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Original article

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Preterm birth and risk of sleep-disordered breathing from childhood into mid-adulthood

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Abstract

Background: Preterm birth (gestational age <37 weeks) has previously been associated with cardiometabolic and neuropsychiatric disorders into adulthood, but has seldom been examined in relation to sleep disorders. We conducted the first population-based study of preterm birth in relation to sleep-disordered breathing (SDB) from childhood into mid-adulthood.

Methods: A national cohort study was conducted of all 4 186 615 singleton live births in Sweden during 1973–2014, who were followed for SDB ascertained from nationwide inpatient and outpatient diagnoses through 2015 (maximum age 43 years). Cox regression was used to examine gestational age at birth in relation to SDB while adjusting for other perinatal and maternal factors, and co-sibling analyses assessed for potential confounding by unmeasured shared familial factors.

Results: There were 171 100 (4.1%) persons diagnosed with SDB in 86.0 million person-years of follow-up. Preterm birth was associated with increased risk of SDB from childhood into mid-adulthood, relative to full-term birth (39–41 weeks) [adjusted hazard ratio (aHR), ages 0–43 years: 1.43; 95% confidence interval (CI), 1.40, 1.46; $P<0.001$; ages 30–43 years: 1.40; 95% CI, 1.34, 1.47; $P<0.001$]. Persons born extremely preterm (<28 weeks) had more than 2-fold risks (aHR, ages 0–43 years: 2.63; 95% CI, 2.41, 2.87; $P<0.001$; ages 30–43 years: 2.22; 95% CI, 1.64, 3.01; $P<0.001$). These associations affected both males and females, but accounted for more SDB cases among males (additive interaction, $P=0.003$). Co-sibling analyses suggested that these findings were only partly due to shared genetic or environmental factors in families.

Conclusions: Preterm-born children and adults need long-term follow-up for anticipatory screening and potential treatment of SDB.

Key words: Premature birth, sleep, sleep apnoea syndromes

Key Messages

- Preterm birth has been associated with cardiometabolic and neuropsychiatric disorders into adulthood, but has rarely been examined in relation to sleep-disordered breathing (SBD), a potential mediator for many of those same disorders.
- In a large national cohort study, preterm birth and extremely preterm birth were associated with 1.4- and 2.6-fold risks of SDB, respectively, from birth up to age 43 years.
- Preterm-born children and adults need long-term follow-up for anticipatory screening and potential treatment of SDB.

Introduction

Preterm birth (gestational age <37 weeks) has a worldwide prevalence of 11%,[1] and has been associated with cardiometabolic[2–8] and neuropsychiatric[9–12] disorders into adulthood. Sleep-disordered breathing (SDB) is a common risk factor or potential mediator for many of those same disorders,[13–17] but has seldom been examined in preterm birth survivors. SDB is characterized by intermittent upper airway obstruction that disrupts normal ventilation during sleep, with symptoms ranging in severity from primary snoring to obstructive sleep apnoea (OSA).[18,19] SDB may potentially play a role in mediating the increased risks of cardiometabolic or neuropsychiatric disorders in preterm-born children and adults. If so, preventive efforts in these patients should include screening, detection and treatment of the underlying sleep disorder. A better understanding of SDB risks in preterm survivors is critically needed to facilitate more effective long-term care of these patients.

A few earlier studies have reported associations between preterm birth and SDB in infancy[20] and childhood.[21–23] However, it is unknown whether an increased risk of SDB persists later in life. The only study to date that included preterm-born adults was a small case-control study that reported a 2-fold risk of chronic snoring in young adults aged 18–27 years who were born preterm with very low birth weight.[24] No population-based cohort studies have examined preterm birth in relation to SDB, and the risks later in adulthood remain unknown.

We conducted a national cohort study of 4.1 million persons in Sweden to examine preterm birth in relation to SDB risk from childhood into mid-adulthood. Our goals were to provide the first population-based risk estimates for SDB associated with gestational age at birth, assess for sex-specific differences and explore the potential influence of shared familial (genetic and/or environmental) factors on these associations using co-sibling analyses. The results may help guide long-term surveillance for SDB in preterm-born children and adults, and inform future investigations of its role as a potential mediator of other chronic disease risks.

Methods

Study population

The Swedish Birth Registry contains prenatal and birth information for nearly all births nationwide since 1973.[25] Using this registry, we identified 4 195 249 singleton live births in Sweden during 1973–2014. We excluded 8634 (0.2%) births that had missing information for gestational age, leaving 4 186 615 births (99.8% of the original cohort) for inclusion in the study. This study was approved by the Ethics Committee of Lund University in Sweden.

Ascertainment of gestational age at birth and sleep-disordered breathing

Gestational age at birth was identified from the Swedish Birth Registry, based on maternal report of last menstrual period in the 1970s and on ultrasound estimation in the 1980s and later. This was examined alternatively as a continuous variable or categorical variable with six groups: extremely preterm (22–27 weeks), very preterm (28–33 weeks), late preterm (34–36 weeks), early-term (37–38 weeks), full-term (39–41 weeks, used as the reference group) and post-term (≥42 weeks). In addition, the first three groups were combined to provide summary estimates for preterm birth (<37 weeks).

The study cohort was followed up for the earliest diagnosis of SDB from birth through 31 December 2015 (maximum age 43 years), using inpatient and outpatient clinical diagnoses. SDB has no specific diagnostic code in Sweden; instead, sleep apnoea and adenotonsillar hypertrophy are regularly used as proxies.[26–29] SDB was therefore identified in the Swedish Hospital Registry and Swedish Outpatient Registry using *International Classification of Diseases* (*ICD*) codes for sleep apnoea (*ICD*-9: 327.2, 780.51, 780.53, 780.57; *ICD*-10: G47.3) and adenotonsillar hypertrophy (*ICD*-8: 500; *ICD*-9: 474B, *ICD*-10: J35.1, J35.3). The Swedish Hospital Registry contains all primary and secondary hospital discharge diagnoses from six populous counties in southern Sweden starting in 1964, and with nationwide coverage starting in 1987; and the Swedish Outpatient Registry contains outpatient diagnoses from all specialty clinics nationwide starting in 2001. To our knowledge, there are no previous validation studies for sleep apnoea and adenotonsillar hypertrophy diagnoses in these registries; however, diagnoses in the Swedish Hospital Registry have been reported to have positive predictive values of at least 85–95% for a wide range of other common conditions.[30]

Other study variables

Other perinatal and maternal characteristics that may be associated with gestational age at birth and SDB risk were identified using the Swedish Birth Registry and national census data, which were linked using an anonymous personal identification number. The following were included as adjustment variables: birth year (continuous), sex, birth order (1, 2, ≥3), congenital anomalies (yes/no, identified using codes 740–759 in *ICD*-8/9 and Q00-Q99 in *ICD*-10), maternal age (continuous), maternal education level (<10, 10–12, >12 years), maternal body mass index (BMI; continuous), maternal smoking (0, 1–9, ≥10 cigarettes/day), preeclampsia (*ICD*-8: 637; *ICD*-9: 624.4–624.7; *ICD*-10: O14-O15) and diabetes mellitus during pregnancy (*ICD*-8: 250; *ICD*-9: 250, 648.0; *ICD*-10: O24, E10-E14). Maternal preeclampsia and diabetes were examined because they have been associated with preterm delivery[31] and maternal SDB,[32,33] though it is unclear whether they are also associated with SDB in the offspring.

Maternal BMI and smoking were assessed at the beginning of prenatal care starting in 1982, and were available for 61.0% and 74.2% of women, respectively. Data were >99% complete for all other variables. Missing data for each covariate were imputed using a standard multiple imputation procedure based on the variable's relationship with all other covariates and SDB.[34]

Statistical analysis

Cox proportional hazards regression was used to compute hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between gestational age at birth and risk of SDB. These associations were examined across the entire age range of 0–43 years and in narrower age ranges (0–9, 10–19, 20–29, 30–43 years) among persons still living in Sweden and without a previous diagnosis of SDB at the beginning of the respective age range. Attained age was used as the Cox model time axis. Individuals were censored at death as identified in the Swedish Death Registry ($n = 42\,696$; 1.0%), or at emigration as determined by absence of a Swedish residential address in census data ($n = 252\,788$; 6.0%). Emigrants and non-emigrants had a similar gestational duration (median, 40 1/7 weeks for both groups), and thus it was unlikely that emigration introduced any substantial bias. Analyses were conducted both unadjusted and adjusted for covariates (as above). The proportional hazards assumption was assessed by examining log-log plots,[35] and was met in each model.

Sex-specific differences were assessed by performing sex-stratified analyses and examining interactions between gestational age at birth and sex in relation to SDB risk on both the additive and the multiplicative scales. Additive interactions were tested using the 'relative excess risk due to interaction' (RERI), which is computed for binary variables as: $\mathrm{RERI_{HR}} = \mathrm{HR_{11}} - \mathrm{HR_{10}} - \mathrm{HR_{01}} + 1$.[36,37] Multiplicative interactions were tested using the ratio of HRs: $\mathrm{HR_{11}} / (\mathrm{HR_{10}}\,\mathrm{HR_{01}})$.[37]

Co-sibling analyses were performed to assess for potential confounding effects of unmeasured shared familial (genetic and/or environmental) factors. These analyses used stratified Cox regression with a separate stratum for each family as identified by the mother's anonymous identification number. A total of 3 504 900 individuals (83.7% of the cohort) had at least one sibling and were included in these analyses. In the stratified Cox model, each set of siblings has its own baseline hazard function that reflects the family's shared genetic and environmental factors, and thus comparisons of different gestational ages at birth are made within the family. In addition, these analyses were further adjusted for the same covariates as in the main analyses.

In secondary analyses, we further adjusted for fetal growth (defined as birthweight standardized for gestational age and sex based on Swedish reference intrauterine growth curves[38]) to explore the effects of gestational age at birth on SDB risk independent of fetal growth. We also examined diagnostic codes more specific for sleep apnoea as a secondary outcome (*ICD*-9: 327.2, 780.51, 780.53, 780.57; *ICD*-10: G47.3; i.e. excluding adenotonsillar

Table 1. Characteristics of study participants by gestational age at birth, Sweden, 1973–2014

	Extremely preterm (22–27 wks) $N = 8129$ *n* (%)	Very preterm (28-33 wks) $N = 43\,516$ *n* (%)	Late preterm (34-36 wks) $N = 155\,626$ *n* (%)	Early-term (37-38 wks) $N = 737\,412$ *n* (%)	Full-term (39-41 wks) $N = 2\,895\,746$ *n* (%)	Post-term (≥42 wks) $N = 346\,186$ *n* (%)
Child characteristics						
Sex						
Male	4435 (54.6)	24 286 (55.8)	84 696 (54.4)	379 645 (51.5)	1 471 045 (50.8)	188 354 (54.4)
Female	3694 (45.4)	19 230 (44.2)	70 930 (45.6)	357 767 (48.5)	1 424 701 (49.2)	157 832 (45.6)
Birth order						
1	4094 (50.4)	22 513 (51.7)	77 533 (49.8)	296 887 (40.3)	1 218 861 (42.1)	172 698 (49.9)
2	2292 (28.2)	12 211 (28.1)	46 346 (29.8)	269 837 (36.6)	1 087 327 (37.5)	111 056 (32.1)
≥3	1743 (21.4)	8792 (20.2)	31 747 (20.4)	170 688 (23.1)	589 558 (20.4)	62 432 (18.0)
Congenital anomalies	219 (2.7)	1115 (2.6)	1775 (1.1)	2733 (0.4)	5024 (0.2)	944 (0.3)
Maternal characteristics						
Age (years)						
<20	356 (4.4)	2056 (4.7)	6464 (4.2)	22 060 (3.0)	84 018 (2.9)	12 962 (3.7)
20-24	1554 (19.1)	8868 (20.4)	33 037 (21.2)	138 918 (18.8)	580 804 (20.1)	76 288 (22.0)
25-29	2378 (29.3)	13 488 (31.0)	50 748 (32.6)	242 523 (32.9)	1 018 704 (35.2)	121 282 (35.0)
30-34	2206 (27.1)	11 552 (26.6)	40 970 (26.3)	210 743 (28.6)	821 392 (28.4)	92 811 (26.8)
35-39	1280 (15.7)	6012 (13.8)	19 826 (12.7)	100 289 (13.6)	330 684 (11.4)	36 880 (10.7)
≥40	355 (4.4)	1540 (3.5)	4581 (2.9)	22 879 (3.1)	60 144 (2.1)	5963 (1.7)
Education (years)						
≤9	1369 (16.8)	7229 (16.6)	24 216 (15.6)	103 813 (14.1)	367 744 (12.7)	48 593 (14.0)
10-12	3867 (47.6)	20 812 (47.8)	73 689 (47.3)	337 757 (45.8)	1 304 617 (45.1)	157 016 (45.4)
>12	2893 (35.6)	15 475 (35.6)	57 721 (37.1)	295 842 (40.1)	1 223 385 (42.2)	140 577 (40.6)
Body mass index						
<18.5	137 (1.7)	1118 (2.6)	4767 (3.1)	21 727 (2.9)	65 593 (2.3)	4649 (1.3)
18.5-24.9	6006 (73.9)	33 733 (77.5)	120 397 (77.4)	565 433 (76.7)	2 279 136 (78.7)	275 210 (79.5)
25.0-29.9	1381 (17.0)	5935 (13.6)	21 157 (13.6)	107 005 (14.5)	404 104 (14.0)	46 599 (13.5)
≥30.0	605 (7.4)	2730 (6.3)	9305 (6.0)	43 247 (5.9)	146 913 (5.1)	19 728 (5.7)
Smoking (cigarettes/day)						
0	5904 (72.6)	30 588 (70.3)	113 066 (72.6)	562 247 (76.3)	2 215 716 (76.5)	247 294 (71.4)
1-9	1731 (21.3)	10 181 (23.4)	33 600 (21.6)	138 227 (18.7)	567 319 (19.6)	87 933 (25.4)
≥10	494 (6.1)	2747 (6.3)	8960 (5.8)	36 938 (5.0)	112 711 (3.9)	10 959 (3.2)
Preeclampsia	1027 (12.6)	7775 (17.8)	15 822 (10.2)	39 087 (5.3)	94 678 (3.3)	11 831 (3.4)
Diabetes mellitus	88 (1.1)	902 (2.1)	3867 (2.5)	11 940 (1.6)	16 748 (0.6)	710 (0.2)

hypertrophy diagnoses). In addition, we examined other perinatal and maternal characteristics (as above) to identify other early-life risk factors for SDB. All statistical tests were two-sided and used an α-level of 0.05. All analyses were conducted using Stata version 15.1.

Results

Table 1 shows perinatal and maternal characteristics by gestational age at birth. Preterm infants were more likely than term infants to be male or firstborn, or have congenital anomalies; and their mothers were more likely to be at the extremes of age, have low education level or high BMI, smoke or have preeclampsia or diabetes during their pregnancy.

Gestational age at birth and risk of SDB

There were 171 100 (4.1%) SDB cases identified in 86.0 million person-years of follow-up, yielding an overall incidence rate of 199.00 per 100 000 person-years across the entire age range examined (0–43 years). The corresponding incidence rates were 281.63 among those born preterm, 220.35 among those born at early term and 191.50 among those born at full term (Table 2).

Across the entire age range (0–43 years), gestational age at birth was inversely associated with SDB risk (adjusted HR per additional week of gestation, 0.95; 95% CI, 0.95, 0.95; $P < 0.001$; Table 2). Preterm and early-term birth were associated with 43% and 12% increased risks of SDB, respectively, relative to full-term birth (adjusted HR, 1.43; 95% CI, 1.40, 1.46; $P < 0.001$; and 1.12; 95% CI,

Table 2. Associations between gestational age at birth and risk of sleep-disordered breathing (SDB), Sweden, 1973–2015

	All					Males				Females			
			Unadjusted	**Adjusted**[a]				**Adjusted**[a]				**Adjusted**[a]	
	Cases	**Rate**[b]	HR (95% CI)	HR (95% CI)	*P*	Cases	**Rate**[b]	HR (95% CI)	*P*	Cases	**Rate**[b]	HR (95% CI)	*P*
Attained ages 0-43 years													
Preterm (<37 weeks)	11 364	281.63	1.49 (1.46, 1.52)	1.43 (1.40, 1.46)	<0.001	6725	303.69	1.43 (1.40, 1.47)	<0.001	4639	254.81	1.42 (1.38, 1.47)	<0.001
Extremely preterm (<28 weeks)	506	640.30	3.51 (3.22, 3.83)	2.63 (2.41, 2.87)	<0.001	306	750.24	2.82 (2.52, 3.16)	<0.001	200	523.02	2.39 (2.08, 2.75)	<0.001
Very preterm (28-33 weeks)	2812	354.27	1.88 (1.81, 1.96)	1.76 (1.70, 1.83)	<0.001	1663	377.60	1.74 (1.66, 1.83)	<0.001	1149	325.19	1.79 (1.69, 1.90)	<0.001
Late preterm (34-36 weeks)	8046	254.44	1.34 (1.31, 1.37)	1.31 (1.28, 1.34)	<0.001	4756	274.40	1.31 (1.27, 1.35)	<0.001	3290	230.23	1.30 (1.25, 1.35)	<0.001
Early-term (37-38 weeks)	32 067	220.35	1.18 (1.16, 1.19)	1.12 (1.10, 1.13)	<0.001	17 953	236.38	1.11 (1.10, 1.13)	<0.001	14 114	202.85	1.12 (1.10, 1.14)	<0.001
Full-term (39-41 weeks)	113 862	191.50	Reference	Reference		63 005	208.55	Reference		50 857	173.88	Reference	
Post-term (≥42 weeks)	13 807	174.10	0.86 (0.84, 0.87)	0.95 (0.94, 0.97)	<0.001	8209	196.28	0.97 (0.94, 0.99)	0.004	5598	149.35	0.94 (0.91, 0.97)	<0.001
Per additional week (trend)			0.93 (0.93, 0.93)	0.95 (0.95, 0.95)	<0.001			0.95 (0.95, 0.95)	<0.001			0.95 (0.94, 0.95)	<0.001
Attained ages 0-9 years													
Preterm (<37 weeks)	5773	336.02	1.57 (1.53, 1.61)	1.51 (1.47, 1.55)	<0.001	3430	365.96	1.49 (1.44, 1.55)	<0.001	2343	300.07	1.53 (1.47, 1.60)	<0.001
Extremely preterm (<28 weeks)	366	906.14	4.26 (3.84, 4.72)	3.06 (2.76, 3.39)	<0.001	229	1083.02	3.25 (2.85, 3.70)	<0.001	137	711.82	2.77 (2.34, 3.28)	<0.001
Very preterm (28-33 weeks)	1482	431.46	2.02 (1.92, 2.13)	1.88 (1.78, 1.98)	<0.001	877	461.12	1.81 (1.69, 1.94)	<0.001	605	394.66	1.98 (1.82, 2.15)	<0.001
Late preterm (34-36 weeks)	3925	294.18	1.38 (1.33, 1.42)	1.35 (1.30, 1.39)	<0.001	2324	320.15	1.33 (1.28, 1.39)	<0.001	1601	263.20	1.37 (1.30, 1.44)	<0.001
Early-term (37-38 weeks)	16 047	252.61	1.18 (1.16, 1.20)	1.12 (1.10, 1.14)	<0.001	9209	281.40	1.13 (1.11, 1.16)	<0.001	6838	222.01	1.11 (1.08, 1.14)	<0.001
Full-term (39-41 weeks)	53 704	213.84	Reference	Reference		30 623	240.43	Reference		23 081	186.48	Reference	
Post-term (≥42 weeks)	5782	188.45	0.88 (0.86, 0.91)	0.98 (0.96, 1.01)	0.23	3680	222.45	1.00 (0.96, 1.03)	0.87	2102	148.68	0.96 (0.92, 1.00)	0.07
Per additional week (trend)			0.93 (0.92, 0.93)	0.94 (0.94, 0.95)	<0.001			0.94 (0.94, 0.95)	<0.001			0.94 (0.94, 0.95)	<0.001
Attained ages 10-19 years													
Preterm (<37 weeks)	1241	100.57	1.13 (1.07, 1.20)	1.14 (1.08, 1.21)	<0.001	602	89.10	1.25 (1.15, 1.36)	<0.001	639	114.45	1.06 (0.97, 1.14)	0.19
Extremely preterm (<28 weeks)	31	132.79	1.50 (1.06, 2.14)	1.27 (0.89, 1.81)	0.18	16	133.69	1.55 (0.95, 2.54)	0.08	15	131.85	1.07 (0.64, 1.77)	0.80
Very preterm (28-33 weeks)	256	105.56	1.19 (1.05, 1.34)	1.19 (1.05, 1.35)	0.006	136	101.47	1.40 (1.18, 1.66)	<0.001	120	110.60	1.02 (0.85, 1.22)	0.85
Late preterm (34-36 weeks)	954	98.55	1.11 (1.04, 1.18)	1.13 (1.05, 1.20)	<0.001	450	84.97	1.20 (1.09, 1.33)	<0.001	504	114.95	1.06 (0.97, 1.16)	0.18
Early-term (37-38 weeks)	4416	99.03	1.11 (1.08, 1.15)	1.07 (1.04, 1.11)	<0.001	1759	75.84	1.05 (0.99, 1.11)	0.08	2657	124.15	1.09 (1.05, 1.14)	<0.001
Full-term (39-41 weeks)	16 075	88.88	Reference	Reference		6461	70.39	Reference		9614	107.93	Reference	
Post-term (≥42 weeks)	1656	70.79	0.80 (0.76, 0.84)	0.92 (0.88, 0.97)	0.002	715	57.86	0.90 (0.84, 0.98)	0.01	941	85.28	0.94 (0.88, 1.00)	0.05
Per additional week (trend)			0.96 (0.95, 0.96)	0.97 (0.97, 0.98)	<0.001			0.96 (0.95, 0.98)	<0.001			0.98 (0.97, 0.99)	<0.001
Attained ages 20-29 years													
Preterm (<37 weeks)	2172	281.57	1.52 (1.45, 1.59)	1.36 (1.30, 1.42)	<0.001	1328	310.79	1.34 (1.26, 1.42)	<0.001	844	245.29	1.40 (1.30, 1.50)	<0.001
Extremely preterm (<28 weeks)	67	573.59	3.23 (2.54, 4.10)	2.34 (1.84, 2.98)	<0.001	37	631.28	2.27 (1.64, 3.14)	<0.001	30	515.50	2.43 (1.70, 3.48)	<0.001
Very preterm (28-33 weeks)	540	362.77	1.97 (1.80, 2.14)	1.69 (1.55, 1.85)	<0.001	311	374.79	1.56 (1.39, 1.75)	<0.001	229	347.64	1.91 (1.68, 2.18)	<0.001
Late preterm (34-36 weeks)	1565	256.20	1.38 (1.31, 1.45)	1.26 (1.19, 1.32)	<0.001	980	289.55	1.26 (1.18, 1.35)	<0.001	585	214.77	1.24 (1.14, 1.35)	<0.001
Early-term (37-38 weeks)	5972	220.36	1.19 (1.16, 1.23)	1.06 (1.03, 1.09)	<0.001	3494	242.52	1.04 (1.00, 1.08)	0.03	2478	195.21	1.08 (1.04, 1.13)	<0.001
Full-term (39-41 weeks)	20 948	185.76	Reference	Reference		12 245	212.63	Reference		8703	157.71	Reference	

(Continued)

Table 2. Continued

	All					Males					Females				
			Unadjusted		Adjusted[a]			Adjusted[a]				Adjusted[a]			
	Cases	Rate[b]	HR (95% CI)		HR (95% CI)	*P*	Cases	Rate[b]	HR (95% CI)	*P*	Cases	Rate[b]	HR (95% CI)	*P*	
Post-term (≥42 weeks)	2437	150.81	0.79 (0.76, 0.83)		1.05 (1.00, 1.09)	0.04	1488	178.00	1.05 (0.99, 1.11)	0.08	949	121.66	1.04 (0.97, 1.11)		0.24
Per additional week (trend)			0.92 (0.92, 0.93)		0.96 (0.96, 0.97)	<0.001			0.97 (0.96, 0.98)	<0.001			0.96 (0.95, 0.97)		<0.001
Attained ages 30-43 years															
Preterm (<37 weeks)	2178	698.93	1.53 (1.46, 1.60)		1.40 (1.34, 1.47)	<0.001	1365	783.25	1.38 (1.31, 1.46)	<0.001	813	591.94	1.44 (1.34, 1.55)		<0.001
Extremely preterm (<28 weeks)	42	1163.65	2.51 (1.85, 3.40)		2.22 (1.64, 3.01)	<0.001	24	1323.90	2.14 (1.43, 3.19)	<0.001	18	1001.94	2.38 (1.50, 3.78)		<0.001
Very preterm (28-33 weeks)	534	906.91	1.98 (1.82, 2.16)		1.82 (1.67, 1.98)	<0.001	339	1020.53	1.80 (1.62, 2.00)	<0.001	195	759.84	1.84 (1.59, 2.12)		<0.001
Late preterm (34-36 weeks)	1602	643.04	1.41 (1.34, 1.48)		1.29 (1.23, 1.36)	<0.001	1002	719.60	1.27 (1.19, 1.36)	<0.001	600	546.03	1.33 (1.23, 1.45)		<0.001
Early-term (37-38 weeks)	5632	546.38	1.21 (1.17, 1.24)		1.12 (1.09, 1.15)	<0.001	3491	620.83	1.11 (1.07, 1.15)	<0.001	2141	457.02	1.13 (1.08, 1.19)		<0.001
Full-term (39-41 weeks)	23 135	464.42	Reference		Reference		13 676	539.05	Reference		9459	386.96	Reference		
Post-term (≥42 weeks)	3932	433.44	0.90 (0.87, 0.94)		0.95 (0.92, 0.99)	0.007	2326	509.81	0.96 (0.92, 1.01)	0.11	1606	356.17	0.94 (0.89, 0.99)		0.02
Per additional week (trend)			0.93 (0.93, 0.94)		0.95 (0.95, 0.96)	<0.001			0.95 (0.95, 0.96)	<0.001			0.95 (0.94, 0.96)		<0.001

[a]Adjusted for child characteristics (birth year, sex, birth order, congenital anomalies) and maternal characteristics (age, education, BMI, smoking, preeclampsia, diabetes).
[b]Incidence rate per 100 000 person-years.

Figure 1 Adjusted hazard ratios for sleep-disordered breathing (SDB) by gestational age at birth relative to full-term birth, Sweden, 1973–2015.

1.10, 1.13; $P<0.001$). Higher risks were observed at earlier gestational ages (Table 2). Persons born extremely preterm had a 2.6-fold risk of SDB (adjusted HR, 2.63; 95% CI, 2.41, 2.87: $P<0.001$). Similar associations were observed among males and females (e.g. adjusted HR comparing preterm to full-term, males: 1.43; 95% CI, 1.40, 1.47; $P<0.001$; females: 1.42; 95% CI, 1.38, 1.47; $P<0.001$).

In analyses of narrower age intervals, preterm birth was strongly associated with increased risk of SDB in early childhood (ages 0–9 years: adjusted HR, 1.51; 95% CI, 1.47, 1.55; $P<0.001$). This association was weaker in later childhood/adolescence (ages 10–19 years: 1.14; 95% CI, 1.08, 1.21; $P<0.001$), then strengthened again in adulthood (ages 20–29 years: 1.36; 95% CI, 1.30, 1.42; $P<0.001$; ages 30–43 years: 1.40; 95% CI, 1.34, 1.47; $P<0.001$). A similar pattern was observed among both males and females (Table 2). Figure 1 shows the adjusted HRs (fitted by cubic spline) for SDB risk by attained age for different gestational age groups.

Interactions between preterm or early-term birth and sex in relation to SDB risk are shown in Supplementary Table 1, available as Supplementary data at *IJE* online. Across the entire age range (0–43 years), preterm-born males had the highest overall SDB incidence rate, which was substantially higher relative to preterm-born females (303.69 vs 254.81 per 100 000 person-years; adjusted HR, 1.20; 95% CI, 1.16, 1.25; $P<0.001$). Furthermore, a moderately positive additive interaction was found between preterm birth and male sex (i.e. the combined effect of these factors on SDB risk exceeded the sum of their separate effects; $P=0.003$; Supplementary Table 1, available as Supplementary data at *IJE* online), indicating that preterm birth accounted for more SDB cases among males.

Co-sibling analyses to control for unmeasured shared familial factors resulted in attenuation of risk estimates by an average of ~8% (Table 3), suggesting that the observed associations were only partly due to shared genetic or environmental factors in families. In analyses of the entire age

Table 3. Co-sibling analyses of gestational age at birth in relation to risk of sleep-disordered breathing (SDB), Sweden, 1973–2015

	All		Males		Females	
	HR (95% CI)[a]	*P*	**HR (95% CI)**[a]	*P*	**HR (95% CI)**[a]	*P*
Attained ages 0-43 years						
Preterm (<37 weeks)	1.35 (1.29, 1.40)	<0.001	1.34 (1.25, 1.44)	<0.001	1.32 (1.21, 1.43)	<0.001
Early-term (37-38 weeks)	1.05 (1.02, 1.07)	<0.001	1.04 (1.00, 1.08)	0.08	1.07 (1.03, 1.13)	0.002
Full-term (39-41 weeks)	Reference		Reference		Reference	
Per additional week	0.96 (0.95, 0.96)	<0.001	0.96 (0.95, 0.97)	<0.001	0.96 (0.95, 0.97)	<0.001
Attained ages 0-9 years						
Preterm (<37 weeks)	1.41 (1.34, 1.48)	<0.001	1.44 (1.32, 1.57)	<0.001	1.35 (1.22, 1.51)	<0.001
Early-term (37-38 weeks)	1.04 (1.01, 1.07)	0.004	1.06 (1.00, 1.11)	0.03	1.04 (0.98, 1.10)	0.25
Full-term (39-41 weeks)	Reference		Reference		Reference	
Per additional week	0.96 (0.95, 0.96)	<0.001	0.95 (0.94, 0.96)	<0.001	0.97 (0.95, 0.98)	<0.001
Attained ages 10-19 years						
Preterm (<37 weeks)	1.10 (0.99, 1.21)	0.07	1.16 (0.96, 1.41)	0.12	1.09 (0.92, 1.31)	0.32
Early-term (37-38 weeks)	1.04 (0.99, 1.10)	0.15	0.93 (0.84, 1.04)	0.23	1.16 (1.06, 1.27)	0.002
Full-term (39-41 weeks)	Reference		Reference		Reference	
Per additional week	0.98 (0.97, 0.99)	0.003	0.98 (0.96, 1.01)	0.25	0.98 (0.95, 1.00)	0.03
Attained ages 20-29 years						
Preterm (<37 weeks)	1.18 (1.06, 1.32)	0.003	1.13 (0.94, 1.37)	0.20	1.21 (0.95, 1.54)	0.12
Early-term (37-38 weeks)	1.01 (0.95, 1.08)	0.74	0.98 (0.88, 1.09)	0.71	1.07 (0.93, 1.23)	0.34
Full-term (39-41 weeks)	Reference		Reference		Reference	
Per additional week	0.98 (0.96, 0.99)	0.004	0.99 (0.96, 1.01)	0.27	0.96 (0.93, 0.99)	0.02
Attained ages 30-43 years						
Preterm (<37 weeks)	1.14 (0.97, 1.35)	0.12	1.09 (0.84, 1.42)	0.51	1.00 (0.65, 1.55)	0.99
Early term (37-38 weeks)	1.06 (0.96, 1.17)	0.28	1.09 (0.93, 1.28)	0.28	0.96 (0.73, 1.27)	0.80
Full-term (39-41 weeks)	Reference		Reference		Reference	
Per additional week	0.97 (0.95, 0.99)	0.01	0.98 (0.95, 1.02)	0.28	0.98 (0.92, 1.04)	0.53

[a]Adjusted for shared familial (genetic and/or environmental) factors, and additionally for specific child characteristics (birth year, sex, birth order, congenital anomalies) and maternal characteristics (age, education, BMI, smoking, preeclampsia, diabetes).

range (0–43 years), the risk estimates decreased only modestly. For example, the adjusted HR for SDB associated with preterm birth was 1.43 (95% CI, 1.40, 1.46) in the main analysis and 1.35 (95% CI, 1.29, 1.40) in the co-sibling analysis.

Secondary analyses

Further adjustment for fetal growth had a negligible effect on any of the risk estimates. A strong inverse association remained between gestational age at birth and SDB risk (e.g. adjusted HR per additional week of gestation, ages 0–43 years: 0.95; 95% CI, 0.95, 0.95; $P<0.001$; ages 30–43 years: 0.95; 95% CI, 0.94, 0.95; $P<0.001$) and an increased risk for preterm relative to full-term births (e.g. adjusted HR, ages 0–43 years: 1.43; 95% CI, 1.40, 1.45; $P<0.001$; ages 30–43 years: 1.42; 95% CI, 1.36, 1.48; $P<0.001$).

When more specific diagnostic codes for sleep apnoea were examined (i.e. by excluding adenotonsillar hypertrophy diagnoses), the overall findings were similar to those for SDB (Supplementary Table 2, available as Supplementary data at *IJE* online). For example, preterm birth was associated with more than a 1.4-fold risk of sleep apnoea across ages 0–43 years, relative to full-term birth (adjusted HR, 1.45; 95% CI, 1.38, 1.53; $P<0.001$). Associations with sleep apnoea were even stronger than for SDB in childhood and adolescence, but weaker in adulthood, though an increased risk was still observed at ages 30–43 years (adjusted HR, 1.15; 95% CI, 1.03, 1.28; $P=0.01$; Supplementary Table 2, available as Supplementary data at *IJE* online).

Analyses of other perinatal and maternal characteristics identified several other risk factors for SDB from birth to age 43 years, in addition to preterm birth and male sex (Table 4). After adjusting for all other factors, congenital anomalies were associated with more than a 3-fold risk of SDB. High maternal BMI and maternal smoking also were associated with increased SDB risk in the offspring. Maternal age was positively associated with SDB risk before adjusting for other factors, but inversely associated after adjusting for birth year. No association was found

Table 4. Associations between perinatal or maternal characteristics and risk of sleep-disordered breathing (SDB) from birth to age 43 years, Sweden, 1973–2015

	SDB		Unadjusted		**Adjusted**[a]	
	Cases	**Rate**[b]	HR (95% CI)	*P*	HR (95% CI)	*P*
Child characteristics						
Gestational age at birth						
Preterm (<37 weeks)	11 364	281.63	1.49 (1.46, 1.52)	<0.001	1.43 (1.40, 1.46)	<0.001
Extremely preterm (<28 weeks)	506	640.30	3.51 (3.22, 3.83)	<0.001	2.63 (2.41, 2.87)	<0.001
Very preterm (28-33 weeks)	2812	354.27	1.88 (1.81, 1.96)	<0.001	1.76 (1.70, 1.83)	<0.001
Late preterm (34-36 weeks)	8046	254.44	1.34 (1.31, 1.37)	<0.001	1.31 (1.28, 1.34)	<0.001
Early-term (37-38 weeks)	32 067	220.35	1.18 (1.16, 1.19)	<0.001	1.12 (1.10, 1.13)	<0.001
Full-term (39-41 weeks)	113 862	191.50	Reference		Reference	
Post-term (≥42 weeks)	13 807	174.10	0.86 (0.84, 0.87)	<0.001	0.95 (0.94, 0.97)	<0.001
Sex						
Male	95 892	216.93	1.20 (1.19, 1.22)	<0.001	1.21 (1.19, 1.22)	<0.001
Female	75 208	180.03	Reference		Reference	
Birth order						
1	77 169	212.58	Reference		Reference	
2	59 495	187.88	0.89 (0.88, 0.90)	<0.001	0.94 (0.93, 0.95)	<0.001
≥3	34.436	191.21	0.92 (0.91, 0.93)	<0.001	1.00 (0.99, 1.02)	0.60
Congenital anomalies						
Yes	627	538.34	2.69 (2.49, 2.91)	<0.001	3.54 (3.27, 3.83)	<0.001
No	170 473	198.54	Reference		Reference	
Maternal characteristics						
Age (years)						
<20	6656	199.71	0.94 (0.92, 0.97)	<0.001	1.13 (1.10, 1.16)	<0.001
20-24	40 729	201.77	1.01 (1.00, 1.02)	0.19	1.11 (1.09, 1.12)	<0.001
25-29	60 657	193.83	Reference		Reference	
30-34	42 926	198.75	1.06 (1.04, 1.07)	<0.001	0.88 (0.87, 0.90)	<0.001
35-39	16 972	209.58	1.13 (1.11, 1.15)	<0.001	0.82 (0.80, 0.83)	<0.001
≥40	3160	215.25	1.16 (1.12, 1.20)	<0.001	0.77 (0.75, 0.80)	<0.001
Education (years)						
≤9	23 553	183.95	0.81 (0.80, 0.83)	<0.001	0.94 (0.93, 0.96)	<0.001
10-12	86 999	209.69	Reference		Reference	
>12	60 548	191.10	0.93 (0.92, 0.94)	<0.001	0.81 (0.80, 0.82)	<0.001
Body mass index						
<18.5	3638	191.74	1.29 (1.25, 1.33)	<0.001	0.94 (0.90, 0.97)	<0.001
18.5-24.9	132 321	178.34	Reference		Reference	
25.0-29.9	24 919	334.85	2.24 (2.21, 2.28)	<0.001	1.14 (1.13, 1.16)	<0.001
≥30.0	10 222	418.34	2.77 (2.71, 2.82)	<0.001	1.21 (1.19, 1.24)	<0.001
Smoking (cigarettes/day)						
0	133 187	189.45	Reference		Reference	
1-9	24 338	208.41	1.08 (1.06, 1.09)	<0.001	1.31 (1.29, 1.33)	<0.001
≥10	13 575	199.14	1.02 (1.00, 1.04)	0.04	1.35 (1.32, 1.38)	<0.001
Preeclampsia						
Yes	7891	184.27	0.85 (0.83, 0.87)	<0.001	0.99 (0.97, 1.01)	0.47
No	163 209	199.78	Reference		Reference	
Diabetes mellitus						
Yes	1513	333.63	1.65 (1.57, 1.74)	<0.001	1.00 (0.95, 1.05)	0.95
No	169 587	198.29	Reference		Reference	

[a]Adjusted for birth year and all other variables included in the table.
[b]SDB incidence rate per 100 000 person-years.

between maternal preeclampsia or diabetes and SDB risk in the offspring, after adjusting for other factors (Table 4).

Discussion

In this large national cohort study, we found a strong inverse association between gestational age at birth and risk of SDB from childhood into mid-adulthood. After adjusting for other perinatal and maternal factors, preterm birth was associated with more than a 40% increased risk of developing SDB. Persons born extremely preterm had more than 2-fold risks. These associations weakened from childhood into adolescence, but strengthened again in adulthood. Both males and females were affected, although preterm birth accounted for more SDB cases among males.

This is by far the largest study of preterm birth in relation to SDB risk, and the first to examine this risk from childhood into mid-adulthood. Previous smaller studies have reported associations between preterm birth and SDB in infancy[20] and childhood,[21–23] as well as other sleep-related disorders in childhood, including irregular sleep patterns[39] and periodic limb movement disorder.[40,41] The largest of these was an Australian cohort study of 398 961 children that reported that low gestational age at birth (but not small for gestational age) was associated with increased risk of sleep apnoea at ages 1 to 6 years (adjusted HR, <32 vs >36 weeks: 2.74; 95% CI, 2.16, 3.49).[22] To our knowledge, only one previous study has examined preterm birth in relation to SDB symptoms in adulthood. A Finnish case-control study of 158 preterm-born adults and 169 term-born controls aged 18–27 years found that preterm birth with very low birthweight was associated with >2-fold odds of chronic snoring (adjusted OR, 2.21; 95% CI, 1.07, 4.54).[24] The present study advances earlier evidence by providing the first population-based risk estimates for SDB associated with gestational age at birth. Our findings from a large cohort show that preterm-born children and adults have a substantially increased SDB risk that extends into the mid-adulthood period.

In addition to preterm birth, our findings identified or confirmed several other risk factors for SDB, including male sex, congenital anomalies, high maternal BMI and maternal smoking. Maternal preeclampsia and diabetes were not associated with SDB risk in the offspring. These findings are largely consistent with previous studies that have reported associations with male sex[42,43] and maternal smoking,[24,44] but not preeclampsia.[24] Obesity is also a well-established risk factor for SDB or sleep apnoea.[42,45] The present study lacked BMI measures in the offspring later in life; however, the association we observed between high maternal BMI and SDB risk may potentially be explained by correlation of BMI between mothers and offspring.

The mechanisms underlying our findings may include craniofacial and upper airway soft tissue abnormalities that are more common in preterm-born children and adults[46] and have been linked with SDB risk.[42] Preterm birth has been associated with facial asymmetry as measured in sagittal occlusal relationships,[46] which may predispose to SDB through altered airway dimensions. Shared genetic factors are also possible, as sleep apnoea is known to have a substantial genetic basis,[47] partly mediated through differences in craniofacial structure.[48] However, our co-sibling analyses suggested that shared familial factors, either genetic or environmental, only partly explained the associations between preterm birth and SDB risk.

SDB has been associated with a wide range of adverse outcomes including neurocognitive and behavioural disorders in childhood,[49–51] and cognitive impairment, depression, metabolic syndrome and cardiovascular disease in adulthood.[13–17] Given the high prevalence of preterm birth (currently 10% in the USA[52] and 11% worldwide[1]), even a modest association with SDB risk may have large clinical and public health impacts because of the wide-ranging downstream effects on other chronic conditions. Our findings suggest that preterm-born children and adults need long-term follow-up for anticipatory screening and targeted treatment for SDB. Future studies will be needed to elucidate the potential role of SDB in mediating other chronic disorders in preterm-born childen and adults.

A major strength of the present study was the ability to examine preterm birth in relation to SDB in a large population-based cohort with follow-up into the fifth decade of life, using highly complete birth and medical registry data. This study design minimizes potential selection or ascertainment biases and provides more robust risk estimates. The results were controlled for other perinatal and maternal factors, as well as unmeasured shared familial factors using co-sibling analyses.

Limitations include the lack of polysomnography or other clinical data to verify diagnoses. Diagnoses in the Swedish Hospital Registry have been reported to have high validity for a wide range of conditions, including cardiovascular diseases, diabetes, asthma and mental disorders.[30] However, to our knowledge, sleep apnoea and adenotonsillar hypertrophy diagnoses have not been specifically validated. Undiagnosed SDB or sleep apnoea is common in the general population, especially for mild cases.[53] In the present study, outpatient diagnoses were unavailable before 2001, which further contributed to under-reporting. It is possible that persons born prematurely are more likely to be diagnosed with SDB because of increased contact with the health care system. However, Sweden's universal health care system may also reduce any differences in health care access or use compared with countries that lack

universal health coverage. Although we controlled for maternal BMI and smoking, we lacked data on BMI or smoking in the offspring later in life. Lastly, despite having the longest follow-up to date (up to 43 years), this was still a relatively young Swedish cohort. Additional follow-up will be needed to examine preterm birth in relation to SDB risk in later adulthood as well as in other diverse populations.

In summary, this large cohort study provides the first population-based risk estimates for SDB associated with gestational age at birth. We found that preterm birth is a strong, independent risk factor for the development of SDB from childhood into mid-adulthood. Preterm-born children and adults need long-term follow-up for screening, detection and potential treatment of SDB.

Supplementary Data

Supplementary data are available at *IJE* online

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Author Contributions

J.S. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: all authors. Acquisition of data: J.S., K.S. Analysis and interpretation of data: all authors. Drafting of the manuscript: C.C. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: C.C., J.S. Obtained funding: C.C., J.S.,K.S.

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