebral palsy and adjustment for comorbidities. However, this association was found only in infancy and not among older age groups. We also identified other perinatal and familial risk factors for VTE, including low maternal age, divorced or widowed maternal marital status, low parental education level, and high birth order. These findings have not been well studied and will need confirmation in other populations. However, they are consistent with previous findings that socioeconomic factors may affect the risk of VTE.[16] Consistent with previous studies, we found that males had increased risk of VTE in infancy,[12,20] whereas females had increased risk in adolescence and young adulthood.[7,12] We also observed a decreased VTE risk among multiple births. This was in contrast to a small study based on 38 VTE cases that showed an opposite finding in infancy[13] and to our knowledge has not otherwise been studied. Family history of VTE in a parent or sibling was also associated with an increased risk of VTE, similar to previous reports.[18,21]

The associations we observed between preterm birth and VTE were partly explained by common comorbidities. The remaining associations may be related to other long-term complications of preterm birth that were unmeasured.[3] A growing body of evidence from human and animal studies has shown that early nutrition and other environmental factors may affect long-term health outcomes in adulthood.[22,23] For instance, maternal exposure to glucocorticoids in pregnancy may induce hypertension and insulin resistance, obesity, and altered muscle mass as well as alterations in the hypothalamic-pituitary-adrenal axis in the adult progeny of several experimental species.[23,24] Obesity is a risk factor for VTE.[25] Preterm birth is associated with diabetes and hypothyroidism,[26,27] which have also been associated with increased risk of VTE.[28,29] Cigarette smoking during pregnancy is a risk factor for preterm birth[30] and may be associated with an increased risk of VTE in the offspring.[13] A better understanding of patterns of human plasticity in response to early nutrition and other environmental factors is needed to further elucidate the link between preterm birth and VTE.[23]

The most important strength of the current study was its ability to examine the association between gestational age at birth and long-term risk of VTE using nationwide birth, hospital, and outpatient registry data for a large national cohort. The results were adjusted for fetal growth as well as other broadly measured potential confounders. Information on common comorbidities enabled us to examine their contribution to the main findings.

Limitations included the unavailability of information on pregnancy complications, procedural interventions such as venous catheterization, and smoking history. VTE was identified from inpatient and outpatient diagnoses, thus we were unable to identify previously silent and undiagnosed events. Information on genetic risk factors[5] was also unavailable, although the results were adjusted for family history of VTE, which is linked to several genetic risk factors.[18,21] Gestational age was estimated by maternal report of last menstrual period rather than ultrasound for earlier birth cohorts. However, we found that the association between gestational age at birth and VTE was consistently strong among different birth cohorts. Finally, preterm infants today may have a different long-term VTE risk from this cohort due to changes in neonatal care and improved survival at earlier gestational ages. It is unclear to what extent our findings in young adulthood are generalizable to later cohorts, and any such comparisons should be made with caution.

## CONCLUSIONS

Among individuals born in Sweden from 1973 through 2008, low gestational age at birth was associated with an increased risk of VTE in infancy, early childhood, and young adulthood. These findings call for better awareness of the long-term risk of VTE among preterm birth survivors. Additional studies are needed to further elucidate the influence of perinatal factors in the pathogenesis and long-term risk of VTE.

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