Obstructive Sleep Apnea (OSA) in Preadolescent Girls is Associated with Delayed Breast Development Compared to Girls without OSA

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Study Objective: Adults with obstructive sleep apnea (OSA) have lower sex steroid levels than controls. We sought to determine whether OSA also interferes with reproductive hormones in adolescence by tracking the pace of pubertal development.

Methods: One hundred seventy-two children in the Tucson Children's Assessment of Sleep Apnea study (TuCASA) underwent two home polysomnographic studies, spaced 4-5 years apart. Height and weight were measured at both visits, and Tanner staging of breasts/genitals and pubic hair were self-assessed by a pictorial questionnaire at follow-up.

Results: Eighty-seven girls and 85 boys, age 8.9 ± 1.6 years (mean $\pm$ SD) at baseline and 13.4 ± 1.6 years at follow-up, participated. Twenty-seven percent of participants were overweight or obese at baseline, and the majority remained so at follow-up. Twenty-six percent of girls and 28% of boys met criteria for OSA, defined as a respiratory disturbance index (RDI) $\geq 1/\text{h}$ associated with a 3% desaturation (RDI 3%), at

baseline. There was an inverse relationship between baseline log RDI 3% and Tanner breast stage at follow-up (coefficient -1.3 , $p = 0.02$) in girls after adjusting for age ($p < 0.001$), body mass index ($p < 0.005$), and ethnicity. Girls with OSA at baseline were more than 1 Tanner breast stage behind girls without OSA at follow-up. OSA did not affect genital development in boys or pubic hair development in either sex.

Conclusions: OSA in preadolescent girls predicts delayed breast development relative to girls without OSA. Sleep fragmentation and/or hypoxia seen in OSA may interfere with reproductive development in girls.

Keywords: Obstructive sleep apnea, puberty, adolescence, sex steroids, lung

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Sleep is an important modulator of reproductive hormone secretion. During the early stages of puberty, there is an increase in hypothalamic gonadotropin-releasing hormone (GnRH) and pituitary luteinizing hormone (LH) secretion in both girls and boys that initially occurs only during sleep.¹ The results of sleep-wake reversal studies, during which subjects remain awake at night and sleep during the day, indicate that LH secretion is related to sleep *per se* rather than to time of day.² The sleep-related augmentation of GnRH/LH secretion is responsible for the increases in testosterone (T) and estradiol secretion that drive pubertal development in boys and girls, respectively.

The impact of disordered sleep on the reproductive axis during adolescence is unknown. However, in adulthood, sleep fragmentation and/or nocturnal hypoxia secondary to obstructive sleep apnea (OSA) is associated with low sex steroid levels,³⁻⁸ which in some cases improve after correction of OSA with continuous positive airway pressure (CPAP) treatment or surgery.^{3,8,9} These findings raise concern that pediatric OSA, which affects 1% to 5% of children,¹⁰ may also diminish reproductive hormone secretion during childhood, potentially interfering with normal pubertal maturation.

BRIEF SUMMARY

Current Knowledge/Study Rationale: During early to mid-puberty, reproductive hormone secretion increases dramatically during sleep compared with wake, raising concern that children with sleep disordered breathing may be at risk for delayed pubertal development. This study was undertaken to determine the impact of sleep disordered breathing on the pace of pubertal development in a community sample of otherwise healthy boys and girls.

Study Impact: The finding that girls with sleep disordered breathing have delayed breast development relative to healthy peers suggests that girls with sleep disorders deserve close monitoring during adolescence to ensure that pubertal milestones are achieved on time. Future studies will be important to determine the impact of sleep disorders on the age of menarche and menstrual cycle regularity.

The Tucson Children's Assessment of Sleep Apnea study (TuCASA) is a prospective cohort study of 6- to 11-year-old children with and without OSA followed over a 4- to 5-year period to investigate the predictors and neurocognitive and physiological sequelae of OSA. As pubertal stage was one of the measures obtained at follow-up, this study represents a unique opportunity to examine the effect of OSA on the pace of pubertal development in otherwise healthy children. Based

Table 1—Subject characteristics at baseline and follow-up visits

	Baseline Examination	Follow-up Examination
Girls (n = 87)		
Age, years, mean (SD)	8.9 (1.7) ^a	13.4 (1.8)
BMI Z-score, mean (SD)	0.2 (1.2)	0.3 (1.1)
Ethnicity	68% Caucasian 32% Hispanic	NA
RDI 3%, events/h, median (IQR)	0.5 (0.3-1) ^a	0.2 (0.1-0.5)
% SDB, RDI 3% ≥ 1	26% (23/87) ^b	10% (9/87)
% Snoring	11.5% (10/87)	5.7% (5/87)
Tanner stage, median (range)		
Breast	NA	3 (1-5)
Pubic hair	NA	3 (1-5)
Boys (n = 85)		
Age, years, mean (SD)	8.8 (1.5) ^a	13.5 (1.5)
BMI Z-score, mean (SD)	0.3 (1.3)	0.3 (1.3)
Ethnicity	68% Caucasian 32% Hispanic	NA
RDI 3%, events/h, median (IQR)	0.6 (0.2-1.1) ^b	0.2 (0.1-0.8)
% SDB, RDI 3% ≥ 1	28% (24/85)	20% (17/85)
% Snoring	18.8% (16/85)	7.1% (6/85)
Tanner stage, median (range)		
Genitals	NA	3 (1-5)
Pubic hair	NA	3 (1-5)

^ap < 0.001, ^bp < 0.05. p-values indicate baseline and follow-up comparisons using unpaired t-tests or χ^2 .

on the close temporal, and likely physiologic, connection between sleep and the reproductive axis during puberty, we hypothesized that children with OSA would have delayed puberty relative to controls.

METHODS

The TuCASA study protocol has been previously described in detail.¹¹ Briefly, nearly 500 Caucasian or Hispanic children, ages 6-11 years, without a chronic medical condition were recruited from the Tucson Unified School District and underwent unattended home polysomnography (PSG). Approximately 5 years later, 304 of the children completed a second in-home PSG study of acceptable quality. Height and weight were measured at each home study visit, and body mass index (BMI) percentiles and standard deviation scores were calculated using the 2000 U.S. Centers for Disease Control and Prevention childhood growth charts.¹² Children with BMI between the 85th and 95th %tile or ≥ 95th %tile for age and gender were considered to be overweight or obese, respectively.¹³ At each home visit, the presence of habitual snoring (defined as snoring loudly “frequently” or “almost always”) was determined by parental report. At the second home study (follow-up) visit, 172 of the children completed a validated pubertal self-assessment questionnaire¹⁴ without parental supervision that consists of simple line drawings based on photographs of the Tanner and Marshall standards for pubic hair and breast or genital development^{15,16}

and a small amount of descriptive text. The 172 children who completed two home PSG studies and a pubertal assessment questionnaire at the follow-up study are the focus of this report.

Unattended overnight PSGs were obtained with the Compumedics PS-2 system (Abbotsford, Victoria, Australia) using the following signals: C3/A2 and C4/A1 electroencephalogram, right and left electrooculogram, a bipolar submental electromyogram, thoracic and abdominal displacement (inductive plethysmography band), airflow (nasal/oral thermistor), nasal pressure cannula, finger pulse oximetry, electrocardiography (single bipolar lead), snoring microphone, body position (Hg gauge sensor), and ambient light.

Scoring of sleep was performed by a single registered polysomnographic technologist using Rechtschaffen and Kales criteria.¹⁷ Arousals were identified using the American Academy of Sleep Medicine criteria.¹⁸ Apneas were scored if the amplitude (peak to trough) of the thermistor airflow signal decreased below 25% of the amplitude at baseline breathing (identified during a period of regular breathing with stable oxygen levels) > 6 sec or 2 breath cycles, as previously described.¹¹ Hypopneas were scored if the amplitude any respiratory signal decreased below 70% of the amplitude of baseline and if the thermistor signal did not meet the criterion for apnea. The respiratory disturbance index (RDI) was defined as the number of apneas and hypopneas associated with a 3% desaturation per hour of total sleep time (RDI 3%). OSA was defined as an RDI ≥ 1 event per hour of total sleep time based on our previous studies,¹⁹ demonstrating that this degree of respiratory disturbance is clinically meaningful (e.g., associated with excessive daytime sleepiness and learning problems).

The TuCASA study was approved by the University of Arizona Institutional Review Board and the Tucson Unified School District Research Committee. Informed consent and assent was obtained from all parents and children, respectively, prior to participation.

Data Analysis

Student's t-test and the χ^2 test were used to compare sleep study parameters at baseline and follow-up (paired t-test) and between boys and girls (unpaired t-test). The effect of OSA at baseline on pubertal stage determined at follow-up was investigated using multiple linear regression, controlling for known predictors of pubertal development (age, BMI, and ethnicity). RDI was log-transformed prior to analysis to improve normality. Statistical analyses were performed using SigmaStat 11 (Systat Software Inc, San Jose, CA).

RESULTS

The study population consisted of 87 girls and 85 boys who were 8.9 ± 1.6 years old (mean ± SD) at the time of their baseline PSG study and 13.4 ± 1.6 years old at follow-up (**Table 1**), with no difference in age between boys and girls. Sixty-eight percent of the cohort was Caucasian; 32% was Hispanic. Twenty-seven percent of children were overweight or obese at baseline with no differences between girls and boys, and the majority (83%) of these children remained obese at follow-up approximately 4 years later. Twenty-six percent of girls and 28% of boys met criteria for OSA (RDI ≥ 1 event/h with 3% desaturation) at

Table 2—Linear regression model for effect of OSA on breast development in girls and genital development in boys, controlling for age, BMI, and ethnicity

Predictor	Coefficient	p-value	95% CI
Girls: Breast Development			
Age at follow-up	0.4	< 0.001	0.28, 0.52
BMI Z-score at follow-up	0.3	< 0.005	0.1, 0.5
Ethnicity	-0.02	0.9	-0.4, 0.4
Log baseline RDI 3%	-1.3	0.02	-2.3, -0.3
Boys: Genital Development			
Age at follow-up	0.4	< 0.001	0.24, 0.56
BMI Z-score at follow-up	-0.05	0.5	-0.23, 0.13
Ethnicity	-0.5	0.03	-1.0, -0.04
Log baseline RDI 3%	1.2	0.06	-0.04, 2.4

baseline (RDI 3% of 1-6.6 in girls with OSA, 1-7.2 in boys with OSA). Parents reported habitual snoring in only 17% of children found to have OSA. At the follow-up study, OSA had persisted in 30% of the subjects diagnosed at baseline, and an additional 12 subjects were newly diagnosed with OSA, for a total of 26 subjects (RDI 3% of 1-5.3 in girls with OSA, 1-7.2 in boys with OSA). There was no difference in the percent of girls (26%) and boys (33%) with OSA at both baseline and follow-up. Only 2 children with OSA at baseline underwent tonsillectomy prior to follow-up, and no child was treated with CPAP.

Self-assessment of Tanner staging at the follow-up visit revealed a median stage of 3 (range 1-5) for pubic hair and breast/genital development in both boys and girls. RDI 3% at visit 1 had no effect on breast/genital stage ascertained at follow-up after controlling for age (β coefficient 0.4, $p < 0.001$), BMI Z-score at visit 2 (coefficient 0.1, $p = 0.07$), and ethnicity (coefficient -0.2, $p = 0.2$). However, when limited to girls, the same linear regression model revealed an inverse relationship between baseline RDI 3% and Tanner breast stage at follow-up, suggesting that OSA delays pubertal development in girls (**Table 2**). On average, girls with OSA at baseline were approximately one Tanner breast stage behind girls without OSA at the follow-up evaluation after controlling for age, BMI, and ethnicity. Higher BMI Z-scores at visit 2 were associated with advanced breast development, but there was no interaction between BMI and RDI 3%, indicating that OSA is associated with slowed pubertal progression in both lean and overweight/obese girls. Older age predicted more mature breast development, as expected, but ethnicity had no effect on Tanner breast stage (**Table 2**). Girls with OSA at baseline were heavier than girls without OSA ($p < 0.01$), but there were no differences in age, ethnicity, arousal index, total sleep time, sleep efficiency, or sleep macroarchitecture between the 2 groups (**Table 3**). There was no relationship between RDI 3% at follow-up and Tanner breast stage; however, this analysis was significantly limited by the small number of girls with OSA at follow-up ($n = 9$).

Similar analyses indicated that there was no relationship between OSA and genital development in boys although there was a trend of slightly more mature genital development (coefficient 1.2, $p = 0.06$) in boys with a history of OSA. However, this trend appears to have been driven by 2 boys without OSA with relatively delayed (Tanner I genitalia at age 13.1 years)

Table 3—Characteristics of girls with and without OSA at the baseline study visit

	RDI 3% ≥ 1 (n = 23)	RDI 3% < 1 (n = 64)
Age, years	8.8 (1.8)	9.0 (1.7)
Ethnicity	60% Caucasian 40% Hispanic	70% Caucasian 30% Hispanic
BMI Z-score	0.3 (1.0) ^a	0.1 (1.1)
RDI 3%, events/h	1.8 (1.3-3.2) ^b	0.4 (0.2-0.5)
Arousal index, events/h	3.4 (1.5)	3.3 (1.3)
Sleep efficiency, %	90.6 (6.3)	91.4 (4.9)
Total sleep time, h	7.8 (1.6)	8.3 (1.3)
Sleep staging		
stage 1, %	3.5 (2.6)	4.1 (3.4)
stage 2, %	54.3 (15.0)	51.7 (5.6)
stage 3/4, %	21.8 (8.5)	22.8 (6.3)
REM, %	20.4 (7.6)	21.5 (4.2)

^a $p < 0.01$, ^b $p < 0.001$. p-values indicate group comparisons using unpaired t-tests or χ^2 . All values are reported as mean (SD) except for RDI 3%, which is reported as median (IQR).

or frankly delayed puberty (Tanner I genitalia at 15.1 years of age) at follow-up, as it was lost after exclusion of these 2 subjects. There was only one girl with delayed puberty, a 14.2-year-old girl with Tanner I breasts who did not have OSA, and her exclusion from the analysis in girls did not impact the results. There was no association between RDI 3% and pubic hair development when girls and boys were analyzed together or separately.

DISCUSSION

Following a prolonged period of childhood quiescence, the central driver of the reproductive axis—the hypothalamic GnRH neuron—reactivates, thereby initiating puberty. Intriguingly, the increase in reproductive hormone secretion during puberty initially occurs only during sleep.¹ The cause of this sleep-specific rise is unknown, but its conservation across a number of species suggests that it has physiologic significance.^{20,21} Furthermore, the sleep sensitivity of GnRH neurons is observed not only during their reactivation during puberty, but reappears in adulthood during the recovery phase of anorexia nervosa²² and hypothalamic amenorrhea,²³ two disorders associated with a prolonged period of diminished GnRH activity.

Given the sensitivity of GnRH neurons to the sleep/wake state, we hypothesized that disordered sleep secondary to OSA would disrupt normal pubertal maturation. Indeed, the current study demonstrates that otherwise healthy preadolescent girls with OSA have delayed pubertal development relative to girls without OSA. Although the increase in GnRH activity with sleep occurs to the same degree in boys as in girls, the reproductive axis in boys appears to be more resistant to disorganized sleep, as OSA did not have a significant effect on pubertal maturation in boys. A similar gender difference is seen in the sensitivity of the reproductive axis to other stressors, such as exercise. Hypogonadism is common among female athletes (so-called hypothalamic amenorrhea) but is

rare among male athletes.²⁴ OSA had no effect on pubarche (the development of pubic hair) in boys or girls. Although pubic hair and genital development occur simultaneously during adolescence, the two are independent processes, with pubic hair development driven primarily by adrenal androgen production and genital development driven solely by maturational changes within the brain.²⁵

An association between OSA and decreased sex steroid and/or gonadotropin levels, as would be predicted to occur in adolescents with OSA and delayed puberty, has previously been reported in adults. Most,^{3-6,8} but not all,^{26,27} studies demonstrate that men with moderate-to-severe OSA have significantly lower T levels than healthy controls and lower^{5,26} or inappropriately normal^{3,4,8} LH levels. Of note, however, many of these studies have been limited by small sample sizes, differences in BMI and/or age between cases and controls, both of which influence serum T, and assessment of gonadal function based on single measurements of T, which is influenced by time of day,²⁸ or LH, which is secreted in a pulsatile manner.²⁹ Only one study has been conducted in adult women with OSA,⁷ and like men with OSA, women with OSA were found to have lower sex steroid levels (estradiol and progesterone) than age- and BMI-matched controls after adjusting for menstrual cycle phase and pre- or postmenopausal status.

The cause of reproductive dysfunction among adults with OSA is unclear but has been attributed to the hypoxia and sleep fragmentation that characterize OSA. Several studies have demonstrated an inverse correlation between T level and the RDI^{4,5} in men; however, studies of total sleep deprivation for 48 hours³⁰ or partial sleep deprivation and sleep fragmentation for 24 hours³¹ reported no adverse effect on gonadotropin or T levels in healthy men. Sleep disruption studies have not yet been conducted in preadolescents whose reproductive axis would be expected to be more vulnerable to sleep disruption than that of adults, given the tight association between LH secretion and sleep during the early stages of puberty.¹ The negative correlation between T and the desaturation index in men with OSA and the finding that mean nocturnal oxygen saturation in men with and without OSA is independently associated with erectile dysfunction³² also suggests that hypoxia may play a role in the lower T levels observed in men with OSA. In a rodent model, intermittent hypoxia without concomitant sleep deprivation activates the inflammatory cascade, increases free radical production, and induces neuronal apoptosis in the hippocampus and cortex³³; however, the effect of hypoxia on the hypothalamus, the seat of the central components of the reproductive axis, including kisspeptin and GnRH neurons,³⁴ has not yet been investigated. Studies are also necessary to determine whether hypoxia and/or sleep disruption explain the defects in reproductive hormone secretion in women with OSA, as observed in men.

In contrast to the above studies in adults with moderate to severe OSA, the children in the current study had relatively mild OSA (RDI 3% 1-7.2) based on conventional scoring methods. However, it is well recognized that standard PSG measures in children, including arousals and the percent time spent in each sleep stage (as were measured in the current study) are likely to underestimate the degree of sleep disruption as they do not correlate with measures of neurobehavioral morbidity.^{35,36} This concept has led to the suggestion that al-

ternative measures, such as the number of subcortical arousals identified by spectral analysis,³⁷ sleep dynamics analyses,³⁸ and autonomic arousal measures,^{39,40} be incorporated into the interpretation of pediatric PSG studies. The use of these more sensitive measures may also help explain why LH pulses, which occur most frequently during slow-wave sleep and rarely during REM sleep during puberty,⁴¹ might be diminished in children with OSA who have the greatest number of obstructive events during REM.⁴² Thus, although the children in the current study appear to have mild OSA according to standard scoring methods, current methods may miss arousals and/or subtle defects in sleep architecture that can explain the detrimental effect of OSA on the reproductive axis in girls during puberty.

Due to the large scale and home-centered approach of the TuCASA study, pubertal staging was determined by a self-assessment questionnaire rather than by a physician's physical examination. It is therefore possible that the present findings are due to an underestimation of pubertal development among girls with OSA. However, a number of studies have demonstrated that adolescent girls (and boys) can accurately determine their degree of pubertal maturation to within one Tanner stage of a trained examiner's assessment using a self-assessment questionnaire that is based on line drawings of pubertal stages.⁴³⁻⁴⁵ While girls with and without OSA were of similar age and ethnic background, girls with OSA were more likely to be overweight or obese. Obesity, however, would be expected to lead to an overestimation rather than underestimation of true breast development, in part due to the difficulty in distinguishing lipomastia from true breast tissue. In a study of 135 girls (mean age 9.3 years), Bonat et al. found that obese girls significantly overestimated their actual breast size (by 0.5 Tanner stages)⁴⁶; other investigators, however, have found that BMI does not bias pubertal assessment in either direction in girls.^{45,47,48} Lastly, although we controlled for BMI in our regression model, the increased incidence of obesity among girls with OSA would be expected to have accelerated, rather than delayed, pubertal development, as recent studies have demonstrated that obese girls enter puberty at a slightly younger age than normal weight girls.⁴⁹ Thus, our estimate of the effect of OSA on female pubertal development is likely to be conservative.

In summary, the current study demonstrates that OSA among preadolescent girls is associated with relatively delayed pubertal maturation. The pathophysiological connection between OSA and the reproductive axis is unknown, but the critical role of the hypothalamus in pubertal development suggests that hypoxia and/or sleep fragmentation may have direct effects on the brain. A central mechanism of action is also suggested by the neuropsychological deficits found in children with OSA⁵⁰ and more recently, by magnetic resonance spectroscopy studies demonstrating neuronal metabolite alterations in children with OSA.⁵¹ While in the current study Tanner breast stage at follow-up remained within the normal range in girls with a history of OSA despite a significant delay relative to girls without OSA, future studies will be necessary to address the important question of whether or not childhood OSA has any long-term effects on the reproductive axis beyond early adolescence.

REFERENCES

- Boyar R, Finkelstein J, Roffwarg H, Kapen S, Weitzman E, Hellman L. Synchronization of augmented luteinizing hormone secretion with sleep during puberty. *N Engl J Med* 1972;287:582-6.
- Kapen S, Boyar RM, Finkelstein JW, Hellman L, Weitzman ED. Effect of sleep-wake cycle reversal on luteinizing hormone secretory pattern in puberty. *J Clin Endocrinol Metab* 1974;39:293-9.
- Grunstein RR, Handelsman DJ, Lawrence SJ, Blackwell C, Caterson ID, Sullivan CE. Neuroendocrine dysfunction in sleep apnea: reversal by continuous positive airways pressure therapy. *J Clin Endocrinol Metab* 1989;68:352-358.
- Hammoud AO, Walker JM, Gibson M, et al. Sleep apnea, reproductive hormones and quality of sexual life in severely obese men. *Obesity (Silver Spring)* 2011;19:1118-23.
- Luboshitzky R, Aviv A, Hefetz A, et al. Decreased pituitary-gonadal secretion in men with obstructive sleep apnea. *J Clin Endocrinol Metab* 2002;87:3394-8.
- Luboshitzky R, Lavie L, Shen-Orr Z, Herer P. Altered luteinizing hormone and testosterone secretion in middle-aged obese men with obstructive sleep apnea. *Obes Res* 2005;13:780-6.
- Netzer NC, Eliasson AH, Strohl KP. Women with sleep apnea have lower levels of sex hormones. *Sleep Breath* 2003;7:25-9.
- Santamaria JD, Prior JC, Fleetham JA. Reversible reproductive dysfunction in men with obstructive sleep apnoea. *Clin Endocrinol (Oxf)* 1988;28:461-70.
- Luboshitzky R, Lavie L, Shen-Orr Z, Lavie P. Pituitary-gonadal function in men with obstructive sleep apnea. The effect of continuous positive airways pressure treatment. *Neuro Endocrinol Lett* 2003;24:463-7.
- Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics* 2012;130:576-84.
- Goodwin JL, Enright PL, Kaemingk KL, et al. Feasibility of using unattended polysomnography in children for research—report of the Tucson Children's Assessment of Sleep Apnea study (TuCASA). *Sleep* 2001;24:937-44.
- Clinical Growth Charts. Centers for Disease Control and Prevention. http://www.cdc.gov/growthcharts/clinical_charts.htm. 2012.
- Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics* 2007;120 Suppl 4:S164-92.
- Taylor SJ, Whincup PH, Hindmarsh PC, Lampe F, Odoki K, Cook DG. Performance of a new pubertal self-assessment questionnaire: a preliminary study. *Paediatr Perinat Epidemiol* 2001;15:88-94.
- Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child* 1969;44:291-303.
- Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child* 1970;45:13-23.
- Rechtschaffen A, Kales A. *A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects*. Washington DC: Washington Public Health Service, US Government Printing Office, 1968.
- EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep* 1992;15:173-84.
- Goodwin JL, Kaemingk KL, Fregosi RF, et al. Clinical outcomes associated with sleep-disordered breathing in Caucasian and Hispanic children—the Tucson Children's Assessment of Sleep Apnea study (TuCASA). *Sleep* 2003;26:587-91.
- Urbanski HF, Ojeda SR. The juvenile-peripubertal transition period in the female rat: establishment of a diurnal pattern of pulsatile luteinizing hormone secretion. *Endocrinology* 1985;117:644-9.
- Watanabe G, Terasawa E. In vivo release of luteinizing hormone releasing hormone increases with puberty in the female rhesus monkey. *Endocrinology* 1989;125:92-9.
- Katz JL, Boyar R, Roffwarg H, Hellman L, Weiner H. Weight and circadian luteinizing hormone secretory pattern in anorexia nervosa. *Psychosom Med* 1978;40:549-67.
- Perkins RB, Hall JE, Martin KA. Neuroendocrine abnormalities in hypothalamic amenorrhea: spectrum, stability, and response to neurotransmitter modulation. *J Clin Endocrinol Metab* 1999;84:1905-11.
- Skarda ST, Burge MR. Prospective evaluation of risk factors for exercise-induced hypogonadism in male runners. *West J Med* 1998;169:9-12.
- Counts DR, Pescovitz OH, Barnes KM, et al. Dissociation of adrenarche and gonadarche in precocious puberty and in isolated hypogonadotropic hypogonadism. *J Clin Endocrinol Metab* 1987;64:1174-8.
- Bratel T, Wennlund A, Carlstrom K. Pituitary reactivity, androgens and catecholamines in obstructive sleep apnoea. Effects of continuous positive airway pressure treatment (CPAP). *Respir Med* 1999;93:1-7.
- Gambineri A, Pelusi C, Pasquali R. Testosterone levels in obese male patients with obstructive sleep apnea syndrome: relation to oxygen desaturation, body weight, fat distribution and the metabolic parameters. *J Endocrinol Invest* 2003;26:493-8.
- Brambilla DJ, Matsumoto AM, Araujo AB, McKinlay JB. The effect of diurnal variation on clinical measurement of serum testosterone and other sex hormone levels in men. *J Clin Endocrinol Metab* 2009;94:907-13.
- Midgley AR Jr., Jaffe RB. Regulation of human gonadotropins. X. Episodic fluctuation of LH during the menstrual cycle. *J Clin Endocrinol Metab* 1971;33:962-9.
- Akerstedt T, Palmblad J, de la TB, Marana R, Gillberg M. Adrenocortical and gonadal steroids during sleep deprivation. *Sleep* 1980;3:23-30.
- Luboshitzky R, Zabari Z, Shen-Orr Z, Herer P, Lavie P. Disruption of the nocturnal testosterone rhythm by sleep fragmentation in normal men. *J Clin Endocrinol Metab* 2001;86:1134-9.
- Budweiser S, Enderlein S, Jorres RA, et al. Sleep apnea is an independent correlate of erectile and sexual dysfunction. *J Sex Med* 2009;6:3147-57.
- Gozal D, Daniel JM, Dohanich GP. Behavioral and anatomical correlates of chronic episodic hypoxia during sleep in the rat. *J Neurosci* 2001;21:2442-50.
- Seminara SB, Crowley WF Jr. Kisspeptin and GPR54: discovery of a novel pathway in reproduction. *J Neuroendocrinol* 2008;20:727-31.
- Lopes MC, Marcus CL. The significance of ASDA arousals in children. *Sleep Med* 2007;9:3-8.
- Paruthi S, Chervin RD. Approaches to the assessment of arousals and sleep disturbance in children. *Sleep Med* 2010;11:622-7.
- Chervin RD, Burns JW, Subotic NS, Roussi C, Thelen B, Ruzicka DL. Method for detection of respiratory cycle-related EEG changes in sleep-disordered breathing. *Sleep* 2004;27:110-5.
- Chervin RD, Fetterolf JL, Ruzicka DL, Thelen BJ, Burns JW. Sleep stage dynamics differ between children with and without obstructive sleep apnea. *Sleep* 2009;32:1325-32.
- Aljadeff G, Gozal D, Schechtman VL, Burrell B, Harper RM, Ward SL. Heart rate variability in children with obstructive sleep apnea. *Sleep* 1997;20:151-7.
- Katz ES, Lutz J, Black C, Marcus CL. Pulse transit time as a measure of arousal and respiratory effort in children with sleep-disordered breathing. *Pediatr Res* 2003;53:580-8.
- Shaw ND, Butler JP, McKinney SM, Nelson SA, Ellenbogen JM, Hall JE. Insights into puberty: the relationship between sleep stages and pulsatile LH secretion. *J Clin Endocrinol Metab* 2012;97:E2055-62.
- Goh DY, Galster P, Marcus CL. Sleep architecture and respiratory disturbances in children with obstructive sleep apnea. *Am J Respir Crit Care Med* 2000;162:682-6.
- Chan NP, Sung RY, Kong AP, Goggins WB, So HK, Nelson EA. Reliability of pubertal self-assessment in Hong Kong Chinese children. *J Paediatr Child Health* 2008;44:353-8.
- Rollof L, Elfving M. Evaluation of self-assessment of pubertal maturation in boys and girls using drawings and orchidometer. *J Pediatr Endocrinol Metab* 2012;25:125-9.
- Wu Y, Schreiber GB, Klementowicz V, Biro F, Wright D. Racial differences in accuracy of self-assessment of sexual maturation among young black and white girls. *J Adolesc Health* 2001;28:197-203.
- Bonat S, Pathomvanich A, Keil MF, Field AE, Yanovski JA. Self-assessment of pubertal stage in overweight children. *Pediatrics* 2002;110:743-7.
- Stephen MD, Bryant WP, Wilson DP. Self-assessment of sexual maturation in children and adolescents with diabetes mellitus. *Endocr Pract* 2008;14:840-5.
- Williams RL, Cheyne KL, Houtkooper LK, Lohman TG. Adolescent self-assessment of sexual maturation. Effects of fatness classification and actual sexual maturation stage. *J Adolesc Health Care* 1988;9:480-2.
- Kaplowitz PB, Slora EJ, Wasserman RC, Pedlow SE, Herman-Giddens ME. Earlier onset of puberty in girls: relation to increased body mass index and race. *Pediatrics* 2001;108:347-53.
- Beebe DW. Neural and neurobehavioral dysfunction in children with obstructive sleep apnea. *PLoS Med* 2006;3:e323.
- Halbower AC, Degaonkar M, Barker PB, et al. Childhood obstructive sleep apnea associates with neuropsychological deficits and neuronal brain injury. *PLoS Med* 2006;3:e301.

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