Cardiovascular Autonomic Control Is Altered in Children Born Preterm with Sleep Disordered Breathing

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Background To assess if the effects of sleep disordered breathing (SDB) on heart rate (HR) and HR variability, as a measure of autonomic control, were more severe in a group of children born preterm compared with a group of children born at term referred to our sleep laboratory for assessment of SDB.

Study design Children (3-12 years of age) referred for polysomnographic assessment of SDB were recruited; 50 born preterm (<37 weeks of gestation) and 50 at term, matched for age and SDB severity. The mean HR and HR variability using power spectral analysis were calculated for each child for wake and sleep, and stages N1, N2, N3, and rapid eye movement sleep.

Results Ex-preterm children were born between 23 and 35 weeks of gestational age (29.3 ± 3.6; mean ± SEM). There were no differences in the demographic, sleep, or respiratory characteristics between the groups. High-frequency power (reflecting parasympathetic activity) was greater in the ex-preterm children in both N2 and N3 ($P < .05$ for both) and total power was greater in N3 ($P < .05$). When the children were divided by SDB severity, these effects were most marked in those preterm born children with moderate to severe disease.

Conclusions Preterm born children matched for age and SDB severity with children born at term showed no differences in sleep characteristics; however, they did exhibit increased parasympathetic tone during non-rapid eye movement sleep. *(J Pediatr 2019;206:83-90).*

Every year 15 million, or 1 in 10 babies, are born preterm (<37 weeks of gestation) worldwide.[1] Babies and children born preterm are at increased risk of mortality and long term morbidity. One such morbidity is sleep disordered breathing (SDB), a spectrum of respiratory disorders ranging from primary snoring which is not associated with significant desaturation or sleep fragmentation to obstructive sleep apnea (OSA), which is characterized by repetitive hypoxia, hypercarbia, and disruption to sleep architecture.[2] SDB affects 4%-11% of children[3]; however, population cohort studies show that SDB is 3-6 times more likely to be found in children born preterm.[4-6] This predisposition persists into adulthood, with twice as many adults who were born preterm having OSA compared with those born at term.[7] It has been suggested that infants born prematurely are predisposed to upper airway obstruction and oxygen desaturation during sleep owing to decreased upper airway muscle tone, a highly compliant chest wall, and high nasal resistance.[8] In infancy[9,10] and childhood,[11] preterm birth is also associated with impaired autonomic cardiovascular control. Autonomic control can be assessed noninvasively using the variation over time of the period between consecutive heart beats modified by the sympathetic and parasympathetic nervous systems, termed heart rate variability (HRV).[12]

In children born at term, SDB of all severities has been associated with adverse effects on the cardiovascular system, with elevated blood pressure and reduced control of both heart rate (HR) and blood pressure.[13-15] Preterm birth (<32 weeks of gestational age) has been associated with an increased risk of heart failure in childhood and early adulthood[16] and with increased HR, blood pressure, and blood pressure variability in early adulthood.[17] An imbalance in autonomic nervous system function, with a predominance of sympathetic activity together with reduced HRV, are indicators of adverse cardiovascular outcomes in adults.[18,19] Studies of children and adolescents born preterm indicate that preterm birth is also associated with reduced HRV when awake, and HR recovery after exercise.[20-22] However, a previous study during sleep in children without SDB did not identify these differences.[11]

This study aimed to compare SDB severity and the effects of SDB on HR and HRV between children born at term and ex-preterm children. We hypothesized

ECG	Electrocardiogram
HR	Heart rate
HRV	Heart rate variability
OAHI	Obstructive apnea hypopnea index
OSA	Obstructive sleep apnea
PSG	Polysomnography
REM	Rapid eye movement
SDB	Sleep disordered breathing

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that those children who were born preterm would exhibit more severe SDB and that HR and HR control would be more severely affected by SDB.

Methods

Ethical approval was obtained from the Monash University and Monash Health Human Research Ethics Committees. Written informed consent was obtained from parents and verbal assent from children.

Between 2011 and 2016, 75 children (25 female/50 male) aged 3-12 years who had been born preterm (<37 weeks gestational age), and 1402 age-matched children (589 female/813 male) who were born at term (38-42 weeks gestational age) underwent overnight polysomnography (PSG) for assessment of SDB at the Melbourne Children's Sleep Center. All children were otherwise healthy with no comorbidities such as craniofacial syndromes, developmental disability, or genetic syndromes, and were not taking any medications known to affect breathing or sleep. For this retrospective study, our sample size calculation showed that we required 50 children in each group to detect a difference in HR of 10 bpm, which we deemed to be clinically significant, with a power of 0.8 and an α of 0.05. From this cohort, 50 children born preterm were randomly selected and matched for month and year of study, age, sex, and SDB severity with 50 children born at term. One child from each group was subsequently excluded owing to electrocardiogram (ECG) artefact (n = 98).

All children underwent overnight PSG, recorded using either a Compumedics Series E or Grael Sleep System (Compumedics, Melbourne, Australia). Before commencement of the PSG study children were weighed and measured and body mass index z-score calculated. Socioeconomic status was defined by matching each child's postcode with the corresponding Australian Bureau of Statistics Socio-Economic Indices for Areas measure.[23] This measure is a composite that includes household income, occupation, highest education level, and ethnicity. Low Statistics Socio-Economic Indices for Areas values indicate an area of social disadvantage and high values indicate an area of advantage.

Briefly, electroencephalogram (Cz, F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, O2-A1), right and left electrooculogram, submental and left and right anterior tibialis muscle electromyogram, and ECG recordings were obtained. Peripheral oxygen saturation was recorded, set to a 2-second averaging time (Masimo Radical Oximeter; Masimo Corporation, Irvine, California). Transcutaneous carbon dioxide was recorded using TINA TCM4 (Radiometer, Copenhagen, Denmark). Abdominal and thoracic respiratory parameters were measured using inductance plethysmography (Pro-Tech zRIPTM Effort Sensor, Pro-Tech Services Inc, Mukilteo, Washington). Oronasal airflow (Sandman BreathSensor, Child Airflow Thermistor, Tyco Healthcare, Manchester, United Kingdom) and nasal pressure (Salter Style, Salter Labs, Arvin, California) were also obtained. ECG was sampled at 512 Hz.

Sleep and respiratory events were scored according to standard guidelines by trained pediatric polysomnographic technicians.[24,25] All respiratory events were >2 missed breaths in duration. An obstructive apnea was defined as the cessation of airflow in association with inspiratory effort; an obstructive hypopnea was defined as a ≥30% decrease in nasal pressure amplitude, associated with work of breathing and an arousal or a ≥3% decrease in oxygen saturation; a central apnea was defined as cessation of airflow without inspiratory effort lasting ≥20 seconds or an event lasting at least the duration of 2 breaths associated with an arousal or a ≥3% oxygen desaturation.[24,25] An obstructive apnea hypopnea index (OAHI) was defined as the total number of obstructive apneas, mixed apneas, and obstructive hypopneas per hour of total sleep time and was used to define SDB severity groups. Primary snoring was defined as an OAHI ≤1 event/hour, mild OSA as an OAHI of >1-≤5 events/hour, and moderate/severe OSA as an OAHI of >5 events/hour. A central apnea hypopnea index was defined as the total number of central apneas and central hypopneas per hour of total sleep time.

PSG data were transferred to specialized data analysis software (LabChart 7.2, ADInstruments, Sydney, Australia) for analysis. Epochs containing wake after sleep onset or artefact were excluded. The mean HR for each child for wake and sleep stages, N1, N2, N3, rapid eye movement (REM) and total sleep across the entire night were calculated.

HRV Analysis

Power spectral analysis of the R-R intervals of the ECG recording from the overnight PSG was used to determine HRV. Total (0.04-0.4 Hz), low-frequency (0.04-0.15 Hz), and high-frequency (0.15-0.4 Hz) power were calculated. Total power reflects overall autonomic activity, low-frequency power reflects both sympathetic and parasympathetic activity, high-frequency power reflects parasympathetic activity, and the low-frequency/high-frequency ratio is a measure of sympathovagal balance. Every 2-minute artifact-free bin from the entire overnight study was selected. Because previous studies by our group have shown that the differences in HRV between SDB severity groups remained when respiratory events and arousals were excluded from the analysis, epochs containing respiratory events and arousals were not removed before the current analysis.[15,26] Two-minute bins were chosen to maximize the number of epochs available for analysis while ensuring an adequate length of time to accommodate enough oscillations within the low-frequency range to detect changes. HRV data were grouped according to sleep stage and a mean value for each subject calculated. The nocturnal fall in HR was calculated as (Wake HR – overall Sleep HR).

Statistical Analyses

Statistical analysis was performed using SigmaPlot (SigmaPlot Version 13.0, Systat Software, San Jose, California). Data were first tested for normality and equal variance. Demographic, PSG, and nocturnal fall in HR data were compared between preterm born and term born groups using an independent 2 sample student *t* tests. A comparison of the severity of SDB was compared between groups with χ^2 analysis. The HRV measures in each sleep stage between SDB severity groups were compared

Table I. Demographic characteristics of the ex-preterm and term children studied

	Ex-preterm	Term	*P* value
n	49	49	
Sex (female/male)	22/27	22/27	NS
Gestational age (wk)	29.3 ± 3.6	40.0 ± 0.0	<.001
Age at study (y)	6.4 ± 3.0	6.3 ± 2.9	NS
Height (cm)	112.8 ± 19.8	118.7 ± 18.1	NS
Weight (kg)	23.2 ± 13.9	25.6 ± 13.0	NS
BMI	17.1 ± 4.2	17.3 ± 3.5	NS
BMI z-score	0.1 ± 1.4	0.5 ± 1.3	NS
SES index	5.6 ± 2.5	5.9 ± 2.1	NS

BMI, body mass index; *NS*, not significant; *SES*, socioeconomic status.
Values are mean ± SEM.

with 2-way analysis of variance with student Newman-Keuls post hoc testing. Pearson correlation analysis was used to test the relationship between gestational age at birth and sleep and HRV variables in the preterm born group. Data are presented as mean ± SEM and a *P* value of <.05 was considered statistically significant.

Results

From the entire cohort of children (n = 1477) studied between 2011 and 2016, there was no difference in SDB severity between the 75 children born preterm (primary snoring, 37%; mild OSA, 28%; moderate/severe OSA, 35%) and the 1042 children born at term (primary snoring, 40%; mild OSA, 30% moderate/severe OSA, 30%).

Demographic data for the study cohort (n = 98) are presented in presented in **Table I**, after 1 child in each group was excluded from analysis owing to artefact in the ECG. Preterm-born children were born between 23 and 35 weeks of gestation (median, 30 weeks of gestation). There were no differences between the groups for sex, age, height, weight, body mass index, body mass index z-score, or socioeconomic status at the time of the study. By design, the preterm born cohort was born at a significantly younger gestational age ($P < .001$).

Sleep and respiratory data are presented in **Table II**. There were no differences between the 2 groups for any of the measures recorded. There were no effects of gestational age at birth on sleep and respiratory measures in the preterm born group.

A comparison of the HR and HRV between the groups is presented in the **Figure**. HR (**Figure**, A) tended to be lower in the ex-preterm children in each sleep state and this reached statistical significance in N3 ($P < .05$). When the nocturnal decrease in HR was compared between groups (Wake HR – overall Sleep HR), the preterm group had a significantly greater decrease in HR (14 ± 1 bpm) compared with the term group (11 ± 1 bpm; $P < .05$). This difference is, however, unlikely to be of clinical significance. High-frequency power (**Figure**, C) was greater in the ex-preterm children in both N2 and N3 ($P < .05$ for both) and total power (**Figure**, D) was greater in N3 ($P < .05$). There was no relationship between gestational age at birth and either HR or any HRV measure in the ex-preterm children.

Table II. Sleep and respiratory characteristics of the ex-preterm and term children studied

	Ex-preterm	Term	*P* value
Time available for sleep (min)	523.9 ± 32.2	529.3 ± 33.0	NS
Sleep period (min)	489.9 ± 39.6	484.0 ± 84.0	NS
Total sleep time (min)	447.6 ± 56.6	452.4 ± 74.8	NS
Sleep efficiency (%)	85.3 ± 8.3	86.6 ± 9.5	NS
Sleep latency (min)	33.0 ± 23.3	30.4 ± 23.3	NS
REM latency (min)	127.1 ± 48.4	127.7 ± 52.6	NS
WASO (min)	41.2 ± 33.2	33.6 ± 30.9	NS
N1%	7.1 ± 4.6	6.4 ± 3.9	NS
N2%	42.5 ± 7.2	44.9 ± 6.4	NS
N3%	28.5 ± 6.5	27.9 ± 5.3	NS
Non-REM%	78.1 ± 6.7	79.2 ± 4.6	NS
REM%	21.9 ± 6.7	20.8 ± 4.6	NS
OAHI	5.9 ± 11.6	7.5 ± 10.6	NS
CnAHI	2.2 ± 2.6	1.5 ± 1.4	NS
REM RDI	13.1 ± 24.8	14.4 ± 22.3	NS
SpO_2 nadir	87.8 ± 7.7	89.9 ± 6.2	NS
Avg SpO_2 drop	3.7 ± 1.8	3.5 ± 1.4	NS
SpO_2>4% drop/h	3.4 ± 10.0	2.4 ± 5.4	NS
% Respiratory arousals	26.5 ± 20.1	31.4 ± 27.0	NS
Avg $TcCO_2$ total sleep time (mm Hg)	47.6 ± 5.6	45.7 ± 5.5	NS

ArI, arousal index; *CnAHI*, central apnea hypopnea index; *OAHI*, obstructive apnea hypopnea index; *RDI*, respiratory disturbance index; *SpO_2*, arterial oxygen saturation; *$TcCO_2$*, transcutaneous carbon dioxide; *WASO*, wake after sleep onset.

Children were divided into SDB severity groups (**Table III**), and HRV measures compared between SDB severity groups within the term and preterm groups. There was no difference in HR between term and preterm groups when awake; however, the HR was higher in the term born children with moderate/severe OSA compared to those born preterm in N2, N3 and REM sleep ($P < .05$ for all) and this just failed to reach statistical significance in N1 ($P = .055$). Furthermore, the HR was higher in the term children with moderate/severe OSA compared with term children with primary snoring in N1 ($P < .01$), N2 ($P < .001$), N3 ($P < .01$), and REM ($P < .01$). In contrast, there were no differences in HR between SDB severity groups in the preterm born children. Within the preterm children, high-frequency power was lower in the primary snoring compared with the moderate/severe OSA group in N2 and N3, and total power was also lower in N3. Within the term children, high-frequency power was higher in the mild OSA compared with the moderate/severe OSA group.

HRV measures in the different SDB severity groups are also compared between the term and preterm children in **Table III**. There were no differences in any HRV measure in awake or REM sleep. In N1, the low-frequency/high-frequency ratio was higher in the preterm children with primary snoring ($P < .01$). In N2 and N3, high-frequency power and total power were higher in the preterm children in the moderate/severe OSA group.

Discussion

Preterm birth is associated with a number of long-term morbidities including deficits in HR and cardiovascular control.[16,17] Sleep-related breathing disorders have significant effects on

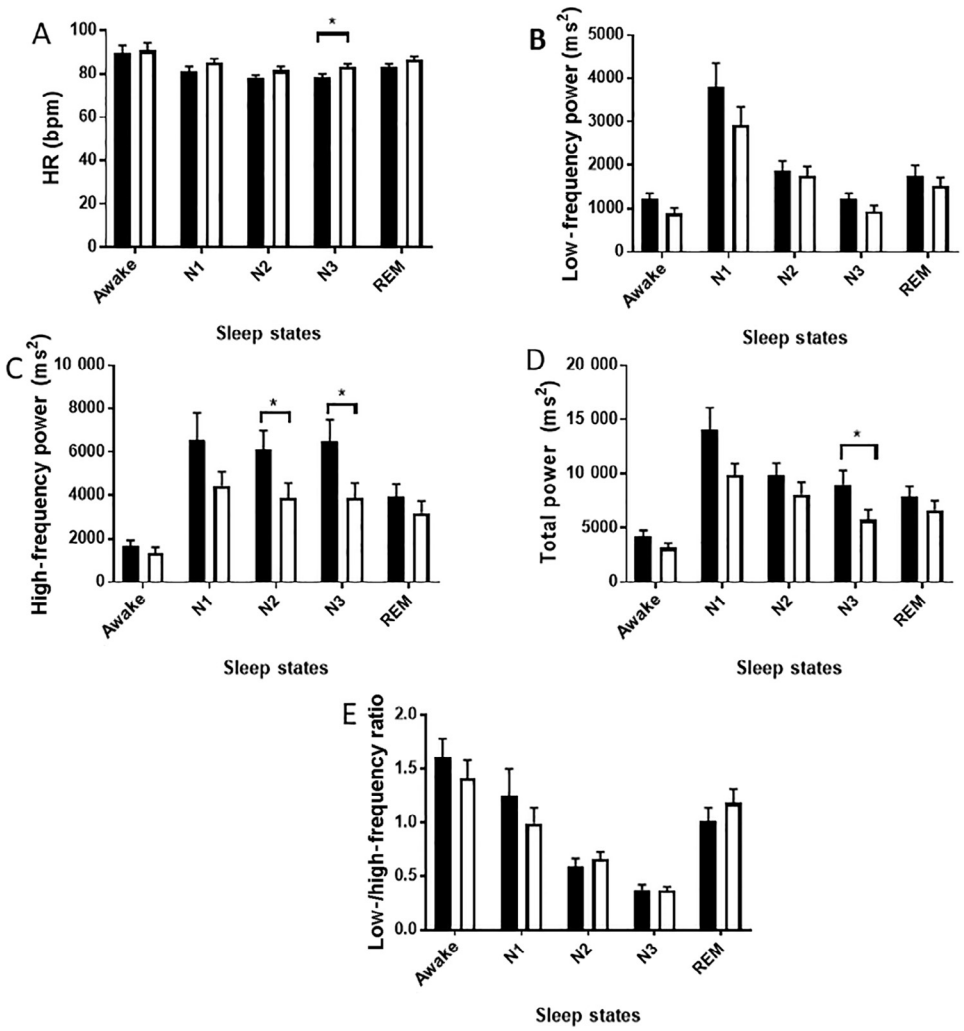

Figure. The effects of sleep state on HR and HRV in ex-preterm and term born children. **A,** HR, **B,** Low-frequency power. **C,** High-frequency power. **D,** Total power. **E,** High-frequency:low-frequency ratio. Black bars indicate ex-preterm children and white bars children born at term. Values are mean ± SEM. * P <0.05.

cardiovascular control in children born at term.[15] Population-based studies have reported that children born preterm have an increased incidence and severity of SDB compared with children born at term.[4,6] Our study of clinically referred children identified that 5% of the referred children were born preterm and there was no difference in severity of SDB between those born preterm and those born at term. Importantly, we found that, in the preterm group as a whole, the HR was lower and total power and high-frequency power were higher in N3 sleep, indicating increased parasympathetic activity. Furthermore, when the children were divided by SDB severity, these effects were most marked in those children with moderate to severe disease.

Previous studies in term born children with SDB have shown a decreased HRV compared with nonsnoring control children and these differences remained after exclusion of SDB events from the analysis.[15] In these studies, we suggested that the acute changes in blood pressure and the tachycardia and bradycardia that are associated with obstructive respiratory events, coupled with the chronic, elevated blood pressure during sleep in children with SDB, adversely impact on the autonomic control of HR during sleep as reflected in reduced HRV in these children. In contrast, in this study, we identified greater high-frequency power in preterm born children with SDB. This finding is supported by a previous study in preterm born children without SDB that also identified increased high-frequency power during sleep compared with term control children.[11] High-frequency HRV is related to respiratory-related changes (sinus arrhythmia) and reflects an important component of the vagal system that is used as a marker of vagal efferent activity to the heart.[12,27,28] It could be that the preterm born children had a more powerful parasympathetic response to changes in blood pressure related to breathing. Children with SDB have an increased work of breathing between as well as during

Table III. Comparison of HRV measures in the different SDB severity groups in preterm and term children‡‡

	Preterm			Term		
	Primary snoring (n = 21)	Mild OSA (n = 12)	Moderate/severe OSA (n = 16)	Primary snoring (n = 18)	Mild OSA (n = 9)	Moderate/severe OSA (n = 22)
Awake						
HR (bpm)	94 ± 3	94 ± 4	95 ± 3	90 ± 3	94 ± 4	101 ± 3
Low frequency (ms^2)	1021.98 ± 199.40	1528.39 ± 262.04	1166.78 ± 241.04	1033.56 ± 204.84	902.79 ± 307.27	681.66 ± 199.38
High-frequency (ms^2)	1135.67 ± 387.29	2241.91 ± 508.99	1917.34 ± 468.21	1843.14 ± 397.89	1374.23 ± 596.85	739.46 ± 387.29
Low frequency/high frequency	1.84 ± 0.25	0.98 ± 0.33	1.71 ± 0.30	1.15 ± 0.25	1.01 ± 0.38	1.80 ± 0.25
Total power (ms^2)	3208.81 ± 728.22	5369.68 ± 957.07	4581.59 ± 880.38	3916 ± 76	3410.28 ± 1122.27	2130.47 ± 728.22
N1						
HR (bpm)	80 ± 2	89 ± 3	83 ± 3	80 ± 3¶	85 ± 4	90 ± 2
Low frequency (ms^2)	3741.74 ± 791.33	3578.23 ± 951.06	3700.23 ± 860.29	2140.44 ± 823.64	2859.84 ± 1008.75	3502.86 ± 692.00
High frequency (ms^2)	4453.07 ± 1566.95	9004.57 ± 1883.25	6655.76 ± 1703.46	4760.50 ± 1630.94	5201.81 ± 1997.48	3834.00 ± 1370.26
Low frequency/high frequency	1.83 ± 0.30†	0.81 ± 0.36	0.88 ± 0.33	0.59 ± 0.31	0.71 ± 0.38	1.41 ± 0.26
Total power (ms^2)	12 472.12 ± 2637.22	16 692.17 ± 3169.55	12 839.41 ± 2866.96	10 144.64 ± 2744.91	10 475.39 ± 3361.81	9320.98 ± 2306.18
N2						
HR (bpm)	75 ± 2	82 ± 3	80 ± 2*	76 ± 2**	81 ± 3	87 ± 2
Low frequency (ms^2)	1796.56 ± 329.88	1506.53 ± 425.87	2278.14 ± 368.82	1734.93 ± 347.72	2124.40 ± 491.75	1504.55 ± 2314.53
High frequency (ms^2)	3883.56 ± 1200.69§	7360.97 ± 1550.08	8260.92 ± 1342.41†	5245.33 ± 1265.64	8054.06 ± 1789.88‡‡	2901.21 ± 1144.81
Low frequency/high frequency	0.65 ± 0.11	0.44 ± 0.14	0.61 ± 0.13	0.49 ± 0.12	0.65 ± 0.17	0.78 ± 0.11
Total power (ms^2)	7302.08 ± 11 647.52	10 190.13 ± 2126.94	12 639.40 ± 1841.98‡	8525.59 ± 1736.64	12 192.82 ± 2455.98	5569.30 ± 1570.85
N3						
HR (bpm)	76 ± 2	82 ± 3	80 ± 2*	78 ± 2¶	83 ± 3	88 ± 2
Low frequency (ms^2)	1263.13 ± 209.83	989.75 ± 270.88	1305.34 ± 234.59	970.85 ± 221.18	1425.53 ± 312.79	673.84 ± 200.06
High frequency (ms^2)	3518.37 ± 1229.06¶	8503.14 ± 1586.71	9014.18 ± 1374.13‡	3780.69 ± 1295.54	7823.68 ± 1832.17††	2261.08 ± 1171.86
Low frequency/high frequency	0.45 ± 0.06	0.29 ± 0.08	0.35 ± 0.07	0.38 ± 0.07	0.37 ± 0.09	0.35 ± 0.06
Total power (ms^2)	6028.28 ± 1582.28§	10 357.57 ± 2042.72	12 018.15 ± 1769.04‡	5611.43 ± 1667.87††	10 767.80 ± 2358.73	3601.77 ± 1508.65
REM						
HR (bpm)	80 ± 2	87 ± 3	85 ± 3*	80 ± 2¶	86 ± 3	92 ± 2
Low frequency (ms^2)	1728.19 ± 330.18	1409.47 ± 426.26	2042.64 ± 369.15	1519.10 ± 348.04	1973.20 ± 492.20	1246.38 ± 314.81
High frequency (ms^2)	3453.27 ± 873.73	4953.55 ± 1127.98	3935.60 ± 976.86	3539.50 ± 920.99	5093.58 ± 1302.48	1952.75 ± 833.07
Low frequency/high frequency	0.96 ± 0.20	0.89 ± 0.25	1.12 ± 0.22	0.89 ± 0.21	0.95 ± 0.29	1.51 ± 0.19
Total power (ms^2)	7228.26 ± 1388.23	8084.44 ± 1792.20	8731.95 ± 1552.09	6942.60 ± 1463.32	9500.92 ± 2069.45	4901.98 ± 1323.63

*$P < .05$ preterm vs term.
†$P < .01$ preterm vs term.
‡$P < .001$ preterm vs term.
§$P < .05$ primary snoring vs moderate/severe OSA.
¶$P < .01$ primary snoring vs moderate/severe OSA.
**$P < .001$ primary snoring vs moderate/severe OSA.
††$P < .05$ primary snoring vs Mild OSA.
‡‡$P < .05$ Mild OSA vs moderate/severe OSA.

respiratory events.[29] It is possible that, even though we matched for SDB severity on the basis of OAHI, the preterm group had more work of breathing owing to upper airway obstruction that was present outside of definable obstructive events. The intrathoracic pressure swing required to achieve a given tidal volume depends on lung volume and lung compliance. Decreased lung compliance as a long-term consequence of preterm birth has been shown in children born preterm,[30] and may be another explanation for increased work of breathing and more marked extrathoracic pressure swings that are being detected by greater high-frequency power. An alternative explanation for our finding of increased parasympathetic activity in the children born preterm could be that the rate of maturation of the autonomic nervous system is altered by preterm birth. Previous studies have identified that infants born preterm have lower parasympathetic activity compared with age-matched term infants at term-equivalent age.[31] When children were followed longitudinally at 2-3 and 6-7 years of age, they exhibited a faster maturation of parasympathetic activity than the term children, so that the differences observed in the neonatal period were no longer evident.[31] This study was, however, limited by the very small number of preterm born children studied (n = 5 at 6-7 years of age) and it did not take sleep state into account. In studies of normal healthy children low-frequency, high-frequency, and total power increased from birth to 6 years of age and then decreased to young adulthood when awake and in both sleep states.[32] Studies by our group have identified that infants born preterm have a slower maturation of both sympathetic[33] and parasympathetic activity, and this difference was most marked in non-REM sleep.[10,33] It could be that the maturation of parasympathetic activity overshoots or does not decrease at the same age as children born at term, perhaps as a response to greater blood pressure variability.[11] We have previously shown that the treatment or spontaneous resolution of SDB in children born at term is associated with a normalization of blood pressure,[34] improvement in blood pressure control,[35] and decrease in HRV, including high-frequency power.[36] We would expect similar results in children born preterm; however, further studies are required to confirm if high-frequency HRV is decreased after treatment of SDB.

In addition to increased high-frequency power, we also observed a lower HR in the preterm born children when asleep and this finding reached statistical significance in N3 sleep. However, the difference between groups was only 4 bpm and is unlikely to be of clinical significance. In a previous smaller study, no difference in HR during sleep was observed between children who had been born preterm and appropriately grown and those born preterm and growth restricted when studied at 5-12 years of age.[11] Studies during awake have also shown no difference in HR, but HR recovery after exercise was slower and overall HRV, measured in the time domain, was decreased in adolescents born preterm compared with those born at term.[21] HR was higher and HRV decreased in another study of children born preterm studied while awake at 9-10 years of age.[20] In that study, children born preterm were younger, shorter, and lighter than term children, in contrast with our study, where these demographic characteristics did not differ between the groups. In young adults, the HR was higher in those born preterm, although as in our study these differences were small and averaged 5 bpm.[17] Decreased HRV has been associated with an increased risk of cardiovascular disease and worse health outcomes in adults.[37]

In our entire clinically referred cohort, we did not identify any differences in the severity of SDB between children who were born at term and those born preterm. This finding is in contrast with previous community-based studies of children[4] and infants,[38,39] which relied on parental questionnaire to assess prevalence and severity of SDB. Five percent of our referred children were born preterm. This is somewhat lower than the expected 8%-10% of preterm children in the general population. This is likely due to our exclusion criteria, because only otherwise healthy children with no comorbidities such as craniofacial syndromes, developmental disability, or genetic syndromes, and who were not taking any medications known to affect breathing or sleep, were included. Thus, a number of preterm born children referred for assessment of SDB would not have been included in this study.

We also did not identify any differences in sleep architecture between the 2 groups of children. This finding is likely related to the fact that significant alterations in sleep architecture are not typically seen between term born children with and without SDB,[40] but highlights that sleep architecture is also relatively preserved in children born preterm who have SDB. There have been limited studies on the effects of preterm birth itself on sleep architecture, and none to date in children with SDB. Preterm birth has been shown to alter the development of melatonin rhythmicity in early infancy[41] and the development of circadian rhythms.[42] Studies of preterm born children using actigraphy have identified shorter sleep duration than population based recommendations for children of this age.[43] Short sleep duration may arise from altered circadian rhythms and both preterm born children[44] and adolescents[45,46] have been reported to have earlier sleep onset and wake times compared with their term born counterparts. In a previous smaller polysomnographic study by our group, preterm born children (n = 13) aged 5-12 years with appropriate weight for gestational age without SDB exhibited shorter sleep durations, decreased sleep efficiency, increased wake after sleep onset, and a decreased amount of non-REM sleep compared with children born at term (n = 20).[47] There were fewer differences in sleep architecture in those preterm born children who were growth restricted (n = 17).[47] In the current study, we did not have access to the birth weights of the children, so were unable to determine if they were appropriately grown or not. It is unclear why sleep architecture was altered in this smaller study of preterm born children; we have previously shown that sleep architecture is not significantly altered by SDB in children born at term,[40] and the current study suggests that sleep architecture is also preserved in preterm born children with SDB.

We acknowledge the limitations of our study. The study was retrospective and we did not have access to data on birth weight or neonatal complications. All of the children were referred for assessment of SDB and we did not have access to a

nonsnoring control group of preterm children recruited from the community. Finally, as a cross-sectional study, we cannot assert causality in our findings.

In conclusion, we have identified that children born preterm had increased parasympathetic activity, and we speculate that this may be a result of increased work of breathing compared with their peers who were born at term with similar SDB severity. Follow-up studies are required to assess the longer term effects of this on cardiovascular outcomes and to assess whether increased work of breathing is involved in the parasympathetic differences observed in this vulnerable group of children. ■

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