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REM and NREM Sleep State Distribution Of Respiratory Events In Habitually Snoring School-Aged Community Children

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Abstract

Background—Studies ascribe different functions to REM and NREM sleep such that their disruption could result in discrepant clinical outcomes. Although sleep architecture is globally preserved in children with OSA, it is considered to be a REMS disorder. Furthermore, body position during sleep affect the occurrence of respiratory events, while the presence of obesity has been claimed to affect sleep state distribution of respiratory disturbance.

Methods—To explore the distribution of respiratory events during REMS and NREMS and its potential predictors, a cross-sectional analysis of 335 overnight sleep studies in snoring children from the community was conducted. The ratio of REMS to NREMS respiratory events was compared, and potential associations were assessed using General Linear Modeling (GLM).

Results—Children were 7.3 ± 1.2 years old and had a BMI z-score of 1.0 ± 1.3 . OAH was 1.7 ± 3 and 45.8% of children had $AHI > 1/\text{hrTST}$. Obstructive respiratory events were 3.8 times more likely in REMS (2.0/hr) than NREMS (0.5/hr), and the GLM revealed distinctive predictive associations for the apneic and hypopneic indices separately, and for body position, the latter indicating that the REMS/NREMS distribution of respiratory events depends on body position.

Conclusion—Obstructive respiratory events are predominantly, albeit not exclusively present in REMS in school-aged children. NREMS respiratory events are more likely in the presence of lower oxyhemoglobin saturations during event, side body position, and in African American children. However, REMS dominance is not affected by either BMI z-score or obesity. Our findings suggest that incorporating comprehensive respiratory event profiles of children may enhance our understanding of the pathophysiology and adverse outcomes in the context of pediatric OSA.

Introduction

Substantial discrepancies have emerged among studies examining the clinical characteristics of pediatric sleep disordered breathing (SDB). Considering the high prevalence of this disorder, as evidenced by a mean in the 10–12% range,(1–3) it is generally believed that the

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Conflict of interest

The authors have no conflicts of interest to disclose in relation to this manuscript.

occurrence of respiratory disturbance will be predominantly manifest during rapid eye movement sleep (REMS) when compared to non-rapid eye movement sleep (NREMS).(4, 5) Moreover, it has been suggested that in children sleep architecture is preserved(4) and that body position does not influence frequency nor severity of respiratory events, (6, 7) even if such findings have been challenged in the context of concurrent presence of obesity.(8, 9)

Hitherto, the most common overnight polysomnographic metric applied to the assessment of the severity of sleep-disordered breathing is the apnea hypopnea index (AHI). This index reflects a composite score essentially composed by the summation of the number of obstructive and central apneic events, and the number of hypopneas per hour of sleep. Tang et al(10) studied the home-based plethysmography, pulse oximetry, body position, and heart rate parameters of 433 children, ages 8–11 years, who were not referred for clinical assessment of SDB, and concluded that different approaches for quantifying respiratory disturbance indices would contribute to substantial variability in the identification and classification of SDB. Furthermore, their findings were suggestive that central apneas in children should be computed, and reported separately from obstructive events. In addition, arousals have been recently proposed as an important protective mechanism for termination of an obstructive apnea event; however, the definition of a respiratory arousal being based on its proximity to a respiratory event should not be mistaken to imply a causal relationship between these two. Independently, the number as well as the duration of arousals may cause sleep fragmentation and disruption of the sleep architecture. As a consequence, respiratory events may exert a distinctive impact on sleep integrity, and therefore on daytime well-being.

In adults with OSA, respiratory events predominantly occur during NREMS, and more recently this pattern was also reported in up to a third of children with moderate to severe OSA.(11) In other words, the ratio of REMS to NREMS OAH1 showed a NREMS predominance in older children with higher arousal indices and less severe desaturations with events. Based on the impression that such pattern was only seldom encountered in our clinical practice, we sought to explore the distribution of REMS and NREMS respiratory events, and analyzed potential predictors towards such distribution.

Methods

Subjects

The study was approved by the University of Louisville Human Research Committee (protocol #474.99), and the Board of the participating schools. Parents were invited to complete the Gozal questionnaire,(12, 13) which in addition to demographic information and significant medical history of the child, included sleep questions, such as difficulty initiating sleep, restless sleep, enuresis, apnea, and other questions such as appetite and overall activity. From the returned questionnaires both non-snoring children and snoring children were randomly selected and invited to the University of Louisville Pediatric Sleep Medicine Center for an overnight polysomnographic assessment. Exclusionary criteria for participation in the study included chronic medical conditions, genetic or craniofacial syndromes, developmental delays, a current Individual Education Plan (IEP) at school indicative of significant learning or other difficulties, current use of psychotropic medications, and the presence of an acute infection.

The polysomnographic records of 335 consecutive children recruited from the Jefferson County Public Schools and the Archdiocese of Louisville Catholic Schools were considered for this analysis.

Measures

Polysomnographic assessment—All children were accompanied by one of their caregivers who slept in the same room. Overnight polysomnography (NPSG) was performed in a quiet, darkened room with an ambient temperature of 24°C. The following sleep parameters were measured: chest and abdominal wall movement by respiratory impedance or inductance plethysmography, heart rate by electrocardiogram (ECG), air flow was triply monitored with a sidestream end-tidal capnograph which also provided breath-by-breath assessment of end-tidal carbon dioxide levels (PETCO₂; BCI SC-300, Menomonee Falls, WI), a nasal pressure cannula, and an oronasal thermistor. Arterial oxygen saturation (SpO₂) was assessed by pulse oximetry (Radical; Masimo; Irvine, CA; model 395), with simultaneous recording of the pulse waveform. The bilateral electro-oculogram (EOG), eight channels of electroencephalogram (EEG), chin and anterior tibial electromyograms (EMG), and analog output from a body position sensor (Braebon Medical Corporation, Ogsdenburg, NY) were also monitored. All measures were digitized using a commercially available polysomnography system (Rembrandt, MedCare Diagnostics, Amsterdam). Tracheal sound was monitored with a microphone sensor (Sleepmate, Midlothian, VA), and a digital time-synchronized video recording was performed.

Sleep architecture was evaluated by standard techniques (14) and by scorers blinded to the condition of the child. The following conventional sleep parameters were evaluated: The proportion of time spent in each sleep stage was expressed as a percentage of total sleep time (TST). This was additionally subdivided into supine, side and prone sleep position. Central, obstructive, and mixed apneic events were counted. Obstructive apneas are defined as the absence of airflow with continued chest wall and abdominal movement for duration of at least 2 breaths. Central apnea was defined as the absence of both airflow and respiratory effort for at least 2 breaths. (2, 15) Hypopneas are defined as a decrease in oronasal flow of $\geq 50\%$ with a corresponding decrease in SpO₂ of 4% or more and/or EEG arousal. (15, 16) The obstructive apnea hypopnea index (OAH) was defined as the number of obstructive apneas and hypopneas per hour of TST. Similarly, indices for apneic events in the supine, side, and prone sleep position were calculated for REMS and NREMS. Spontaneous arousals (SAI) and Respiratory arousals (RAI) were defined as recommended by the American Sleep Disorders Association Task Force report, and were expressed as the total number of arousals per hour of sleep time. (16, 17)

Adiposity assessment—Height was measured (to 0.1cm) with a stadiometer (Holtain, Crymch, United Kingdom) and children were weighed (to 0.1kg) with a calibrated scale. Body mass index (BMI) was calculated and the z-score was generated using the online BMI z-score calculator provided by the Centers for Disease Control and Prevention 2000 growth standards and software (<http://www.cdc.gov/epiinfo/>) (Epi Info [Centers for Disease Control and Prevention, Atlanta, GA]). A BMI between 15th–84th percentile for age and gender was defined as normal weight [N], whereas BMI <5th percentile for age being underweight, BMI $\geq 5^{\text{th}}$ and <15th percentile being at risk underweight, BMI $\geq 85^{\text{th}}$ and <95th percentile being overweight, and BMI $\geq 95^{\text{th}}$ percentile as obese.

Statistical analyses

A commercially available software Statistica [StatSoft, Inc. (2009). STATISTICA version 10.0, www.statsoft.com] was used for all statistical analyses. Descriptive analyses were conducted to describe the sample, with non-parametric analyses being conducted for group comparisons such as Wilcoxon Matched Pair Test or Mann-Whitney U test (MW-U). Differences between REMS and NREMS proportions were calculated by the difference test. General Linear Modeling was conducted with as covariates age, gender, ethnicity, BMI z-score, OAH, Nadir SpO₂, average End Tidal CO₂ (PETCO₂), SAI, RAI, desaturation index

$\geq 2\%$ ($DI \geq 2\%$) and Stage 1 %TST when predicting the apneic polysomnographic profile across the sleep positions. Standardized Beta coefficients (β) $\pm$ Standard Error of β and 95% Confidence Intervals (95%CI) are reported. A log transformation was used to reduce heteroscedasticity in the distribution of the difference in REMS and NREMS respiratory events (by convention a mathematically 0.5 was added to each; $\log(\text{REMS events} + 0.5) - \log(\text{NREMS events} + 0.5)$). Polygons reflect the distribution of the difference of the REMS and NREMS respiratory events across sleep positions. A p value < 0.05 was considered to achieve statistical significance.

Results

Children were 7.3 ± 1.2 years old [38.6% girls, 57.5% White Non-Hispanic (WNH), 29.9% African American (AA), 12.6% Mixed ethnicity (M)] and had a BMI z-score of 1.0 ± 1.3 [2.1% underweight, 5.1% at risk underweight, 42.5% normal weight, 13% overweight and 37.3% obese]. OAH1 was $1.7 \pm 3/\text{hrTST}$ (min.: 0 to max.: 30.91), and 45.8% of children had $AHI > 1/\text{hrTST}$. Descriptives of the NPSG can be found in Table 1. In addition, among the covariates the $DI \geq 2\%$ was higher in REMS than NREMS ($2.6 \pm 8.3/\text{hr}$ versus $0.9 \pm 2.5/\text{hr}$, Wilcoxon Matched Pair Test= 8.0, $p=0.00001$), whereas SAI was lower in REMS ($7.4 \pm 6.4/\text{hr}$ versus $21.7 \pm 47.4/\text{hr}$ in NREMS, Wilcoxon Matched Pair Test= 14.3, $p=0.0000$) and RAI was significantly different between REMS and NREMS ($1.3 \pm 2.1/\text{hr}$ versus $2.0 \pm 3.7/\text{hr}$, Wilcoxon Matched Pair Test= 3.2, $p=0.001$).

All sleep positions

In general, 10.5% of the children had an equal amount of respiratory events in REMS and NREMS, 18.6% had a NREMS predominance and 70.9% had a REMS predominance (Table 2), such that throughout the night a child was about 3.8 times more likely to show respiratory events in REMS sleep. The time spent in REMS or NREMS as percentage of TST (%TST) was different between the predominance groups (for REM %TST: REMS predominance: 18.6 ± 8.3 versus NREMS predominance: 17.6 ± 10.3 , MW-U=2.4, $p=0.02$, and NREM %TST: resp., 82.2 ± 13.8 versus 82.8 ± 4.7 , MW-U=-1.9, $p=0.05$). Thus, children had significantly more REMS events. Indeed, the median for NREMS was 0.5 h^{-1} (Q_{25} : 0.2 to Q_{75} : 1.2 h^{-1}) whereas for REMS it was 2.0 h^{-1} (Q_{25} : 0.7 to Q_{75} : 4.8 h^{-1}) which is shown by the polygon (Figure 1). Furthermore, a higher value of Nadir SpO_2 significantly predicted a NREMS predominance of respiratory events (β : -0.17 ± 0.07 , 95%CI: -0.31 to -0.03 , $p=0.02$).

With respect to the apneic and hypopneic indices, a higher proportion of REMS events was found for the OAH1 (3.6 times), the AI (Apnea Index; 2.8 times), the Central Apnea Index (CAI; 2.4 times), Hypopnea Index (HI; 2.1 times) and Obstructive HI (OHI; 2 times)(Table 2) with time spent in REMS %TST or NREMS %TST only different for the AI and CAI predominance groups. Children with REMS_AI predominance versus NREMS_AI predominance spent significantly more time in REMS %TST (19.2 ± 10.3 versus 16.8 ± 4.9 , MW-U=2.5, $p=0.01$) and less in NREMS %TST (81.7 ± 14.8 versus 83.0 ± 5.0 , MW-U=-2.8, $p=0.005$), and likewise for the CAI (resp., REMS %TST : 19.7 ± 10.8 versus 16.8 ± 3.8 , MW-U=2.9, $p=0.004$, and NREMS %TST: 81.5 ± 16.3 versus 82.3 ± 3.9 , MW-U=2.9, $p=0.004$).

Regarding the apneic indices, the predictive pattern of state predominance was also different, with a high SAI being significantly predictive towards REMS_AHI predominance (β : 0.15 ± 0.07 , 95%CI: 0.2 to 0.28, $p=0.03$). In comparison to WNH, AA had a significant predominance towards NREMS_AI (β : -0.20 ± 0.08 , 95%CI: -0.36 to -0.03 , $p=0.02$) and NREMS_CA1 (β : -0.24 ± 0.08 , 95%CI: -0.40 to -0.07 , $p=0.005$). A high OAH1 was predictive of REMS_OAI (β : 0.33 ± 0.10 , 95%CI: 0.15 to 0.52, $p=0.0007$), while a high

RAI was predictive of NREMS_mixed apnea index (MAI) (β : -0.14 ± 0.06 , 95%CI: -0.26 to -0.01 , $p=0.03$).

Regarding hypopnea indices (HI), predominance of NREMS_HI was associated with a higher Nadir SpO_2 (β : -0.21 ± 0.07 , 95%CI: -0.35 to -0.07 , $p=0.002$). A higher Nadir SpO_2 (β : -0.22 ± 0.07 , 95%CI: -0.36 to -0.09 , $p=0.001$) and a higher Stage 1 %TST (β : -0.13 ± 0.06 , 95%CI: -0.24 to -0.02 , $p=0.03$) were predictive of NREMS_obstructive HI (OHI). A higher OAH1 (β : 0.21 ± 0.09 , 95%CI: 0.04 to 0.39 , $p=0.02$) and a higher Stage 1 %TST (β : 0.52 ± 0.05 , 95%CI: 0.42 to 0.61 , $p=0.00001$) were predictive of REMS_mixed HI (MHI).

Before reporting sub-analyses per body position during the night, given that children slept more in side position (Table 2) we analyzed potential contributors (OAH1, weight, gender and ethnicity) to such body positions. Namely, boys slept more in supine (β : 0.15 ± 0.07 , 95%CI: 0.02 to 0.28 , $p=0.03$), children with higher weight slept less on their side (β : -0.14 ± 0.06 , 95%CI: -0.25 to -0.03 , $p=0.02$) and AA, in comparison to WNH, slept more prone (β : 0.18 ± 0.08 , 95%CI: 0.02 to 0.34 , $p=0.03$).

Supine position

Children had a predominance of REMS_supine events (2.2 times) (Table 2) while time spent in each state was not different (for REMS %TST: REMS_supine predominance: 19.4 ± 9.8 versus NREMS_supine predominance: 19.1 ± 10.7 , MW-U=1.5, $p=0.13$, and NREMS %TST: 82.4 ± 17.6 versus 81.7 ± 5.2 , MW-U=-1.1, $p=0.25$). Median for NREMS_supine events was 1.5 h^{-1} (Q₂₅: 0.0 to Q₇₅: 4.1 h^{-1}) whereas for REMS_supine events was 5.5 h^{-1} (Q₂₅: 0.0 to Q₇₅: 17.1 h^{-1}) which is shown by the polygon (Figure 1). Overall in the supine sleep position, a gender by ethnicity effect was found predictive towards state dependent respiratory events, such that being a female AA in comparison to a female WNH a predominance of REMS_supine respiratory events was found (β : -0.25 ± 0.11 , 95%CI: -0.46 to -0.03 , $p=0.04$).

The proportion of events in REMS_supine versus NREMS_supine were also higher for AHI (1.6 times) and OAI (1.4 times), but time spent in each state was only different for AHI (AHI: for REMS %TST: REMS_supine predominance: 19.5 ± 9.8 versus NREMS_supine predominance: 17.8 ± 9.5 , MW-U=2.9, $p=0.003$, and NREMS %TST: resp., 82.3 ± 17.5 versus 82.6 ± 5.2 , MW-U=-2.7, $p=0.007$, and for OAI: for REMS %TST: 19.0 ± 7.6 versus 17.2 ± 5.3 , MW-U=1.1, $p=0.25$, and NREMS %TST: resp., 80.3 ± 5.5 versus 82.3 ± 6.4 , MW-U=-1.1, $p=0.27$).

The predictive pattern of the apneic indices indicated that a high desaturation index $\geq 2\%$ was predictive for NREMS_supine MAI predominance (β : -0.39 ± 0.10 , 95%CI: -0.59 to -0.20 , $p=0.00001$), none of the other indices such as the AHI, AI, CAI, OAI showed predictive associations.

Regarding hypopnea indices (HI), only the total (HI) and OHI showed associations. Namely, a higher Nadir SpO_2 was predictive for NREMS_supine HI predominance (β : -0.19 ± 0.08 , 95%CI: -0.34 to -0.04 , $p=0.01$), and being a female AA versus female WNH was predictive for REMS_supine HI predominance (β : -0.26 ± 0.10 , 95%CI: -0.45 to -0.07 , $p=0.01$). The same predictors were associated with OHI; i.e., resp., a higher Nadir SpO_2 (β : -0.20 ± 0.08 , 95%CI: -0.35 to -0.06 , $p=0.007$) with NREMS_supine OHI predominance, and being a female AA with REMS_supine OHI predominance (β : -0.27 ± 0.10 , 95%CI: -0.45 to -0.08 , $p=0.006$).

Side position

Our subjects had about 2.4 times more respiratory events in REMS_side than NREMS_side (Table 2) with a difference between side predominance groups only for REMS %TST (i.e., REMS_side predominance: 18.7 ± 9.0 versus NREMS_side predominance: 17.6 ± 9.8 , MW-U=2.4, $p=0.02$, and NREMS %TST: resp., 82.4 ± 16.0 versus 82.3 ± 4.6 , MW-U=-1.8, $p=0.07$). Median for NREMS_side events was 1.5 h^{-1} (Q_{25} : 0.0 to Q_{75} : 3.5 h^{-1}) whereas for REMS_side events was 5.1 h^{-1} (Q_{25} : 0.0 to Q_{75} : 13.1 h^{-1}) which is shown by the polygon (Figure 1). Being AA, in comparison to WNH, significantly predicted a NREMS_side predominance of respiratory events (β : -0.19 ± 0.09 , 95%CI: -0.37 to -0.01 , $p=0.04$).

The proportion of events in REMS_side versus NREMS_side were furthermore higher for AHI (2.1 times), AI (2.1 times), and CAI (2.1 times), while time spent in each state was different among the predominance groups. Namely, for AHI for REMS %TST: REMS_side predominance: 18.7 ± 9.0 versus NREMS_side predominance: 17.7 ± 9.5 , MW-U=2.0, $p=0.04$, and NREMS %TST: 82.5 ± 16.1 versus 82.1 ± 5.2 , MW-U=-1.5, $p=0.14$; and for AI for REMS %TST: 19.1 ± 9.5 versus 18.1 ± 10.9 , MW-U=2.2, $p=0.03$, and NREMS %TST: resp., 82.0 ± 17.5 versus 82.6 ± 5.1 , MW-U=-2.5, $p=0.01$; and for CAI for REMS %TST: 19.6 ± 10.3 versus 18.3 ± 11.3 , MW-U=2.2, $p=0.03$, and NREMS %TST: resp., 82.0 ± 19.2 versus 82.2 ± 4.5 , MW-U=-2.2, $p=0.03$, respectively.

A distinctive pattern of associations was found for side position. NREMS_side AHI predominance was predicted by a higher RAI (β : -0.15 ± 0.07 , 95%CI: -0.27 to -0.02 , $p=0.03$), higher average ET CO₂ (β : -0.16 ± 0.07 , 95%CI: -0.29 to -0.03 , $p=0.01$), being AA, in comparison to WNH (β : -0.20 ± 0.09 , 95%CI: -0.37 to -0.03 , $p=0.02$), while REMS_side AHI predominance was associated with mixed ethnicity, in comparison to WNH (β : 0.18 ± 0.09 , 95%CI: 0.01 to 0.35 , $p=0.04$). A similar trend in terms of ethnicity was found for side AI; i.e., NREMS_side AI predominance for being AA, in comparison to WNH (β : -0.25 ± 0.09 , 95%CI: -0.42 to -0.07 , $p=0.005$), and a REMS_side AI predominance was associated with mixed ethnicity, in comparison to WNH (β : 0.18 ± 0.09 , 95%CI: 0.0 to 0.34 , $p=0.048$). A REMS_side CAI predominance was found to be associated with higher SAI (β : 0.15 ± 0.07 , 95%CI: 0.0 to 0.29 , $p=0.046$), whereas being AA, in comparison to WNH was associated with NREMS_side CAI predominance (β : -0.21 ± 0.09 , 95%CI: -0.39 to -0.04 , $p=0.02$). A REMS_side OAI predominance was associated with OAH (β : 0.36 ± 0.09 , 95%CI: 0.15 to 0.57 , $p=0.0007$), and a REMS_side MAI predominance was associated with desaturation index $\geq 2\%$ (β : 0.33 ± 0.10 , 95%CI: 0.13 to 0.53 , $p=0.001$).

Regarding the hypopneic indices the HI, OHI, MHI showed associations. NREMS_side HI predominance was predicted by a higher Nadir SpO₂ (β : -0.20 ± 0.08 , 95%CI: -0.35 to -0.05 , $p=0.01$), and average ET CO₂ (β : -0.23 ± 0.07 , 95%CI: -0.36 to -0.10 , $p=0.0007$) which was similar for the OHI; i.e., a higher Nadir SpO₂ (β : -0.20 ± 0.08 , 95%CI: -0.35 to -0.05 , $p=0.009$), and average ET CO₂ (β : -0.23 ± 0.07 , 95%CI: -0.36 to -0.10 , $p=0.0006$). NREMS_side MHI predominance was predicted by a higher desaturation index $\geq 2\%$ (β : -0.20 ± 0.09 , 95%CI: -0.39 to -0.02 , $p=0.03$), and REMS_side HI predominance was predicted by a higher OAH (β : 0.27 ± 0.10 , 95%CI: 0.08 to 0.47 , $p=0.005$), and Stage 1 %TST (β : 0.45 ± 0.06 , 95%CI: 0.34 to 0.56 , $p=0.000001$).

Prone position

Although few children slept prone during the NPSG, a distributional difference in CAI events was found. Namely, children were 3.1 times more likely to have NREMS_prone CAI events. The time spent in each state was not different among the CAI predominance groups; namely, for REMS %TST: REMS_prone predominance: 17.3 ± 4.4 versus NREMS_prone

predominance: 20.1 ± 16.2 , MW-U=0.4, $p=0.66$, and NREMS %TST: resp., 81.0 ± 4.8 versus 81.7 ± 5.0 , MW-U=-0.8, $p=0.44$. For illustration, the distribution of all respiratory events in prone is presented in Figure 1 [Median for NREMS_prone events was 0 h^{-1} (Q_{25} : 0.0 to Q_{75} : 2.5 h^{-1}) whereas for REMS_prone events was 0 h^{-1} (Q_{25} : 0.0 to Q_{75} : 11.3 h^{-1}).

Regarding the apneic indices, a higher OAH1 was associated with NREMS_prone AHI predominance (β : -0.43 ± 0.15 , 95%CI: -0.72 to -0.13 , $p=0.005$). A higher OAH1 was also associated with NREMS_prone CAI predominance (β : -0.31 ± 0.15 , 95%CI: -0.62 to 0.0 , $p=0.046$) whilst being a boy, in comparison to a girl, was predictive for REMS_prone CAI predominance (β : 0.27 ± 0.12 , 95%CI: 0.03 to 0.51 , $p=0.03$). A higher Nadir SpO₂ was predictive of NREMS_prone OAI predominance (β : -0.24 ± 0.12 , 95%CI: -0.48 to -0.01 , $p=0.042$).

For the hypopneic indices, a NREMS_prone predominance was found for HI and OHI. Namely, a higher OAH1 was associated with NREMS_prone HI predominance (β : -0.36 ± 0.15 , 95%CI: -0.66 to -0.06 , $p=0.02$), and with NREMS_prone OHI (β : -0.36 ± 0.15 , 95%CI: -0.66 to -0.07 , $p=0.02$).

Discussion

This study shows that respiratory events are 3.8 times more likely to occur in REMS in school-aged children. However, predominance of NREMS respiratory events is not uncommon, and occurs about 1/6 of children. Current findings also suggest that depending on sleep position the respiratory event profiles of children are modified, and therefore need to be considered as potential confounders in our exploration and understanding of pathophysiological mechanisms and outcomes.

Some methodological issues deserve comment before discussing the findings in more detail. Children included were recruited from the community and their NPSG results (i.e., scored using Rechtschaffen and Kales criteria) were retrospectively analyzed. Namely, only the children with complete sleep data regarding the respiratory events were included, yet they were not different from those with incomplete data. An advantage of this retrospective cross-sectional analysis is that NPSG data were acquired over several years, and therefore scoring of polysomnographic parameters was not affected by scorer dependency. Furthermore, all sleep studies were scored by trained technicians who were blinded to the condition of the child. However, we should point out that our analyses were restricted to the severity of the events, and did not include the duration of the events. Finally, no data on tonsillar size was incorporated into the analyses, even though it has been proposed as potentially affecting respiratory disturbances differently, depending on body position during sleep.(18)

Studies ascribe different functions to REM and NREM sleep such that their disruption might result in different clinical outcomes. For instance, REM and NREM sleep have been assigned different roles in memory and learning processes. Overall, a NREMS predominance of respiratory events was more likely in children with milder desaturations during events.(11) In contrast to Verginis et al, (11) we did not find either an age or an arousal index effect. A high respiratory arousal index was indicative for increased NREMS_mixed apnea events and NREMS_side AHI events. Moreover, we found an impact of ethnicity on state distribution of respiratory events, such that being African American was associated with more NREMS_apneic and central apneic events independent of body position. Of note, neither BMI z-score, nor BMI category were associated with a sleep state predominance of respiratory events. It is possible that the dual categorization into obese and non-obese subsamples in the literature may account for the disparities in our findings and

others. Furthermore, studies on the density of respiratory events in relation to body position during sleep provide disparate findings as well.(7, 8, 19–21) For instance, Fernandes do Prado and colleagues (7) suggested that children with OSA may breathe best in the supine position, while others(8) reported no differences in AHI among body positions in a matched sample of control children and children with OSA. In a clinical referral cohort of children diagnosed with OSA, we found no differences in OAH1, but significant differences in apnea index, with worse apnea indices in the supine position.(8) Furthermore, obese children seemed to prefer the prone position at the expense of the side position, and to exhibit more severe OAH1 and AI in the supine position when compared to non-obese children with OSA of similar severity. (8) However, we did not explore REMS and NREMS predominance. Although children in our current study slept significantly more in side body position, their sleep-related body position median respiratory events in REMS and in NREMS were comparable. In the supine position, mild desaturations were associated with NREMS respiratory event predominance, and in the prone position, more severe obstructive sleep apnea (higher OAH1) was present independent of sleep state. Thus, it is possible that the pathophysiological mechanisms and outcomes of these children are heterogeneous because of sleep state and body position dependencies. Other findings of interest, such as the NREMS predominance of central apneic events in prone, and the increased likelihood of REMS central apneas in boys in a prone position raise specific questions as to the impact of body position on gender-related susceptibility to central apnea. These findings are reminiscent of the unique vulnerability to SIDS afforded by the prone position and the reduced arousability that characterizes sleep in this body position in infants.(22–26) Notwithstanding, the implications of such findings remain elusive in school-aged children. In addition, our findings suggest that side sleeping may be associated with more NREMS events, as well as with more severe hypoxemia, hypoventilation, or fragmented sleep. Especially, African American's respiratory events during side sleeping are predominantly in NREMS.

Regardless of body position, more severe obstructive sleep apnea as well as more spontaneous arousals were predictive of REMS predominance of respiratory events. In particular, REMS predominance when side sleeping was overall associated with more severe obstructive sleep apnea indices, and this was also the case for African American girls when they slept supine during REMS.

Based on aforementioned comparisons between the REMS and NREMS predominance groups, it is likely that differences in sleep architecture due to respiratory events will occur in the 2 groups. Indeed, children with REMS predominance tend to spend more time in REMS, but are not distinguishable as far as age, gender, or BMI z-score, from those children who exhibit NREMS predominance. Other investigators (4, 11) did not find such alterations in sleep architecture, and while a small, but statistically significant impact of respiratory events on sleep architecture was also reported.(8, 27, 28)

In adults, NREMS-predominant disease occupies approximately 80% or more of the totality of patients being evaluated for OSA in clinical sleep laboratories, and appears to exhibit more severe clinical phenotype than REMS-predominant disease, the latter being preferentially circumscribed to younger women.(29–32) We here show that in pre-pubertal children the exact inverse pattern occurs, such that REMS-predominant disease is by far the most common form of OSA occupying in excess of 80% of the cases. Thus, it is very likely that different pathophysiological mechanisms will be operational in these 2 OSA categories, and it is also plausible that hormonal changes during puberty or thereafter, lead to the reversal of REMS-NREMS OSA predominance. Further exploration of the changes longitudinally during transition from childhood to adolescence to adulthood may shed some light into this issue, particularly considering the higher risk of recurrence of OSA after

adolescence in children who were previously diagnosed and treated for OSA during childhood.(33–35)

In summary, respiratory events in children are clearly REMS-related, yet NREMS predominance of respiratory events occurs in a sizable minority of pre-pubertal children, for whom this pattern cannot be readily predicted from specific demographic features. The presence of NREMS predominance is associated with less severe oxyhemoglobin desaturations and appears to be more prevalent among African Americans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

REMS	Rapid Eye Movement sleep
NREMS	Non-Rapid Eye Movement sleep
OAH	Obstructive Apnea-Hypopnea Index
AI	Apnea Index
OAI	Obstructive Apnea Index
MAI	Mixed Apnea Index
CAI	Central Apnea Index
HI	Hypopnea Index
OHI	Obstructive Hypopnea Index
CHI	Central Hypopnea Index
MHI	Mixed Hypopnea Index

Figure 1.
 Polygon of REMS-NREMS distributions of respiratory events (log scale of ratio REMS : NREMS)
 To the right side of the (1:1) ratio: REMS predominance, and to the left side of the 1:1 ratio: NREMS predominance

Table 1

Polysomnographic characteristics of the cohort

NPSG parameter	Total sample
Sleep Efficiency Index (%)	89.4 ± 20.6 [87.2 – 91.6]
Sleep Onset Latency (min)	26.0 ± 24.9 [23.3 – 28.7]
REM Onset Latency (min)	167.3 ± 70.2 [159.7 – 174.9]
Wake After Sleep Onset (%)	8.7 ± 7.7 [7.9 – 9.5]
Total Sleep Time (min.)	467.7 ± 49.7 [462.4 – 473.1]
Supine TST (min.)	165.7 ± 124.7 [152.3 – 179.2]
Side TST (min.)	215.4 ± 127.6 [201.7 – 229.2]
Prone TST (min.)	30.4 ± 64.6 [23.5 – 37.4]
S1 (%)	5.5 ± 4.7 [5.0 – 6.0]
S2 (%)	45.3 ± 7.6 [44.5 – 46.1]
SWS (%)	31.6 ± 13.7 [30.1 – 33.1]
REM (%)	18.8 ± 9.9 [17.7 – 19.8]
OAHI h ⁻¹	1.7 ± 3.0 [1.4 – 2.0]
Nadir SpO ₂ (%)	91.4 ± 5.6 [90.7 – 92.0]
Desaturation index ≥2%	1.1 ± 3.1 [0.8 – 1.4]
Average End Tidal CO ₂ (mmHg)	33.0 ± 16.1 [31.3 – 34.8]
SAI	9.7 ± 7.4 [8.9 – 10.5]
RAI	1.1 ± 2.0 [0.9 – 1.3]

Data are presented as mean ± standard deviation [95% C.I.].

Table 2

Differences in REMS and NREMS proportions of respiratory events

	proportion in REM = NREM	proportion in REM>NREM	proportion in REM<NREM	p- value
All night (n=335)	%	%	%	
All respiratory events	10.5	70.9	70.9	0.0000
Apnea Hypopnea Index	12.0	68.9	19.2	0.0000
Apnea Index	23.9	56.1	20.0	0.000
Central Apnea Index	35.8	45.1	19.1	0.0003
Obstructive Apnea Index	66.3	20.3	13.4	0.345
Mixed Apnea Index	86.3	7.5	6.3	0.379
Hypopnea Index	27.3	48.9	23.7	0.0002
Central Hypopnea Index	97.3	1.8	0.9	0.722
Obstructive Hypopnea Index	28.1	48.1	23.9	0.0003
Mixed Hypopnea Index	97.9	0.9	1.2	0.899
Supine (n=288)				
All respiratory events	15.5	58.4	26.2	0.0000
Apnea Hypopnea Index	21.5	47.9	30.6	0.01
Apnea Index	42.0	34.7	23.3	0.115
Central Apnea Index	55.6	23.6	20.8	0.704
Obstructive Apnea Index	77.1	13.5	9.4	0.001
Mixed Apnea Index	92.4	3.8	3.8	1
Hypopnea Index	38.5	29.2	32.3	0.656
Central Hypopnea Index	97.9	1.0	1.0	1
Obstructive Hypopnea Index	39.6	28.8	31.6	0.688
Mixed Hypopnea Index	98.6	0.3	1.0	0.501
Side (n=296)				
All respiratory events	11.7	62.0	26.3	0.0000
Apnea Hypopnea Index	15.2	57.1	27.7	0.0000
Apnea Index	34.8	44.3	20.9	0.002
Central Apnea Index	47.0	35.8	17.2	0.017
Obstructive Apnea Index	74.7	11.8	13.5	0.826
Mixed Apnea Index	89.9	6.1	4.1	0.283
Hypopnea Index	37.8	37.2	25	0.083
Central Hypopnea Index	98.6	1.0	0.3	0.504
Obstructive Hypopnea Index	38.5	36.5	25.0	0.102
Mixed Hypopnea Index	98.6	0.7	0.7	1
Prone (n=122)				
All respiratory events	41.9	37.8	20.3	0.239

	proportion in REM = NREM	proportion in REM>NREM	proportion in REM<NREM	p- value
Apnea Hypopnea Index	54.1	23.0	23.0	1
Apnea Index	63.9	12.3	23.8	0.365
Central Apnea Index	72.1	9.0	18.9	0.0001
Obstructive Apnea Index	83.6	4.9	11.5	0.067
Mixed Apnea Index	99.2	-	0.8	-
Hypopnea Index	68.0	16.4	15.6	0.946
Central Hypopnea Index	96.7	0.8	2.5	0.365
Obstructive Hypopnea Index	68.0	16.4	15.6	0.946
Mixed Hypopnea Index	97.5	-	2.5	-