



ORIGINAL ARTICLE

## Being Born Too Small and Too Early May Alter Sleep in Childhood

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### Abstract

**Study Objectives:** Fetal growth restriction (FGR) occurs in up to 10% of pregnancies and is associated with increased risk of prematurity and neurodevelopmental impairment. FGR also alters sleep-state distribution in utero and maturation in infancy. Currently, limited data on the long-term associations of FGR and childhood sleep exist. Accordingly, we assessed the associations between preterm birth and FGR and sleep in children aged 5–12 years.

**Methods:** Seventeen children born preterm and FGR, 15 children born preterm but appropriately grown (appropriate birth weight for gestational age [AGA]), and 20 term AGA children (controls) were studied using overnight polysomnography. Sleep macroarchitecture was assessed using standard criteria, and sleep microarchitecture was assessed using spectral analysis of the electroencephalogram (C4-M1) with total,  $\delta$  (0.5–3.9 Hz),  $\theta$  (4.0–7.9 Hz),  $\alpha$  (8.0–11.9 Hz),  $\sigma$  (12.0–13.9 Hz), and  $\beta$  power (14.0–30 Hz) calculated.

**Results:** For sleep macroarchitecture, preterm FGR children had higher N2% compared with term AGA children ( $p < .05$ ). Preterm AGA children had reduced total sleep time, NREM%, and sleep efficiency compared with term AGA children ( $p < .05$  for all). For sleep microarchitecture, preterm FGR children had a higher amount of total,  $\delta$  and  $\alpha$  power compared with both groups ( $p < .05$ ). Sigma and  $\beta$  power was lowest in the preterm AGA group compared with both groups ( $p < .05$  for both).

**Conclusions:** Prematurity and FGR were associated with altered sleep macro- and microarchitecture measures indicative of reduced sleep quantity and quality in childhood. As sleep disturbance can affect both behavior and neurodevelopment in children, sleep in FGR and preterm children warrants further investigation.

### Statement of Significance

Fetal growth restriction (FGR) is a major obstetric complication affecting up to 10% of pregnancies leading to increased risk of preterm birth and neurodevelopmental impairment. FGR alters the development of sleep in fetal life and infancy; however, few studies have investigated the long-term impact on sleep. This novel study assessed both sleep macro- and microarchitecture in children born preterm and FGR. Being born preterm and FGR was associated with reduced sleep quality, whereas being born preterm with an appropriate birth weight for gestational age was associated with both reduced sleep quantity and quality. This study highlights the potential need for clinical follow-up of sleep and investigation of the effects of poor sleep on neurodevelopment in this population.

**Keywords:** fetal growth restriction, preterm birth, pediatric, EEG spectral analysis, sleep.

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## Introduction

Fetal growth restriction (FGR) is defined as an estimated fetal weight and/or birth weight at or below the 10th percentile for gestation and sex. FGR is associated with an increased risk of preterm birth (<37 weeks gestation), perinatal mortality, and short- and long-term morbidity.<sup>1</sup>

The major cause of severe FGR is placental insufficiency which compromises the delivery of oxygen and essential nutrients to the growing fetus. Consequently, severe FGR results in fetal asymmetry, where head growth is spared relative to body growth, known as the “head sparing” effect. These fetal adaptations are critical to optimize oxygen and nutrient delivery to the brain and heart of a compromised fetus and involve complex cardiovascular and metabolic changes. These adaptations do not always overcome the poor in utero environment, however, leading to high risk of neurodevelopmental impairment, including motor and sensory deficits, cognitive and learning difficulties, and cerebral palsy.<sup>2</sup> Underpinning these deficits, FGR is associated with altered brain structure, with reduced total brain and cortical gray matter volume.<sup>3</sup> In particular, both the hippocampus and the cerebellum are affected.<sup>4</sup>

In addition to cardiovascular changes, alterations in sleep patterning in utero also occur in the growth-restricted fetus. These alterations in sleep may arise from abnormal brain function due to hypoxic damage or impaired maturation.<sup>5</sup> It is speculated, also, that sleep patterning is altered in utero to preserve energy in the FGR fetus.<sup>6</sup> Specifically, the compromised fetus exhibits changes in the organization of sleep states,<sup>6</sup> favoring a state that requires reduced energy needs, in a reduced oxygen environment.<sup>7,8</sup> Although these adaptations are beneficial in the short-term, they may program the fetus for long-term sleep disturbances.<sup>9</sup>

It has been established that sleep expression is influenced by maternal, in utero as well as neonatal factors via gene-environment interactions that continually alter brain connectivity. Both FGR and preterm birth are known to alter brain connectivity, responsible for expressing sleep behavior.<sup>10,11</sup> Gestational age at birth is also known to influence brain development as connectivities at the time of birth are altered by the prenatal and postnatal experience.<sup>12</sup> Therefore, early life programming may have significant impact on sleep.<sup>13</sup> Although human data are scarce, studies suggest that FGR may alter the maturation of sleep circadian rhythms in neonatal life and based on actigraphy data, sleep efficiency (SE) later in life.<sup>14</sup> Compounding these sleep disturbances, being born preterm, whether the infant is growth restricted or not, is associated with altered maturation of sleep in infancy.<sup>15</sup> This is of particular concern, as sleep is the main behavioral state during the neonatal period and is known to be important for neurological development.<sup>16</sup> Poor sleep in childhood is also related to neurocognitive impairment<sup>17</sup> and in adulthood metabolic disorders and cardiovascular disease.<sup>18</sup>

To date, studies investigating sleep quantity and quality following FGR have been limited. The gold standard for assessment of sleep quantity and quality is overnight polysomnography (PSG). In order to determine whether sleep has been disrupted, PSG allows a detailed assessment of sleep macroarchitecture, which refers to the cyclical pattern of sleep as it shifts between nonrapid eye movement (NREM) and rapid eye movement (REM) sleep.<sup>19</sup> A more sensitive measure of sleep quality can also be quantified by investigation of sleep microarchitecture. Sleep

microarchitecture refers to the quantification of individual electroencephalogram (EEG) waveforms ( $\delta$ ,  $\theta$ ,  $\alpha$ ,  $\sigma$ , and  $\beta$ ) that occur during sleep and is assessed in the frequency domain using power spectral analysis.<sup>19</sup> In children, complimentary assessment of sleep micro- as well as macroarchitecture is believed to provide a more sensitive measure of sleep quantity and quality, as unlike sleep macroarchitecture, sleep microarchitecture has been associated with neurological and behavioral outcomes in children who exhibit sleep disturbance.<sup>20</sup>

Currently, there are no studies which have utilized PSG to assess sleep quantity and quality using both sleep macro- and microarchitecture analyses in children born FGR and preterm. Accordingly, this study aimed to address this gap in knowledge. We hypothesized that children born preterm and FGR would have poor sleep quantity and quality compared with term-born controls.

## Subjects and Methods

Approval for this study was obtained from the Monash Health and Monash University human research ethics committees. Written parental consent and verbal assent was obtained from the children prior to the commencement of each study. No monetary incentive for participation was provided.

Children aged between 5 and 12 years were recruited for each group. Eighteen children born between 24 and 36 weeks of gestational age were identified and recruited from a cohort of FGR pregnancies delivered at Monash Medical Centre.<sup>21</sup> As described, FGR was defined by estimated fetal weight <10th percentile for gestation, together with either absent or reversed end-diastolic flow of the umbilical artery identified on fetal Doppler ultrasound, of these children, five children were severely growth restricted with a birthweight of <3% for gender and age. Fifteen children born preterm with a birthweight appropriate for gestational age (AGA) and between 24 and 36 weeks gestational age were recruited from a cohort of infants born at Monash Medical Centre and from the community between 2001 and 2010. Twenty full-term AGA children with gestational age range of 38–42 weeks were recruited from the community. This study was part of a larger project, which also investigated the effects preterm birth and FGR on cardiovascular structure, function, and control.<sup>22</sup>

### Polysomnography

All children underwent overnight PSG at the Melbourne Children's Sleep Centre using a commercial sleep recording system (Series E Sleep System, Compumedics, Melbourne, Australia) and standard pediatric recording techniques, as described previously.<sup>23,24</sup> Prior to commencement of the PSG study, children were weighed and measured and body mass index (BMI) z-score calculated.

Electrodes for recording EEG (C4-M1, O2-M1, F4-M1), left and right electrooculograms (EOG), submental electromyogram (EMG), and electrocardiogram (ECG) were attached. The ECG signal was digitized at a sampling rate of 512 Hz. Leg movements were measured by EMG of the left and right anterior tibialis muscle. Thoracic and abdominal breathing movements (Pro-Tech zRIP™ Effort Sensor, Pro-Tech Services Inc., Mukilteo, WA, USA), oxygen saturation (Massimo, Radical 7, Irvine, CA, USA), transcutaneous carbon dioxide (TcCO<sub>2</sub>, TCM4/40, Radiometer, Copenhagen,

Denmark), nasal pressure, and oronasal airflow were also recorded. In addition, continuous blood pressure recordings were made using finger photoplethysmography (Finometer™, Finapres Medical Systems, Amsterdam, The Netherlands).

### Sleep Macroarchitecture

Following the PSG study, sleep architecture was assessed by the same trained technician and scored in 30-second epochs according to standard criteria as NREM stages N1, N2, and N3 and REM sleep.<sup>25</sup> In addition to sleep staging, respiratory disturbance during sleep was also assessed. Respiratory event scoring was performed in accordance with international standards.<sup>25</sup> Briefly, respiratory events of greater than two respiratory cycles in duration were scored and the obstructive apnea-hypopnea index (OAHI) (total number of obstructive apneas, mixed apneas, and obstructive hypopneas per hour of total sleep time [TST]) was calculated. Following PSG scoring, data were transferred via European data format to data analysis software (LabChart 7.2, ADInstruments, Sydney, Australia) for detailed EEG microarchitecture analysis.

Standard measures of sleep quality were calculated for each participant and included as follows: the duration of each sleep stage (N1, N2, N3 REM), expressed as a percentage of TST. Wake after sleep onset (WASO) was defined as the amount of WASO until lights on at the end of the study. WASO percentage (WASO%) was calculated as the percentage of time awake during the sleep period time (SPT), with SPT defined as the amount of time in minutes from sleep onset until lights on at the end of the study. TST was defined as SPT excluding all periods of wake. Other variables calculated included time in bed (TIB), sleep latency, REM latency, and SE. TIB was defined as the time between lights off and lights on. Sleep latency was defined as the period from lights off to the first three consecutive epochs of N1 sleep or an epoch of any other stage. REM latency was defined as the period from sleep onset to the first epoch of REM sleep. SE was defined as the ratio of TST to TIB.

### Sleep Microarchitecture—Spectral Analysis

Microarchitecture was assessed using spectral analysis of the EEG signal<sup>26</sup> performed in Labchart 7.2 (ADInstruments, Sydney, Australia). Raw EEG signals were recorded using a band-pass filter ranging from 0.3 to 100 Hz and a sampling frequency of 512 Hz. Spectral analysis was performed on the primary EEG channel (C4-M1). To remove any low or high frequency artifact from the signal, entire EEG time series was digitally filtered using a band-pass filter ranging from 0.5 to 30 Hz. Thirty-second epochs containing significant artifact, defined as a 30-second epoch containing >10 seconds of movement artifact that interrupted the EEG signal, were excluded from analysis. In all studies, the first epoch of the recording was deleted, as well as the last epoch if it did not run for the full 30 seconds. The following frequency bands were set as  $\delta$  (0.5–3.9 Hz),  $\theta$  (4–7.9 Hz),  $\alpha$  (8–11.9 Hz),  $\sigma$  (12–13.9 Hz), and  $\beta$  power (14–30 Hz).<sup>27</sup> Spectral analysis was run using a fast Fourier transform (FFT) size of 1,024 over the entire PSG recording with a Hanning window, which allowed edge effects to be avoided.<sup>28</sup> The FFT output provided a total power for 2-second blocks with a frequency resolution of 0.5 Hz. These 0.5-Hz frequency bins were subsequently summed within five frequency bands, producing a single power value for each band. In addition, total power for each 2-second block was determined (0.5–30 Hz). As EEG power is known to be affected by sleep stage

in children,<sup>27</sup> a mean value for each frequency was calculated for each 30-second epoch and then averaged per sleep stage within each child.

### Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp. Armonk, NY). For each variable, normality was assessed using Shapiro–Wilk tests. Nonparametric data were log transformed to achieve normality. Mean values for demographic and sleep variables were compared between groups with one-way analysis of variance (ANOVA). For all birth outcomes and obstetric complications, dichotomous variables were analyzed using two-group binominal comparisons (Fisher exact test) between preterm FGR and preterm AGA groups. Pearson's correlation analysis was performed between macro- and microarchitecture measures and a number of birth characteristics: gestational age at birth, birthweight, birth weight percentile,<sup>29</sup> head circumference,<sup>30</sup> head circumference percentile, head circumference to weight ratio, together with a number of demographic characteristics at the time of the study: age, weight, height, and BMI z-score. "Study age" was the only variable significantly correlated with both sleep macro- and microarchitecture measures and therefore was entered as a covariate and accounted for in each statistical model wherever appropriate. To compare sleep macroarchitecture indices, a general linear model univariate analysis was performed to compare the fixed effect of "group." To assess sleep microarchitecture, a linear mixed model analysis was used to assess the main effects of "group" and "sleep stage," with sleep stage entered as a repeated measure for all microarchitecture indices. Subject was entered as a random effect. Bonferroni post hoc comparison was performed on significant main effects. Data are presented as mean  $\pm$  sem, with significance taken at the  $p < .05$  level.

## Results

### Demographics

The demographics of the children are presented in [Table 1](#). In total, 17 preterm FGR children (eight females/nine males; mean gestational age  $30 \pm 1$  weeks, mean birth weight  $1129 \pm 118$  g); 13 preterm AGA children (seven females/six males; mean gestation  $29 \pm 1$  weeks; mean birth weight  $1506 \pm 204$  g) and 20 full-term AGA children (nine females/11 males; mean gestation  $40 \pm 0$ ; mean birth weight  $3509 \pm 85$  g) were included in the analysis. One preterm FGR child and two preterm AGA children were excluded from the sleep analysis as their TST was less than 4 hours. Those children that had less than 4 hours sleep were either ill on the night or had extreme anxiousness with difficulty sleeping throughout the night. The majority of children were developing normally at the time of the study. Two preterm FGR children had neurodevelopmental delay and one preterm AGA child had documented left hemiparesis with mild cerebral palsy. Exclusion of these children from statistical analysis did not change group differences between sleep macro- or microarchitecture results; therefore, we have chosen to leave these children in the final group comparisons. There was no difference in gestational age at birth between the preterm FGR and preterm AGA groups. As expected, average birthweight and birthweight percentiles were lower in the preterm FGR group than both the

preterm AGA group (birthweight  $p < .001$ , birth weight percentile  $p = .007$ ) and the term AGA group (birthweight  $p < .001$ , birth weight percentile  $p = .002$ ). Head circumference was smaller in the preterm FGR and AGA groups compared with the term AGA group ( $p < .001$  for both). However, there were no differences in head circumference percentile between the groups. Apgar scores at 5 minutes were lower in the preterm FGR compared with the term AGA group ( $p = .035$ ). Maternal obstetric histories identified that the cause of FGR was probably from placental insufficiency associated with hypertensive pregnancy disorders such as pre-eclampsia and maternal hypertension. Premature delivery in the preterm AGA group was associated with pre-eclampsia, pre-existing maternal disease, infection, or occurred spontaneously. There were no differences between the three groups for age, weight, and BMI z-scores at the time of study (aged 5–12).

## Sleep Macroarchitecture

### Effect of Preterm Birth and FGR

The sleep macroarchitecture measures are presented in Table 2. Preterm FGR children had similar macroarchitecture compared with the term AGA group with the exception of N2%, which was higher in preterm FGR children compared with both the preterm AGA ( $p < .001$ ) and term AGA groups ( $p = .014$ ). Preterm FGR children also had a lower proportion of N3 sleep, with N3% averaging lowest of the three groups and significantly reduced when compared with preterm AGA children ( $p = .006$ ). In contrast, the preterm AGA group showed a number of differences in macroarchitecture measures compared with both preterm FGR and term AGA

groups. Preterm AGA children had shorter sleep duration with TST averaging 45 minutes less than preterm FGR ( $p = .05$ ) and 64 minutes less than term AGA children ( $p = .008$ ). Preterm AGA children had a reduced amount of NREM sleep, averaging 48 minutes less compared with term AGA children ( $p = .003$ ) and 40 minutes less than preterm FGR children ( $p = .013$ ). In preterm AGA children, SE was lower compared with term AGA children ( $p = .022$ ), N3% was higher compared with preterm FGR children ( $p = .006$ ), and WASO% was higher compared with term AGA children ( $p = .047$ ). No differences between time available for sleep, SPT, OAH, and arousal index were identified between the three groups.

### Associations With Gestational Age, Birthweight, and Head Circumference

Correlation analysis performed within each group revealed no significant associations between sleep macroarchitecture measures for the preterm FGR group. However, the preterm AGA group had a significant negative association between gestational age and SE ( $p < .045$ ,  $r = -0.563$ ) and a positive association between gestational age and WASO% ( $p = .023$ ,  $r = 0.623$ ). There was a tendency for gestational age to be positively correlated with NREM% and negatively correlated with REM%; however, this just failed to reach significance ( $p = .056$  for both). For term AGA children, gestational age (which ranged from 37 to 42 weeks) was positively correlated with NREM% ( $p = .040$ ,  $r = 0.501$ ) and negatively correlated with REM% ( $p = .040$ ,  $r = -0.501$ ). There were no associations in any group between birthweight, head circumference percentiles, or head circumference to weight ratio with any of the sleep macroarchitecture measures.

Table 1. Demographics of Preterm FGR Children, Preterm AGA Children, and Term AGA Children Aged Between 5 and 12 years

	Preterm FGR (n = 17)	Preterm AGA (n = 13)	Term AGA (n = 20)	p
Birth outcomes				
Gender	8F/9M	7F/6M	9F/11M	
Gestation age (wk)	30 ± 1 <sup>a</sup>	29 ± 1 <sup>b</sup>	40 ± 0	<.001
Birth weight (g)	1129 ± 118 <sup>a</sup>	1506 ± 204 <sup>b,c</sup>	3509 ± 85	<.001
Birth height (cm)	37 ± 1 <sup>a</sup>	41 ± 2	50 ± 1	.028
Head circumference (cm)	27 ± 1 <sup>a</sup>	29 ± 1 <sup>b</sup>	34 ± 1	<.001
Birth weight percentile (%)	8 ± 3 <sup>a</sup>	46 ± 7 <sup>b,c</sup>	49 ± 6	.001
Head circumference percentile (%)	30 ± 8	64 ± 7 <sup>c</sup>	42 ± 6	.020
Apgar at 1 min	6 ± 1	6 ± 0	7 ± 0	.109
Apgar at 5 min	8 ± 0 <sup>a</sup>	8 ± 0	9 ± 0	.040
Oxygen supplementation, n (%)	16(94)	9(69)	0	.138
Assisted ventilation, n (%)	14(82)	9(69)	0	.666
Respiratory distress syndrome, n (%)	11(65)	7(54)	0	.711
Bronchopulmonary dysplasia, n (%)	5(29)	7(54)	0	.264
Patent ductus arteriosus, n (%)	2(12)	5(38)	0	.190
Intraventricular haemorrhage, n (%)	0(0)	1(8)	0	.433
Neurodevelopmental impairment, n (%)	2(12)	1(8)	0	1.000
Obstetric complications				
Pre-eclampsia/hypertension, n (%)	7(41)	2(15)	0	.229
Gestational hypertension, n (%)	1(6)	0(0)	0	1.000
Essential hypertension, n (%)	1(6)	2(15)	0	.565
Pre-existing maternal disease, n (%)	5(29)	4(31)	0	1.000
Study details				
Age at study (y)	9 ± 0.6	9 ± 0.5	9 ± 0.5	.430
Weight at study (kg)	33 ± 4	28 ± 3	30 ± 2	.624
BMI z-score	-0.3 ± 0.5	-0.1 ± 0.4	0.1 ± 0.2	.741

<sup>a</sup> $p < .05$  preterm FGR vs term.

<sup>b</sup> $p < .05$  preterm AGA vs term AGA.

<sup>c</sup> $p < .05$  preterm FGR vs preterm AGA.

**Table 2.** Sleep Macroarchitecture Measures in Preterm FGR Children, Preterm AGA Children and Term AGA Children Aged Between 5 and 12 years

	Preterm FGR (n = 17)	Preterm AGA (n = 13)	Term AGA (n = 20)	p
Time available to sleep (min)	509 ± 8	497 ± 9 <sup>a,b</sup>	513 ± 6	.250
Sleep onset latency (min)	38 ± 6	38 ± 10	24 ± 3	.275
Sleep period time (min)	448 ± 22	457 ± 13	486 ± 8	.344
Total sleep time (min)	409 ± 13	364 ± 17 <sup>b</sup>	428 ± 12	.008
Sleep efficiency (%)	80 ± 2	73 ± 4 <sup>b</sup>	83 ± 2	.014
REM latency (min)	165 ± 15	145 ± 16	141 ± 13	.425
N1 (min)	25 ± 2	29 ± 3	29 ± 3	.354
N2 (min)	198 ± 13 <sup>c</sup>	154 ± 10 <sup>a,b</sup>	189 ± 12	.010
N3 (min)	101 ± 5	112 ± 4	118 ± 6	.223
NREM (min)	335 ± 9	295 ± 12 <sup>a,b</sup>	343 ± 8	.021
REM (min)	65 ± 7	68 ± 6	84 ± 5	.069
N1%	6 ± 1	8 ± 1	9 ± 2	.287
N2%	50 ± 3 <sup>c</sup>	42 ± 1 <sup>a</sup>	44 ± 2	<.001
N3%	25 ± 1	32 ± 1 <sup>a</sup>	28 ± 2	.007
NREM%	84 ± 1	82 ± 1	81 ± 1	.153
REM%	17 ± 1	18 ± 1	19 ± 1	.133
WASO%	12 ± 2	20 ± 3 <sup>b</sup>	12 ± 2	.029
OAH1	0.4 ± 0.1	0.5 ± 0.3	0.4 ± 0.2	.757
Arousal index	11 ± 1	11 ± 1	12 ± 1	.970

<sup>a</sup>p < .05 preterm FGR vs preterm AGA.

<sup>b</sup>p < .05 preterm AGA vs term AGA.

<sup>c</sup>p < .05 preterm FGR vs term.

N1 = nonrapid eye movement sleep stage 1; N2 = nonrapid eye movement sleep stage 2; N3 = nonrapid eye movement sleep stage 3; NREM = nonrapid eye movement sleep; REM = rapid eye movement sleep; WASO% = wake after sleep onset percentage; OAH1 = obstructive apnea hypopnea index.

## Sleep Microarchitecture

### Effects of Preterm Birth and FGR

Figure 1 compares the sleep microarchitecture measures between the three groups. The mixed model analysis revealed a significant effect of group for total power (Figure 1a) (main effect group,  $p = .005$ ) and  $\delta$  power (Figure 1b) (main effect group,  $p = .005$ ). Overall preterm FGR children had a higher amount of total (Figure 1a) and  $\delta$  power (Figure 1b) compared with both the preterm AGA group (total power,  $p = .008$ ;  $\delta$  power,  $p = .010$ ) and term AGA group (total power,  $p = .028$ ;  $\delta$  power,  $p = .019$ ). For  $\theta$  power (Figure 1c), there was a significant interaction (group  $\times$  stage,  $p = .035$ ), with  $\theta$  power being significantly higher in preterm FGR group compared with the preterm AGA group in N3 ( $p = .042$ ). Similarly for  $\alpha$  power (Figure 1d), there was a significant interaction (group  $\times$  stage,  $p = .007$ ), with  $\alpha$  power being significantly higher in the preterm FGR group compared with the preterm AGA group ( $p < .001$ ) and term AGA group ( $p = .043$ ) during N2 and higher compared with the preterm AGA group ( $p = .006$ ) during N3. Alpha power was also lower in preterm AGA group compared with the term AGA group ( $p = .019$ ) during N2. For  $\sigma$  (Figure 1e) and  $\beta$  (Figure 1f) power, a significant main effect of group was identified ( $\sigma$  main effect group,  $p < .001$ ;  $\beta$  main effect group,  $p = .001$ ), where spectral power was lowest in the preterm AGA group compared with both term AGA ( $\sigma$ ,  $p = .035$ ;  $\beta$ ,  $p = .037$ ) and preterm FGR groups ( $\sigma$ ,  $p < .001$ ;  $\beta$ ,  $p = .001$ ).

### Effects of Sleep Stage

Figure 2 compares the sleep stage effects on sleep microarchitecture in the three groups. In general, NREM sleep stages had higher power compared with REM for most frequency ranges. There was a main effect of sleep stage for both total (Figure 2a) (main effect stage,  $p < .001$ ) and  $\delta$  (Figure 2b) (main effect stage,  $p < .001$ ) power, with  $\delta$  power increasing with the depth of sleep,

i.e.,  $N1 < N2 < N3$  ( $p < .05$  for all) in NREM sleep. A significant interaction was identified for  $\theta$  (Figure 2c) (group  $\times$  stage,  $p = .035$ ) and  $\alpha$  (Figure 2d) (group  $\times$  stage,  $p = .007$ ) power measures. Post hoc tests within each group revealed that  $\theta$  power was higher in N2 and N3 compared with N1 preterm FGR (N1 vs N2,  $p = .001$ ; N1 vs N3,  $p < .001$ ), preterm AGA (N1 vs N2,  $p = .003$ ; N1 vs N3,  $p < .001$ ), and term AGA (N1 vs N2,  $p < .001$ ; N1 vs N3,  $p < .001$ ) children. Alpha power was higher in N2 and N3 compared with N1 in the preterm FGR (N1 vs N2,  $p < .004$ ; N1 vs N3,  $p < .001$ ) and term AGA groups (N1 vs N2,  $p < .008$ ; N1 vs N3,  $p < .001$ ).

For the faster frequencies, a main effect of sleep stage for  $\sigma$  (main effect stage,  $p < .001$ ) and  $\beta$  (main effect stage,  $p < .001$ ) power was observed. Sigma power (Figure 2e) was lower in N1 compared with N2 and N3 (N1 vs N2,  $p < .001$ ; N1 vs N3,  $p < .001$ ), but higher in N2 compared with N3 ( $p < .001$ ). Sigma power was lowest in REM sleep compared with the other sleep stages (REM vs N1,  $p = .001$ , REM vs N2,  $p < .001$ ; REM vs N3,  $p < .001$ ). In contrast,  $\beta$  power (Figure 2f) was higher in N1 compared with N2 and N3 sleep (N1 vs N2,  $p = .042$ , N1 vs N3,  $p = .001$ ). Beta power was lowest in REM sleep compared with NREM sleep stages (REM vs N1,  $p < .001$ , REM vs N2,  $p < .001$ ).

### Associations With Gestational Age and Birthweight

Correlation analysis performed within each group revealed no significant associations among gestational age, birth weight, and head circumference or head circumference to weight ratio with any sleep microarchitecture measures.

## Discussion

FGR is associated with altered development of sleep, beginning in utero and continuing throughout infancy.<sup>31,32</sup> Currently, it is unclear whether these associations persist into childhood. To the best of our knowledge, this study was the first to assess

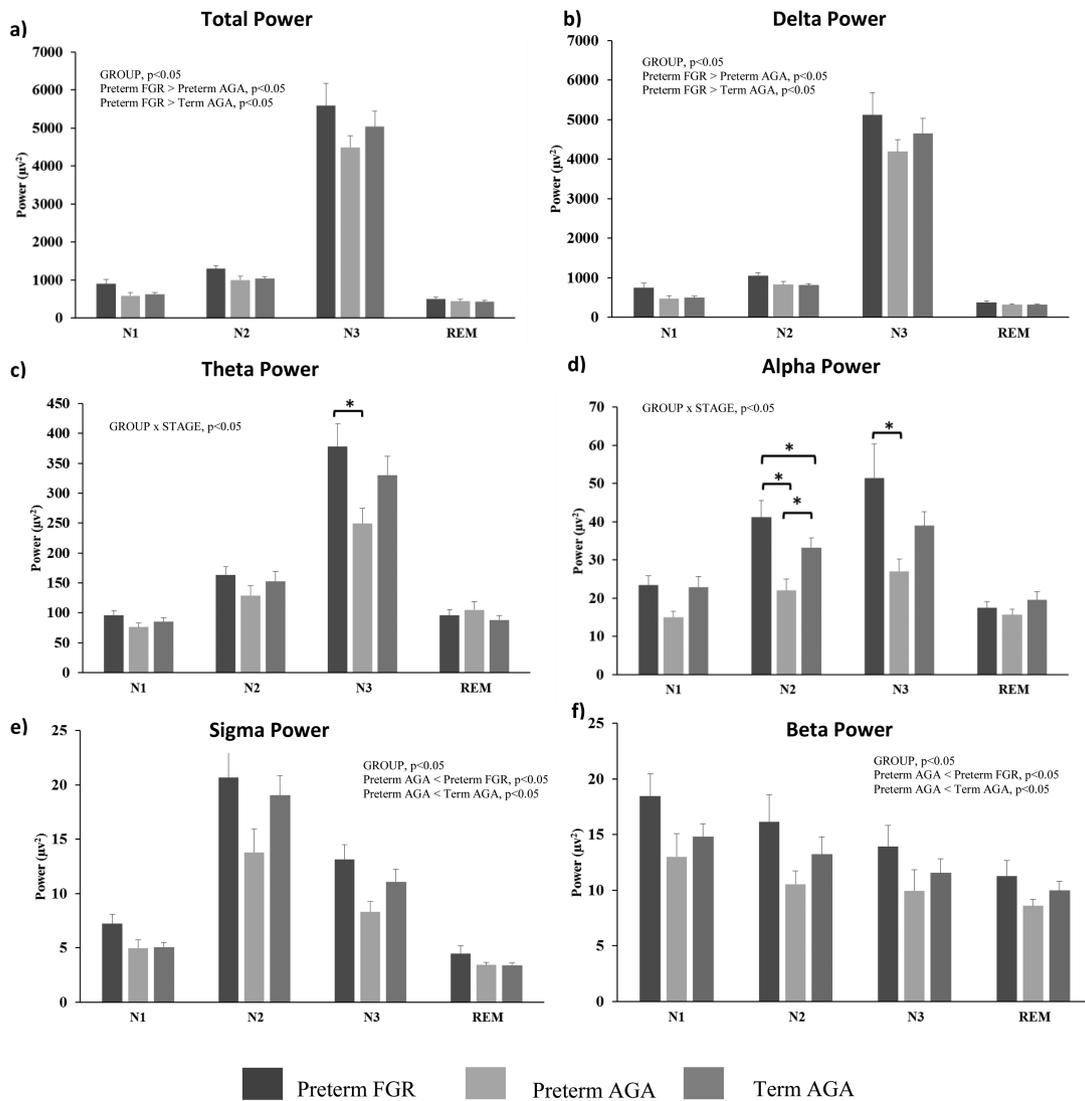


Figure 1. Comparison by group of power spectral values for total (0.5–30 Hz),  $\delta$  (0.5–3.9 Hz),  $\theta$  (4.0–7.9 Hz),  $\alpha$  (8.0–11.9 Hz),  $\sigma$  (12.0–13.9 Hz), and  $\beta$  (14.0–30 Hz) frequency bands in children aged 5–12 born preterm FGR, preterm AGA, and term AGA during N1, N2, N3, and REM sleep. \* $p < .05$

sleep quantity and quality in school-aged children born preterm with an appropriate birth weight for gestational age as well as the children born preterm with FGR. Using PSG, this study identified that being born preterm AGA was associated with altered sleep macroarchitecture, whereas severe FGR was associated with alterations in sleep microarchitecture. Overall, these findings suggest that premature birth and FGR may have long-term effects on sleep quality and quantity that persists beyond infancy and into childhood.

## Sleep Macroarchitecture

### Preterm FGR Children

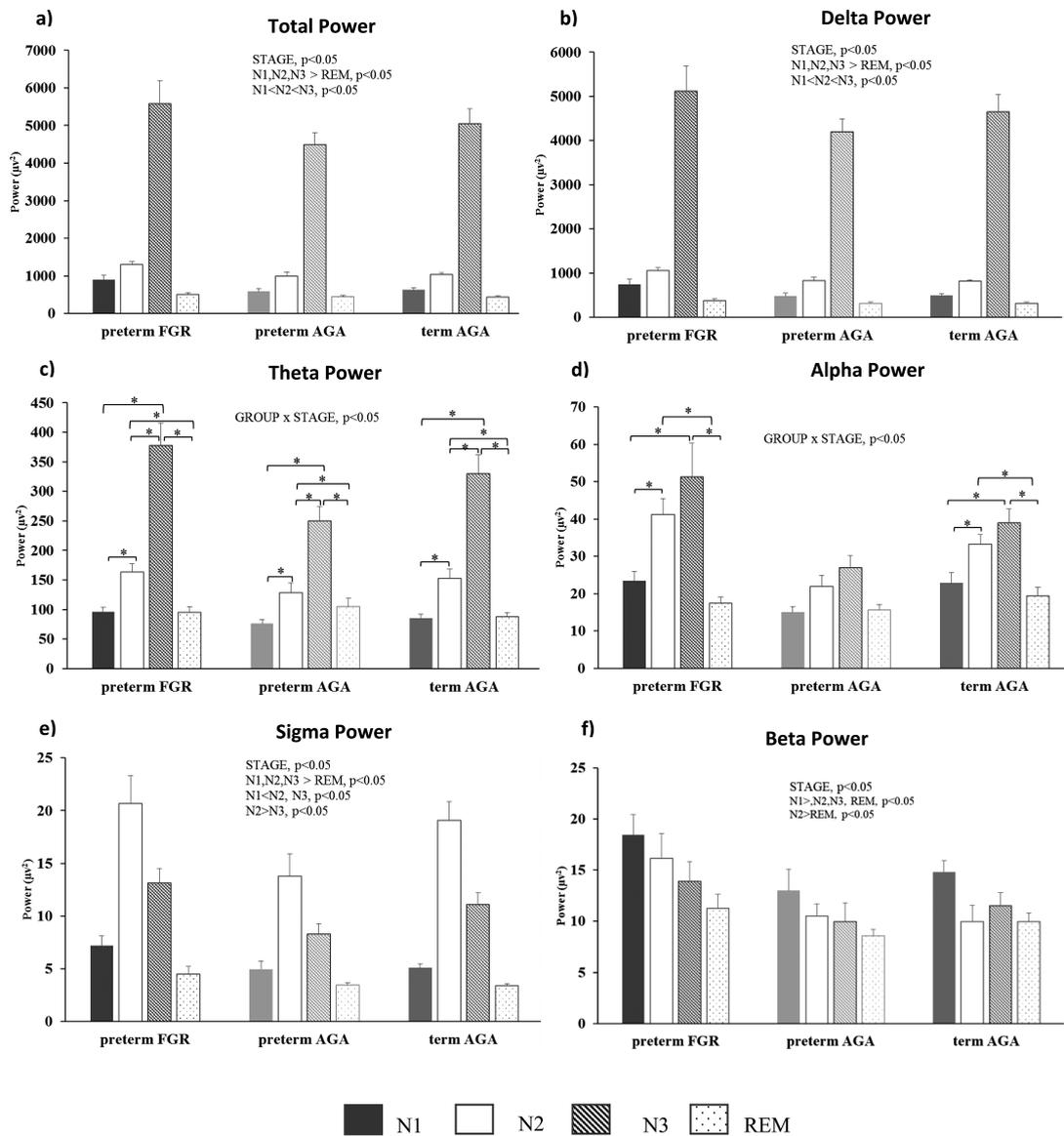
Compared with the term AGA group, preterm FGR children had few differences in sleep macroarchitecture, with the exception of a higher proportion of time spent in N2 sleep (N2%). The higher proportion of N2 sleep appeared to be at the expense of N3 sleep. Preterm FGR children averaged the lowest N3%, with this difference being significant when compared with preterm AGA children, but not term AGA children (Table 2). These

alterations in sleep stage proportion in preterm FGR children may reflect poorer sleep quality, as higher amounts of N2 sleep may be indicative of less restorative sleep, at the cost of deeper sleep stages, i.e., N3 sleep.

In this study, preterm FGR children exhibited no evidence of significant sleep fragmentation as assessed by sleep macroarchitecture indices. These findings are in contrast to previous actigraphic studies in children, which reported that FGR children aged 4–7 years had higher rates of poor sleep (defined as sleep efficiency <90% or three or more awakenings during night), when compared with age-matched children born at term.<sup>33</sup> Of note, the FGR group studied by Leitner et al. consisted of both preterm born and term born FGR children and were studied at a younger age group compared with the children in this study.<sup>33</sup>

### Preterm AGA Children

In contrast to the preterm FGR children, preterm AGA children showed a number of significant alterations in sleep macroarchitecture measures. This group had the lowest amount of sleep (45–64 minutes less TST) when compared with children born



**Figure 2.** Comparison by sleep stage of power spectral values for total (0.5–30 Hz),  $\delta$  (0.5–3.9 Hz),  $\theta$  (4.0–7.9 Hz),  $\alpha$  (8.0–11.9 Hz),  $\sigma$  (12.0–13.9 Hz),  $\beta$  (14.0–30 Hz) frequency bands in children aged 5–12 born preterm FGR, preterm AGA, and term AGA during N1, N2, N3, and REM sleep. \* $p < .05$ .

preterm FGR and term AGA. Shorter sleep duration in preterm AGA children has been suggested previously.<sup>34</sup> Using actigraphy studies, children born preterm aged 7–12 averaged 8 hours sleep per night, 1 hour less than population recommendations for their age.<sup>34</sup> Short sleep duration may arise due to altered circadian rhythms in children born preterm. Previous studies show that prematurity is associated with earlier sleep onset times compared in both children<sup>35</sup> and adolescents.<sup>36,37</sup> This tendency to go to bed earlier may indicate an earlier sleep phase.<sup>35</sup> However, as our study was not designed to investigate circadian rhythms, we were unable to explore these effects.

Parallel with shorter sleep duration, the preterm AGA group also had reduced amounts of NREM sleep (by 40–48 minutes); in particular, N2 sleep was significantly shorter compared with the other groups and the proportion of N3 sleep (N3%) was highest in the preterm AGA group. Shorter sleep duration and a higher proportion of N3 sleep may reflect compensatory sleep recovery. It is thought that an increase in the proportion of N3 sleep,

to repay sleep debt, occurs due to poor quality sleep or excessive daytime sleepiness.<sup>38</sup> Indeed, preterm AGA children had evidence of sleep disruption with higher proportion of WASO% and reduced SE. Interestingly, in the preterm AGA group, gestational age at birth was negatively associated with SE, that is, those children who were born at later gestational ages had lower SE. Normal maturation of sleep begins in utero, we know that sleep state can be clearly identifiable after 32 weeks gestation in the fetus<sup>39</sup> and that circadian rhythmicity also begins in fetal life.<sup>40,41</sup> Therefore, mid-late premature birth may disrupt a critical window of sleep maturation and have long-term effects on sleep into childhood. Regardless of gestational age, our results indicate that poor sleep quantity and quality is evident in preterm AGA children, which is consistent with previous studies.<sup>42</sup> Perkinson-Gloor et al.<sup>42</sup> showed that children born very preterm (<32 weeks) had poor sleep quality with higher amounts of nocturnal awakenings, higher amounts of N2, and reduced amounts of slow wave sleep. Although our macroarchitecture measures

do not completely align with those reported by Perkinson-Gloor et al.<sup>42</sup> taken together, both our studies indicate that prematurity is associated with altered sleep with significant sleep disruption during childhood.

A potential confounder in this study, particularly relevant to the preterm AGA group, is the presence of obstructive sleep apnea which can cause significant sleep disruption and is known to be at increased risk in children born prematurely.<sup>43</sup> In this cohort of children, three of the 17 preterm FGR group, two of the 15 preterm AGA group, and one of the term AGA group had an OAH1 above one event per hour (the definition of pediatric obstructive sleep apnea<sup>44</sup>). However, there were no differences in the OAH1 between the three groups and the mean OAH1 was <1 event per hour within each group. We also performed correlation analysis between OAH1 and sleep macro- and microarchitecture measures and found no statistically significant associations, confirming that sleep disruption in the preterm AGA group was not associated with presence of obstructive sleep apnea. We have also addressed this question in previous studies and shown no differences in spectral power between groups of children across the spectrum of severities of sleep-disordered breathing.<sup>27</sup>

In summary, sleep macroarchitecture was different in preterm FGR children, with an altered proportion of N2 and N3 sleep, though there was no evidence of sleep disruption. In contrast, children born preterm AGA had reduced sleep quantity and evidence of sleep disruption compared with both term-born children and preterm FGR children.

## Sleep Microarchitecture

### Preterm FGR Children

To the best of our knowledge, this is the first study to use power spectral analysis of the EEG to assess sleep quality in preterm FGR children. Unlike macroarchitecture sleep quality measures, sleep microarchitecture measures were different in preterm FGR children compared with the other two groups. Total,  $\delta$ ,  $\theta$ , and  $\alpha$  power were higher in the preterm FGR group compared with children in the preterm AGA (group,  $p < .05$ ) and the term AGA (group,  $p < .05$ ) group.

Higher  $\delta$  power in the preterm FGR children may be due to a number of factors. Delta waves reflect “deep sleep” which are thought to be vital for restoration. An increase in  $\delta$  activity occurs in recovery sleep after sleep deprivation.<sup>45</sup> The increase in EEG power across both low and high frequencies in this study is also similar to what is seen in adaptive sleep recovery in experimental animal models of sleep restriction.<sup>46</sup> In addition,  $\delta$  power (also known as slow wave activity) and its dissipation over the night are a physiological marker of the homeostatic regulation of sleep and are indicative of neuronal maturation and neuronal recovery.<sup>47</sup> Accordingly,  $\delta$  waves are an index of sleep pressure. Thus, it is possible that the higher  $\delta$  power in preterm FGR children may reflect a compensatory response to increased sleep pressure.

The increase in  $\delta$  power in preterm FGR children may arise from sleep disruption, not identified by sleep macroarchitecture measures. Preterm FGR had higher  $\alpha$  power in both N2 and N3 compared with the preterm AGA group. Alpha oscillations are associated with arousals and brief states of awakening that occur during sleep (microarousals).<sup>48</sup> More specifically,  $\alpha$  power

during REM sleep has been suggested to indicate the occurrence of microarousals, which cause sleep to be unstable for short periods of time.<sup>49,50</sup> Additionally, increased  $\alpha$  power within NREM sleep has been associated with sleep fragility (unstable sleep) and awareness of one's external environment during sleep.<sup>51</sup> Thus, increased  $\alpha$  power has been suggested to indicate increased arousability and alertness during sleep. This may explain the higher number of nocturnal awakenings identified in the study by Leitner et al.<sup>33</sup> in the home environment.

To date, only two studies have investigated the potential effects of being born preterm and FGR on EEG activity during sleep;<sup>52,53</sup> however, both of these studies were performed in infants, not children. Consistent with our study, higher  $\delta$  power was observed in infants born preterm FGR compared with control neonates within the first 48 hours of life. However, in contrast to our findings, Yerushalmy-Feler et al.<sup>52</sup> found  $\theta$ ,  $\alpha$ , and  $\beta$  relative power to be lower in the preterm FGR group when compared with controls, perhaps reflecting a compensatory reduction in brain EEG due to chronic hypoxia. In addition to sleep quality, higher  $\delta$  power could potentially reflect a delay in EEG maturation in preterm FGR children. During infancy and childhood,  $\delta$  power decreases with age, due to synaptic pruning and thickening of the cortex. Similarly, studies in term-born FGR infants identified higher relative  $\delta$  power with a decrease in relative  $\theta$  power compared with those born term AGA, suggesting a delay in EEG maturation.<sup>53</sup>

### Preterm AGA Children

Assessment of sleep microarchitecture in the preterm AGA group also yielded some interesting findings. Compared with preterm FGR, the preterm AGA children had lower  $\delta$  power, which may reflect nonrestorative sleep. Of interest,  $\sigma$  power was also reduced in this group. Sigma power reflects spindle density. Sleep spindles are transient EEG events considered to be the hallmark feature of N2 sleep<sup>54</sup> and, like  $\delta$  power, are known to reflect sleep depth. In preterm AGA children, reduced  $\sigma$  power may reflect a reduction in spindle density. Reduced  $\sigma$  power and sleep spindles occur during recovery sleep following total or selective sleep deprivation; however, this reduction usually occurs with an increase in  $\delta$  activity.<sup>55</sup> The preterm AGA children in this study had reduced  $\delta$ , rather than an increase, and could reflect a mismatch between the known reciprocal relationship between  $\delta$  and  $\sigma$  power. Like  $\sigma$  power,  $\beta$  power was significantly lower in the preterm AGA compared with the other groups. Importantly, EEG oscillations in the  $\beta$  frequency are associated with GABAergic transmission; GABAergic neuronal loss is known to occur preterm infants and is thought to play a significant role in the pathogenesis of neurological deficits in children.<sup>56</sup>

### Speculations—Preterm FGR vs Preterm AGA vs Term AGA

In regards to sleep macroarchitecture, it was intriguing to find that the preterm FGR children were more similar to the term AGA group than the preterm AGA group. We are unsure of why this would be the case. This may not be so surprising as the specific neuropathology of preterm FGR is complex and distinct from that in infants born preterm without FGR.<sup>57</sup> What this finding highlights is that the changes in sleep quantity and quality that may occur due to preterm FGR and preterm AGA may follow a different etiology. It is possible that that chronic hypoxia during fetal life in preterm FGR children may result in

heightened adaptive processes to conserve sleep, whereas prematurity alone involves disruption of maturational processes which have a long-term effect on neuronal pathways involved in sleep maintenance.

### Clinical Implications

In children, sleep disruption and poor sleep quality impair cognitive functioning, concentration, daytime alertness, and overall behavior.<sup>17</sup> NREM and REM sleep are important for memory consolidation and neurological growth and repair.<sup>58</sup> It has been well established that many infants born preterm and FGR go on to have neurodevelopmental and behavioral impairments. Few studies have investigated the interrelationship among prematurity, sleep, and neurodevelopmental impairment during childhood. One study showed, in toddlers born preterm AGA, that those with sleep or wake patterns closely aligned with the 24-hour circadian cycle had higher abbreviated intelligence quotient scores at 3 years of age.<sup>59</sup> In another larger study, very preterm children (born <32 weeks GA) had more behavioral and emotional problems which were associated with poorer sleep quality (more N2 sleep, less slow wave sleep) compared with full-term children.<sup>42</sup> To date, the relationship between poor sleep and neurodevelopment in children born preterm FGR has not been explored. Indeed, there is the potential that poor sleep could exacerbate neurodevelopmental deficits in this population.

The mechanisms which underlie differences in sleep in preterm and FGR children compared with controls are unknown. The alterations in sleep may arise from differences in brain structure or function in children born preterm and FGR. FGR has long-term effects on brain structure, in particular the hippocampus and the cerebellum,<sup>4</sup> which play a role in sleep, learning, and memory consolidation.<sup>60</sup> The FGR children in this study showed an increase in  $\theta$  power, potentially reflecting alterations in hippocampal and cortical activity, however what this increase means is unclear and deserves further study. Further investigation on early life programming with gene-environment interactions (epigenetics) that influence developmental brain plasticity during critical or sensitive periods of brain and sleep maturation would be imperative to further explore these mechanisms,<sup>61</sup> particularly, as it is known that fetal state behaviors predict adolescent performance later in life.<sup>62</sup>

Currently, sleep in childhood is not routinely monitored in children born preterm or FGR. In line with the data from this study and the possible clinical implications, our study highlights the potential importance for these children to receive clinical follow-up and possibly intervention to improve their quality of sleep. Finally, further investigation is required to uncover the physiological mechanisms behind this reduced sleep quality, in order for targeted therapies to be developed in this population.

### Limitations

We acknowledge the limitations of this study. Although beyond the scope of the paper, we are unsure of the relevance of our findings for structural cortical changes, and short- and long-term neurodevelopmental outcome. We suspect that a study of  $\delta$  power dissipation throughout the night with addition of neurodevelopmental assessment and frontal lobe EEG would provide essential information on brain and sleep maturation in

these children and deserves further study. In addition, the preterm FGR group in this study represented a heterogeneous group, including a wide range of birthweight percentiles and gestational ages. We have, to the best of our ability, adjusted for these factors; however, a study with larger numbers which include more preterm FGR children born <3% for birthweight (reflecting those who have severe FGR) may provide further information on the long-term implications of FGR on sleep.

As this work was part of a much larger study investigating cardiovascular structure and control,<sup>22</sup> we originally powered the study to identify differences in cardiac structure between groups. However, we did perform a priori power analysis to determine differences in sleep quality. Based on our previous sleep studies in children,<sup>27</sup> to detect a significant change in SE of 10% with a SD of 5% and a power level 0.8 and  $\alpha$  of 0.002, we would require  $n = 12$  participants within each group. Therefore, the power to detect a significant difference with consideration of multiple comparisons at least in sleep macroarchitecture was adequate. We chose SE as the primary outcome, as lower birth weight is associated with lower sleep efficiency (assessed by actigraphy) in children<sup>13</sup> and to replicate a clinically relevant measure as normal spectral EEG values have not been established. Nonetheless, in this study, we did identify significant differences in sleep parameters with our small sample size, which marry to those previously published in preterm children,<sup>34</sup> and therefore, we are confident that our findings are robust.

We are also aware that many maternal and perinatal factors (such as maternal administration of betamethasone, infection, and respiratory distress syndrome) may contribute to long-term brain maturation, EEG activity, and sleep. This study focused on the association between preterm birth and FGR on sleep in children, and therefore, cause and effect has not been proven. Many potential confounders exist, in association with preterm birth or FGR, as to make a conclusion that preterm birth or FGR actually causes changes in sleep in children. Future case-controlled studies with a higher sample size in addition to experimental animal models, controlling for confounders, would be beneficial in exploring the relationship among preterm birth, FGR, and sleep.

Similar to previous studies,<sup>52,53</sup> we chose to analyze EEG power recorded from one central lead. However, recording from one channel does not assess the regional differences among multiple brain regions known to be affected by FGR and preterm birth. Multichannel EEG analysis may reveal different or additional differences between groups and should be considered in future studies.

### Conclusions

The collective findings of this study demonstrate that both FGR and preterm birth may alter sleep quality in children when compared with term-born AGA controls. Assessing sleep using the conventional sleep quality measures, we found sleep quantity and quality to be reduced in children born preterm AGA. On the other hand, spectral analysis of EEG patterns revealed that children born preterm FGR had altered sleep microarchitecture, potentially reflecting sleep disruption. These results indicate that sleep quality may be reduced in children born preterm and FGR. Given the importance of sleep on neurodevelopment and behavior, this study highlights the need for further investigation and perhaps routine clinical follow-up in this population.

## Work Performed

Department of Paediatrics, The Ritchie Centre, Hudson Institute of Medical Research, Monash University.

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## Disclosure Statement

None declared.

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