

SUPPLEMENTAL MATERIAL

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Supplemental Results.

Sensitivity Analyses

In sensitivity analyses that examined alternatives to multiple imputation for missing data, all results were similar to the main findings and the conclusions were unchanged. For example, the adjusted HR for stroke at ages 18-43 years comparing preterm vs. full-term was 1.40 (95% CI, 1.06-1.84; $P=0.02$) when restricting to women with complete data, and 1.26 (1.11-1.42; $P<0.001$) when coding missing data as a separate category. In the complete case analysis, adjustment for maternal smoking and BMI had only a modest effect on risk estimates (i.e., were not major confounders).

Secondary Analyses

In a secondary co-sibling analysis that compared only the first preterm-born individual in each family (90.0% of all persons born preterm) with their full-term siblings, all risk estimates were little changed. For example, comparing preterm vs. full-term, the adjusted HR for any stroke was 1.20 (95% CI, 0.94-1.54), for hemorrhagic stroke was 1.08 (0.78-1.50), and for ischemic stroke was 1.22 (0.81-1.84).

The main risk estimates were negligibly affected by additional adjustment for fetal growth. When adjusted for each other and all other covariates, both preterm birth and SGA were associated with significantly increased risk of stroke (1.27; 95% CI, 1.12-1.43; $P<0.001$ and 1.14; 1.04-1.24; $P=0.003$, respectively; $P=0.16$ for difference in HRs). Preterm birth was associated with significantly increased stroke risks among persons born SGA and those who were not (Table IV). No interaction was found between preterm birth and SGA on the additive ($P=0.14$) nor multiplicative ($P=0.17$) scale.

The percentage of all preterm-born individuals who survived to age 18 years was 91.4% for those born in the 1970s, 94.7% for those born in the 1980s, and 95.4% for those born in the 1990s. Potential interactions between preterm birth and birth year in relation to stroke risk were explored after follow-up to ages 18-26 years (thus allowing consistent follow-up ages across different birth years). A trend of stronger associations by later birth years was observed (Table V). For example, the adjusted HR for stroke associated with preterm birth was 1.03 (95% CI, 0.66-1.60; $P=0.90$) for persons born in 1973-1979, 1.17 (0.89-1.55; $P=0.26$) for those born in 1980-1989, and 1.64 (1.08-2.50; $P=0.02$) for those born in 1990-1994. However, no significant interaction between preterm birth and birth year was found on the additive ($P=0.26$) nor multiplicative ($P=0.42$) scale (Table VI).

In exploratory analyses, both spontaneous and medically indicated preterm birth appeared to be associated with increased stroke risk (adjusted HR, 1.76; 95% CI, 0.98-3.15; and 1.97; 1.06-3.69, respectively; Table VII). However, this information was available for only a smaller subcohort born in 1990 or later who had sufficient follow-up into early adulthood, thus reducing precision.

Table I. International Classification of Diseases (ICD) codes used in the analyses.

Diagnosis	ICD-8	ICD-9	ICD-10
Stroke			
Any stroke	430-431, 433-434	430-432, 433.X1, 434	I60-I64
Hemorrhagic stroke	430-431	430-432	I60-I62
Ischemic stroke	433-434	433.X1, 434	I63
Stroke, unspecified	--	--	I64
Preeclampsia	637	624.4-624.7	O14-O15
Other hypertensive disorders	400-404	401-405, 642.0-642.3, 642.9	I10-I15, O10-O11, O13, O15-O16
Diabetes mellitus	250	250, 648.0, 648.8	E10-E14, O24

Table II. Associations between gestational age at birth (1973-1994) and risk of stroke (1991-2015), stratified by sex,* Sweden.

	Cases	Rate	Unadjusted	Adjusted [†]		AF _e [‡] (%)	PAR [§] (%)
			HR (95% CI)	HR (95% CI)	P		
Men							
Preterm (<37 wks)	152	21.2	1.31 (1.11, 1.55)	1.25 (1.06, 1.48)	0.009	22.5	1.9
Early preterm (<34 wks)	32	21.5	1.35 (0.95, 1.91)	1.26 (0.89, 1.79)	0.20	23.8	0.5
Late preterm (34-36 wks)	120	21.1	1.30 (1.08, 1.57)	1.25 (1.04, 1.50)	0.02	22.1	1.5
Early term (37-38 wks)	413	17.2	1.08 (0.97, 1.20)	1.05 (0.94, 1.17)	0.39	4.7	1.0
Full-term (39-41 wks)	1,618	16.4	Reference	Reference			
Post-term (≥42 wks)	266	17.7	1.01 (0.89, 1.15)	1.03 (0.90, 1.17)	0.66	6.9	1.0
Per additional week (trend)			0.97 (0.95, 0.99)	0.98 (0.96, 0.99)	0.02		
Women							
Preterm (<37 wks)	131	22.7	1.31 (1.10, 1.56)	1.28 (1.07, 1.53)	0.007	21.7	1.6
Early preterm (<34 wks)	34	28.5	1.66 (1.18, 2.34)	1.61 (1.15, 2.27)	0.006	37.6	0.7
Late preterm (34-36 wks)	97	21.2	1.22 (0.99, 1.50)	1.19 (0.97, 1.46)	0.09	16.1	0.9
Early term (37-38 wks)	354	16.9	0.99 (0.89, 1.11)	0.98 (0.87, 1.10)	0.70	(5.0) [#]	(0.9) ^{**}
Full-term (39-41 wks)	1,685	17.8	Reference	Reference			
Post-term (≥42 wks)	242	17.0	0.88 (0.77, 1.01)	0.89 (0.78, 1.02)	0.10	(4.8) [#]	(0.6) ^{**}
Per additional week (trend)			0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.008		

^{*}Wald tests for interaction between preterm birth and sex: additive scale, $P=0.93$; multiplicative scale, $P=0.96$.

[†]Adjusted for child characteristics (age, birth year, birth order), maternal characteristics (age, education, birth country or region, BMI, smoking, preeclampsia, other hypertensive disorders, diabetes), and paternal characteristics (age, education).

[‡]Attributable fraction among the exposed.

[§]Population attributable fraction.

^{||}Stroke incidence rate per 100,000 person-years.

[#]Prevented fraction among the exposed.

^{**}Population prevented fraction.

Table III. Interactions between preterm birth and sex (1973-1994) in relation to stroke risk (1991-2015), Sweden.

	Gestational age at birth				HRs (95% CI) for preterm vs. full-term within sex strata
	Full-term (39-41 wks)		Preterm (<37 wks)		
	No. (rate) [*]	HR (95% CI) [†]	No. (rate) [*]	HR (95% CI) [†]	
Sex					
Men	1,618 (16.4)	Reference	152 (21.2)	1.27 (1.07, 1.50); <i>P</i> =0.005	1.27 (1.07, 1.50); <i>P</i> =0.005
Women	1,685 (17.8)	1.09 (1.01, 1.16); <i>P</i> =0.02	131 (22.7)	1.37 (1.14, 1.63); <i>P</i> =0.001	1.26 (1.03, 1.48); <i>P</i> =0.02
HRs (95% CI) for women vs. men within gestational age strata		1.09 (1.01, 1.16); <i>P</i> =0.02		1.08 (0.83, 1.33); <i>P</i> =0.54	
Interaction on additive scale: RERI (95% CI)			0.01 (-0.30, 0.33);	<i>P</i> =0.93	
Interaction on multiplicative scale: HR ratio (95% CI)			0.99 (0.75, 1.23);	<i>P</i> =0.96	

^{*}Number of strokes and incidence rate per 100,000 person-years.

[†]Adjusted for child characteristics (age, birth year, birth order), maternal characteristics (age, education, birth country or region, BMI, smoking, preeclampsia, other hypertensive disorders, diabetes), and paternal characteristics (age, education).

HR = hazard ratio, RERI = relative excess risk due to interaction

Table IV. Interactions between preterm birth and fetal growth (1973-1994) in relation to stroke risk at ages 18-43 years (1991-2015), Sweden.

	Gestational age at birth				HRs (95% CI) for preterm vs. full-term within fetal growth strata
	Full-term (39-41 wks)		Preterm (<37 wks)		
	No. (rate)*	HR (95% CI)†	No. (rate)*	HR (95% CI)†	
Fetal growth					
Appropriate for gestational age (AGA)	2,613 (19.0)	Reference	205 (23.2)	1.21 (1.05, 1.39); <i>P</i> =0.009	1.21 (1.05, 1.39); <i>P</i> =0.009
Small for gestational age (SGA)	690 (12.4)	1.01 (0.88, 1.16); <i>P</i> =0.90	78 (19.1)	1.50 (1.17, 1.93); <i>P</i> =0.001	1.49 (1.14, 1.84); <i>P</i> =0.006
HRs (95% CI) for SGA vs. AGA within gestational age strata		1.01 (0.88, 1.16); <i>P</i> =0.90		1.24 (0.89, 1.60); <i>P</i> =0.17	
Interaction on additive scale: RERI (95% CI)			0.29 (-0.10, 0.67);	<i>P</i> =0.14	
Interaction on multiplicative scale: HR ratio (95% CI)			1.23 (0.90, 1.57);	<i>P</i> =0.17	

*Number of strokes and incidence rate per 100,000 person-years.

†Adjusted for child characteristics (age, sex, birth year, birth order), maternal characteristics (age, education, birth country or region, BMI, smoking, preeclampsia, other hypertensive disorders, diabetes), and paternal characteristics (age, education).

HR = hazard ratio, RERI = relative excess risk due to interaction

Table V. Associations between gestational age at birth (1973-1994) and risk of stroke (1991-2015) at ages 18-26 years, stratified by birth decade, Sweden.

	Cases	Rate [‡]	Unadjusted	Adjusted [*]	P
			HR (95% CI)	HR (95% CI)	
Born in 1973-1979					
Preterm (<37 wks)	21	9.7	1.08 (0.69, 1.68)	1.03 (0.66, 1.60)	0.90
Early preterm (<34 wks)	5	11.6	1.29 (0.54, 3.13)	1.21 (0.50, 2.93)	0.67
Late preterm (34-36 wks)	16	9.2	1.03 (0.62, 1.70)	0.98 (0.59, 1.62)	0.94
Early term (37-38 wks)	55	7.7	0.86 (0.66, 1.14)	0.84 (0.63, 1.11)	0.22
Full-term (39-41 wks)	321	9.0	Reference	Reference	
Post-term (≥42 wks)	58	8.6	0.95 (0.72, 1.26)	0.96 (0.72, 1.27)	0.77
Per additional week (trend)			1.00 (0.95, 1.05)	1.00 (0.95, 1.06)	0.83
Born in 1980-1989					
Preterm (<37 wks)	55	14.8	1.23 (0.93, 1.62)	1.17 (0.89, 1.55)	0.26
Early preterm (<34 wks)	16	20.5	1.70 (1.04, 2.80)	1.59 (0.97, 2.62)	0.07
Late preterm (34-36 wks)	39	13.2	1.10 (0.80, 1.52)	1.06 (0.76, 1.47)	0.73
Early term (37-38 wks)	165	12.3	1.02 (0.86, 1.21)	0.99 (0.83, 1.17)	0.87
Full-term (39-41 wks)	601	12.0	Reference	Reference	
Post-term (≥42 wks)	59	10.3	0.85 (0.65, 1.12)	0.88 (0.67, 1.15)	0.35
Per additional week (trend)			0.96 (0.93, 1.00)	0.97 (0.94, 1.01)	0.18
Born in 1990-1994					
Preterm (<37 wks)	25	17.1	1.67 (1.11, 2.53)	1.64 (1.08, 2.50)	0.02
Early preterm (<34 wks)	6	17.9	1.75 (0.78, 3.94)	1.71 (0.75, 3.87)	0.20
Late preterm (34-36 wks)	19	16.9	1.65 (1.03, 2.64)	1.62 (1.01, 2.60)	0.05
Early term (37-38 wks)	74	13.6	1.33 (1.02, 1.74)	1.32 (1.02, 1.73)	0.04
Full-term (39-41 wks)	216	10.2	Reference	Reference	
Post-term (≥42 wks)	31	14.3	1.40 (0.96, 2.04)	1.37 (0.94, 2.00)	0.10
Per additional week (trend)			0.95 (0.90, 1.00)	0.95 (0.90, 1.00)	0.05

^{*}Adjusted for child characteristics (age, sex, birth year, birth order), maternal characteristics (age, education, birth country or region, BMI, smoking, preeclampsia, other hypertensive disorders, diabetes), and paternal characteristics (age, education).

[‡]Stroke incidence rate per 100,000 person-years.

Table VI. Interactions between preterm birth and birth year (1973-1994) in relation to stroke risk at ages 18-26 years (1991-2015), Sweden.

	Gestational age at birth				HRs (95% CI) for preterm vs. full-term within birth year strata
	Full-term (39-41 wks)		Preterm (<37 wks)		
Birth year	No. (rate)*	HR (95% CI)†	No. (rate)*	HR (95% CI)†	
<1985	568 (9.6)	Reference	43 (11.1)	1.12 (0.82, 1.52); <i>P</i> =0.48	1.12 (0.82, 1.52); <i>P</i> =0.48
≥1985	570 (11.9)	1.31 (1.15, 1.48); <i>P</i> <0.001	58 (16.7)	1.76 (1.33, 2.31); <i>P</i> <0.001	1.34 (0.98, 1.71); <i>P</i> =0.06
HRs (95% CI) for women vs. men within gestational age strata		1.31 (1.15, 1.48); <i>P</i> <0.001		1.57 (0.95, 2.20); <i>P</i> =0.07	
Interaction on additive scale: RERI (95% CI)			0.33 (-0.24, 0.91); <i>P</i> =0.26		
Interaction on multiplicative scale: HR ratio (95% CI)			1.20 (0.71, 1.70); <i>P</i> =0.42		

*Number of strokes and incidence rate per 100,000 person-years.

†Adjusted for child characteristics (age, sex, birth order), maternal characteristics (age, education, birth country or region, BMI, smoking, preeclampsia, other hypertensive disorders, diabetes), and paternal characteristics (age, education).

HR = hazard ratio, RERI = relative excess risk due to interaction

Table VII. Spontaneous or medically indicated birth (1990-1994) and subsequent risk of stroke (2008-2015), Sweden.

	Cases	Rate ^a	HR (95% CI) [†]	<i>P</i>	<i>P</i> for difference in HRs
Preterm					0.78
Spontaneous	12	17.6	1.76 (0.98, 3.15)	0.06	
Medically indicated	11	19.8	1.97 (1.06, 3.69)	0.03	
Early term					0.26
Spontaneous	37	12.0	1.22 (0.86, 1.74)	0.26	
Medically indicated	24	16.6	1.65 (1.08, 2.53)	0.02	
Full-term	216	10.2	Reference		

^aStroke incidence rate per 100,000 person-years.

[†]Adjusted for child characteristics (age, sex, birth year, birth order), maternal characteristics (age, education, birth country or region, BMI, smoking, preeclampsia, other hypertensive disorders, diabetes), and paternal characteristics (age, education).