LONG-TERM EFFECTS OF CAFFEINE THERAPY FOR APNEA OF PREMATURITY ON SLEEP AT SCHOOL-AGE

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Scientific Knowledge on the Subject

Therapeutic caffeine administration for apnea of prematurity has been shown to have beneficial short and long-term effects on survival and neurodevelopmental disabilities. Animal studies have suggested that neonatal caffeine has long-term detrimental effects on sleep and control of breathing, but corresponding human studies have not been performed.

What This Study Adds to the Field

This study shows that therapeutic neonatal caffeine administration has no long-term effects on sleep quality or quantity, or on pathologic conditions during sleep. This finding should allay concerns about the long-term effects of the drug on sleep. In addition, this study demonstrates a higher than expected prevalence of obstructive sleep apnea syndrome and periodic limb movements during sleep in ex-preterm infants.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

Abbreviations

AHI – Apnea Hypopnea Index

BMI –Body Mass Index

OSAS – Obstructive Sleep Apnea Syndrome

PLMS - Periodic Limb Movements During Sleep

ABSTRACT

Rationale: Apnea of prematurity is a common condition that is usually treated with caffeine, an adenosine receptor blocker that has powerful influences on the central nervous system. However, little is known about the long-term effects of caffeine on sleep in the developing brain.

Objectives: We hypothesized that neonatal caffeine use resulted in long-term abnormalities in sleep architecture and breathing during sleep.

Methods: 201 ex-preterm children aged 5-12 years who participated as neonates in a double-blind, randomized controlled clinical trial of caffeine versus placebo underwent actigraphy, polysomnography and parental sleep questionnaires. Co-primary outcomes were total sleep time on actigraphy and apnea hypopnea index on polysomnography.

Results: There were no significant differences in primary outcomes between the caffeine group *vs* placebo [adjusted mean difference of -6.7 (95%CI -15.3,2.0) minutes, P=0.13 for actigraphic total sleep time; and adjusted rate ratio (caffeine/placebo) for apnea hypopnea index of 0.89 (95%CI 0.55,1.43), P=0.63]. Polysomnographic total recording time and total sleep time were longer in the caffeine group, but there was no difference in sleep efficiency between groups. The percentage of children with obstructive sleep apnea (8.2% of caffeine group *vs* 11.0% of placebo, p=0.22) or elevated periodic limb movements of sleep (17.5% in caffeine group *vs* 11% in placebo group) was high but did not differ significantly between groups.

Conclusions: Therapeutic neonatal caffeine administration has no long-term effects on sleep duration or sleep apnea during childhood. Ex-preterm infants, regardless of caffeine status, are at risk for obstructive sleep apnea and periodic limb movements in later childhood.

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INTRODUCTION

Apnea of prematurity is common, occurring in more than three-quarters of infants born prior to 30 weeks gestation.[1] It is typically treated with methylxanthines, primarily caffeine. Indeed, a study of 220 hospitals showed that caffeine was the most commonly used drug in infants <32 weeks gestation.[2] The Caffeine for Apnea of Prematurity (CAP) trial randomized 2006 preterm infants to neonatal caffeine therapy or placebo and showed beneficial results, with caffeine resulting in lower rates of bronchopulmonary dysplasia and severe retinopathy of prematurity before discharge, and reduced risks of cerebral palsy and cognitive delay at 18 months compared to placebo[3,4]; by 5 years of age, benefits on cognitive development were attenuated but there were still benefits on motor development.[5,6] However, little is known about the long-term effects of caffeine, which is an adenosine receptor blocker, on sleep regulation in the developing brain. In particular, it is not known whether caffeine has long-term adverse effects on sleep architecture and ventilatory control, which could result in an increased prevalence of sleep disorders later in childhood such as insomnia or obstructive sleep apnea syndrome (OSAS).

Although the acute sleep suppressing effects of caffeine administration are well known in daily life and from research[7], studies have not evaluated the effects of chronic caffeine use on sleep. Studies across the age spectrum have shown that methylxanthines result in decreased sleep time and fragmented sleep[8,9], and can also lead to decreased rapid eye movement/active sleep in neonates.[10] This may have important clinical consequences as sleep, and in particular rapid eye movement sleep, is thought to be important for memory and learning.[11] Methylxanthines are also known to modulate ventilatory control, which is a determinant of upper airway collapsibility.[12] Animal studies have shown that neonatal caffeine administration can chronically

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affect ventilation during adulthood, resulting in increased baseline ventilation and a decreased ventilatory response to hypercapnia.[13] Children who were born prematurely have an elevated risk of developing OSAS[14], but it is not known whether this is due, at least in part, to the effect of neonatal caffeine exposure on ventilatory control.

We hypothesized that caffeine therapy for apnea of prematurity, while beneficial in the short term, would result in long-term abnormalities in sleep patterns and in breathing during sleep. We therefore obtained both subjective and objective measures of sleep in a cohort of children who had been randomized to masked caffeine or placebo as neonates in the CAP trial.

Some of these data were presented in abstract form at the American Thoracic Society May 2014 and the SLEEP 2014 conference, June 2014.[15]

METHODS

See online supplement for details.

This was a prospective follow-up study of the CAP trial. A subsample of 4 CAP sites was selected based on recruitment/retention rates and geographic clustering. The research ethics board approved the study, and written informed consent was obtained from parents/guardians. Children underwent two weeks of actigraphy and one night of comprehensive ambulatory home polysomnography; data were scored and interpreted centrally. Caregivers completed sleep diaries and questionnaires. Investigators and subjects/families remained blinded as to whether the subject had received caffeine or placebo as a neonate. The co-primary outcomes were

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average total sleep time based on multiple nights of actigraphy, and the obstructive apnea hypopnea index (AHI) from polysomnography.

Children were studied at age 5-12 years. Subjects were born prematurely, weighed 500-1,250 g at birth, did not have major congenital anomalies or syndromes, were considered by their clinicians to be candidates for methylxanthine therapy during the first 10 days of life, and were randomized to caffeine or placebo for a median of 6 weeks during the neonatal period.[3] The study sample included 6 (3%) children with moderate to severe cerebral palsy or developmental delays.

Actigraphy was performed for two weeks (Actiwatch 2). Actigraphy is a validated technique for measuring sleep *vs* wakefulness based on movement, using a wristwatch-like device, and was used primarily to assess sleep quality and quantity during normal daily life.[16] The actigraph was worn on the non-dominant wrist. The Actiwatch 2 has been validated compared to in-lab polysomnography in this age group.[17] However, further validation was performed by an epoch-by-epoch comparison of actigraphy and simultaneous ambulatory polysomnography in a random sample of 20 subjects.

Subjects underwent one night of unattended, ambulatory polysomnography. The primary purpose of polysomnography was to detect sleep-related medical conditions, such as OSAS, rather than sleep quality, as sleep quality may be affected by instrumentation. Details of the polysomnography technique and quality have been published.[18] In brief, technologists went to the home to apply and remove monitoring leads at the child's usual bed/wake times.

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Electroencephalograms, electrooculograms, submental and tibial electromyograms, chest and abdominal wall movement, ECG, airflow (nasal pressure and oronasal thermistor) and arterial oxygen saturation with pulse waveform were monitored. Studies were scored using standard pediatric rules.[19]

The caregiver completed the National Sleep Foundation 2004 Sleep In America questionnaire[20], the Pediatric Sleep Questionnaire Sleep Related Breathing Disorder Scale, and a restless legs syndrome questionnaire.[21]

Statistics

AHI was compared between groups using a Poisson regression model incorporating adjustment for pre-specified covariates of center, age, gender, race, and maternal education.[22] Treatment effect and confidence interval were expressed as rate ratios. Average total sleep time was compared between groups with a weighted (inverse variance) regression model[23] with adjustment for the above covariates as well as weekend nights and season. Data were compared between groups using Student's t-tests (or equivalent non-parametric tests) for quantitative data and chi-squared tests for categorical data. p-values <0.05 were considered significant. The target sample size of 200 was anticipated to yield 90% power for a 2.5% decrease in actigraphic mean sleep time (0.21 hours, which was considered clinically meaningful) and 80% power to detect a mean difference in AHI of 1.5 events/hr.

RESULTS

Study enrollment is shown in Figure 1; 201 subjects were recruited. The only demographic difference between those who enrolled *vs* those who declined was a higher maternal education level in those who enrolled (p=0.028).

Subject characteristics are shown in Table 1. Reflective of the original CAP population[3], this was primarily a Caucasian population with a high level of maternal education.

Based on caregiver report, current caffeine intake of the children was low, with 26.0% of the caffeine group and 23.5% of the placebo group reporting any use (p=0.74). In both groups, average intake was one caffeine-containing drink per day for those with any exposure to caffeine.

Actigraphy

Actigraphy was initially unsatisfactory in 26 (13%) of 201 subjects, and was repeated successfully in 16. For logistic reasons, actigraphy was not repeated in 10 subjects. Thus, there were 191 (95%) successful actigraphy studies (Figure 1). The actigraph was worn for 13.2±2.1 days in the caffeine group and 13.4±2.0 days in the placebo group (p=0.60). The pilot study of actigraphy compared to polysomnography showed good sensitivity to detect sleep (0.87) but weak specificity to detect wake after sleep onset (0.48), similar to that reported in the literature.[16] Actigraphy was less specific in children with PLMS; in participants with a periodic limb movement index >5/hr, wake after sleep onset was similar to those with an index ≤5/hr during polysomnography (50.1 ± 22.4 [SD] *vs* 45.4 ± 26.0 minutes, respectively; p=0.46) but was

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significantly greater on actigraphy (113.4 $\pm$ 85.9 *vs* 83.2 $\pm$ 38.2 minutes; p=0.010), indicating

that movement from the PLMS (probably due to trunk or arm movements) resulted in false

positive wake time on actigraphy.

Summary actigraphy data (excluding the polysomnography night) are shown in Table 2. There

was no significant difference between groups in the co-primary outcome of actigraphic total sleep

time. There were no statistically significant differences in any of the secondary actigraphic

outcomes, including sleep onset latency and sleep efficiency.

Polysomnography

Successful home polysomnography was obtained in 197 (98%) subjects (Figure 1)[18]. Results

are shown in Table 3. Polysomnographic total recording time and total sleep time were both

longer in the caffeine group compared to placebo, but there was no difference in sleep efficiency

or sleep architecture between the groups.

The co-primary outcome of the AHI did not differ significantly between groups (Table 3). A

large proportion of children in both group had OSAS (defined as an AHI $\geq$2/hr[24]): 8.2% of the

caffeine group and 11.0% of the placebo group (total of 9.6%). The highest AHI was 47.6/hr.

Further, 24% of the caffeine group and 29% of the placebo group had either an elevated AHI

and/or a history of adenoidectomy/tonsillectomy, the usual treatment for childhood OSAS.[25]

However the proportion of children with OSAS did not differ between groups. There was no

significant relationship between AHI and obesity (p=0.28 with the categorical variable, and

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p=0.59 for BMI-Z score). Central apneas were rare, with the highest central apnea index being 3.3/hr.

PLMS were common. The PLMS index was higher in the caffeine group than the placebo group, but this difference was no longer significant when corrected for covariates (Table 3). The proportion of subjects with a PLMS index in the pathologic range ($>5/hr$[26]) was high (17.5% in the caffeine group *vs* 11% in the placebo group; 14% overall; Table 3), but did not differ significantly between groups. Seven (3.5%) children had a PLMS index in the severe range ($>15/hr$), with the highest index being 35/hr.

Questionnaires

The National Sleep Foundation Questionnaire data corroborated the actigraphy results. Most children in both groups usually went to bed between 20:00-20:59 and awoke between 7:00-7:29. Although questionnaire data did not show significant differences in usual nocturnal (579±99 *vs* 563±91 min, p=0.22) or nap (29±114 *vs* 27±186 min, p=0.93) sleep time between caffeine and controls, respectively, caregivers in the caffeine group thought that their child needed more sleep than control caregivers (610±73 *vs* 584±64 min, p=0.007).

21.1% of caregivers in the caffeine group *vs* 19.0% of placebo (P = 0.73) answered yes to the broad question "Do you think your child has a sleep problem?" The mean Pediatric Sleep Questionnaire scores were in the normal range and did not differ between groups (Table 4). There was no difference in the restless legs syndrome score between groups (Table 4).

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DISCUSSION

This randomized, controlled, double-blind study of ex-preterm infants found no long-term effect of neonatal caffeine therapy on objective or subjective sleep measures at school-age, but did show that ex-preterm infants had a high prevalence of OSAS and PLMS compared with the general population.[27, 28]

Caffeine is the standard treatment for apnea of prematurity, and is used widely in neonatal care. Nevertheless, despite the marked effect of caffeine upon sleep regulation, the long-term effects of therapeutic caffeine administration on sleep and ventilatory control in ex-preterm infants have not been studied. Caffeine blocks adenosine, a sleep-promoting agent.[29] In rodents, caffeine administration during early life results in permanent changes in adenosine receptor function during adulthood.[30] Rats who received neonatal caffeine have sleep disruption as adults, including increased sleep latency, decreased sleep time and sleep fragmentation.[13] Further, long-term animal studies have shown that rats who received methylxanthines during early life had increased resting ventilation and blunted hypercapnic ventilatory responses during adulthood.[13] Thus, animal studies suggest that neonatal caffeine administration can lead to permanent abnormalities in sleep regulation and ventilatory control. However, corresponding human studies had not previously been performed.

In the current study, there was no difference in sleep quality or quantity on actigraphy between children exposed to caffeine versus placebo. Given the tightness of the 95% confidence intervals, it is highly unlikely that this study failed to detect a true clinically important adverse effect of caffeine on sleep. Actigraphy and questionnaires showed bedtimes and total time in bed

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similar to those reported in the literature for school-aged children.[20] Consistent with the literature, there was a discrepancy between the actigraphic and polysomnographic measures of sleep architecture.[16, 17] Although time in bed (actigraphy) and total recording time (polysomnography) were similar, actigraphy demonstrated a lower sleep efficiency, longer sleep latency and increased wake time after sleep onset. This demonstrates a known limitation of actigraphy use in school-aged children. Young children move frequently during sleep, and therefore actigraphy is sensitive at detecting sleep, but has decreased specificity in discriminating between sleep and wakefulness[16, 17]; the specificity was most likely lowered further by the high prevalence of PLMS. Nevertheless, the actigraphy data supported the questionnaire data showing no difference in actual sleep time between caffeine and placebo groups.

Polysomnography showed a longer total recording time and longer total sleep time in the caffeine group compared to placebo, although sleep efficiency was the same. The reason for this longer sleep time, even when controlled for center, is unclear. Polysomnographic recordings were started and ended at the child's usual bedtime and wake time, and questionnaires and actigraphy (which are better indicators of habitual sleep times) showed no significant difference in bedtimes, wake times or total sleep time between groups, although caregivers of the caffeine group did note that they *thought* their children needed more sleep. Further, polysomnography recorded sleep duration during a single night, whereas actigraphy recorded sleep duration for two weeks. Thus, the estimate of sleep duration obtained with actigraphy is bound to be more accurate and representative of the children's actual sleep duration. Thus, it is likely that these finding were due to chance. There were no other differences in polysomnographic parameters between groups, and no difference in the co-primary outcome of AHI. The observed standard

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deviation of AHI was somewhat larger than the value used to determine sample size. Post-hoc

power calculations indicate that the study had 80% power to detect a true mean AHI difference

of 2.8 events/hour.

Of interest, however, was the high prevalence of both OSAS and periodic limb movements in

both groups of children. The prevalence of OSAS in the school-aged population is estimated at

1-4%.[27] In contrast, polysomnography demonstrated OSAS in 9.6% (95%CI 5.9% to 14.7%) of

children in the current study. This may underestimate the incidence of OSAS, as many children

received prior treatment with adenotonsillectomy. Adenotonsillectomy is the primary treatment

for childhood OSAS.[25] 26% of children in this study had either an elevated AHI or a prior

history of adenotonsillectomy. Although the indications for adenotonsillectomy in these subjects

were not available, in general the commonest indication for adenotonsillectomy is obstructed

breathing[31], with 59-69% of tonsillectomies in the United States being performed for

obstruction.[32] Thus, these data suggest that as many as a quarter of very low birth weight infants

may develop OSAS. Several studies have indicated that ex-preterm infants have a higher

prevalence of OSAS during the school-aged years.[14, 33, 34] However, these studies showed an

interaction between the known OSAS risk factors of African American race[35, 36], obesity[35], low

socioeconomic status[37] and prematurity. The current study differs in that the majority of subjects

was Caucasian, non-obese and of higher socioeconomic status (based on maternal education) and

yet still showed a markedly increased prevalence of OSAS, indicating that prematurity was the

most important risk factor. Possible factors that may be hypothesized to contribute to OSAS in

ex-preterm infants include palatal deformation secondary to intubation[38], hypotonia and

abnormalities in ventilatory control. Hibbs *et al* reported that neonatal methylxanthine use was

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associated with a two-fold increase in childhood OSAS,[39] which was not borne out in the current randomized, controlled trial.

The current study is the first, to our knowledge, demonstrating a high prevalence of PLMS in ex-preterm infants. PLMS are repetitive, stereotypical movements of the legs during sleep, that may be associated with wake symptoms of restless legs. The significance of PLMS is controversial, but they have been reported to be associated with sleep fragmentation, excessive daytime sleepiness and autonomic disturbances.[40] Studies of healthy children have shown a PLMS prevalence of 5-8%.[28, 41] In comparison, 14.2% (95%CI 9.7% to 19.9%) of children in the current study had PLMS in the pathologic range. The reasons for this increased prevalence are unclear. High caffeine intake in adults has been reported to be a risk factor for restless legs syndrome[42] and PLMS.[43] Nevertheless, although children in the caffeine group had a tendency towards a higher PLMS index, this was not statistically significant. Both groups of children had minimal caffeine intake at the time of the study. PLMS in children are frequently associated with iron deficiency[44], for which ex-preterm children may potentially be at increased risk.

Strengths of this study include the randomized, blinded design, and the large cohort. A limitation is that, as with any study, only a portion of patients approached agreed to the study, and hence it is possible that those with concerns about their child's sleep may have been more likely to consent. Nevertheless, no differences were noted between the caffeine and placebo groups.

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Neonatal caffeine use for apnea of prematurity has been shown to decrease morbidity in

premature infants, and is thus used widely in neonatal intensive care units. This study has shown

that therapeutic neonatal caffeine administration has no long-term effects on sleep quality or

quantity, or on pathologic conditions during sleep such as OSAS. This finding should allay

concerns about the long-term effects of the drug on sleep. In addition, this study demonstrated a

higher than expected prevalence of OSAS and PLMS in ex-preterm infants.

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FIGURE LEGEND

Details of study enrollment are shown. Planned enrollment was 200 subjects. Surviving

children from the four participating Caffeine for Apnea of Prematurity (CAP) trial centers were

eligible if they lived within an approximate 2-hour radius of the participating sleep center.

Eligible families were consecutively approached, but recruitment was terminated when 201

subjects were recruited.

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Table 1: Study Group

Characteristic	Caffeine (n=98)	Placebo (n=103)	P-Value
Age (yr)	9.1 (1.9)	9.3 (2.1)	0.58
Males	58 (59.1%)	57 (55.3%)	0.68
Maternal race			
White	80 (81.6%)	88 (85.4%)	0.47
Asian	11 (11.2%)	9 (8.7%)	
Black	5 (5.1%)	6 (5.8%)	
Other	2 (2.0%)	0 (0.0%)	
Site			
Canada	51 (52.0%)	62 (60.2%)	0.24
Australia	47 (48.0%)	41 (39.8%)	
Gestational age (weeks)	27.2 (1.6)	27.3 (1.7)	0.94
Birth weight (g)	987 (164)	953 (174)	0.16
BMI z-score*	-0.12 (1.33)	-0.17 (1.11)	0.75
Weight class*			
Obese (BMI >95th percentile)	11 (11.2%)	4 (3.4%)	0.12
BMI 5-95th percentile	76 (77.6%)	86 (84.3%)	

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Failure to thrive (BMI <5th percentile)	11 (11.2%)	12 (11.8)%	
Time between study and anthropometric measurements (yr)	0.79 (1.87)	1.18 (1.76)	0.14
Maternal education			
Did not finish high school or equivalent	18 (18.4%)	12 (11.7%)	0.29
Completed high school or equivalent	31 (31.6%)	41 (39.8%)	
Attended college/university	49 (50.0%)	50 (48.5%)	

Data shown as mean (SD) or N (%).

* N = 200

Table 2: Actigraphy Results

Outcome	Weighted Mean (SD)		Unadjusted Difference Mean (95% CI)* P Value	Adjusted for Covariates† Mean (95% CI) P Value
	Caffeine (n=94)	Placebo (n=97)		
Primary outcome				
Total sleep time (duration of sleep in sleep period) (min)	488.3 (3.7)	493.3 (3.4)	-5.1 (-15.0,4.9) P=0.32	-6.7 (-15.3,2.0) P=0.13
Secondary outcomes				
Bedtime (clock time)§	21:30 (5.4)	21:32 (4.8)	-0.02 (-0.26,0.22) P=0.88	-0.05 (-0.27,0.17) P=0.65
Time in bed (from reported bedtime to wake time) (min)	614.3 (4.0)	614.3 (3.8)	-0.1 (-10.9,10.8) P=0.99	-2.1 (-11.3,7.2) P=0.66
Sleep period (from sleep onset to sleep offset) (min)	564.3 (4.1)	566.0 (3.9)	-1.7 (-12.8,9.4) P=0.76	-4.4 (-12.8,4.0) P=0.30
Sleep efficiency (total sleep time/time in bed) (%)	79.7 (0.5)	80.5 (0.5)	-0.8 (-2.2,0.6) P=0.26	-0.8 (-2.2,0.6) P=0.26
Sleep onset latency (min)	27.4 (1.6)	26.6 (1.6)	0.7 (-4.0,5.5) P=0.76	1.1 (-3.6,5.7) P=0.65
Wake after sleep onset	76.0	72.7	3.3 (-3.1,9.8)	2.3 (-3.9,8.4)

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(min)	(2.4)	(2.3)	P=0.31	P=0.48
Average activity during sleep period	16.8 (0.7)	16.6 (1.1)	0.2 (-2.3,2.7) P=0.88	-0.1 (-2.7,2.5) P=0.93

* Caffeine – Placebo

† Covariates: Center, age at assessment, gender, race, maternal education, proportion of weekend nights, season.

§ SD provided in minutes. Data obtained from sleep diary.

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Table 3: Polysomnography Results

Variable	Unadjusted Results			Adjusted for covariates‡
	Caffeine Mean (SD), Median (IQR) or N(%) N=97	Placebo Mean (SD), Median (IQR) or N(%) N=100	Mean difference* rate ratio§ or Odds Ratio† (95% CI) P	Mean difference rate ratio§ or Odds Ratio† (95% CI) P
PRIMARY OUTCOME				
Obstructive apnea hypopnea index (N/hr)	0.3 (0.1,0.6)	0.3 (0.1,0.8)	0.95§ (0.58,1.53) P=0.82	0.89§ (0.55,1.43) P=0.63
SECONDARY OUTCOMES				
Sleep Architecture				
Lights off (evening; clock time)¶	21:23 (51)	21:27 (62)	-4* (-21,12) P=0.60	-4* (-19,10) P=0.59
Lights on (morning; clock time)¶	7:24 (44)	7:09 (51)	15* (1,28) P=0.034	12* (-1,26) P=0.077
Total recording time (min)**	600.7 (52.7)	579.6 (66.9)	21.1* (3.9,38.3) P=0.017	19.2* (3.3,35.2) P=0.019

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Total sleep time (TST)(min)**	551.0 (52.7)	531.9 (63.5)	19.2* (2.5,35.8) P=0.024	18.3* (3.0,33.5) P=0.020
Sleep efficiency (%)**	91.8 (4.9)	91.8 (4.4)	-0.1* (-1.4,1.3) P=0.94	0.1* (-1.3,1.4) P=0.91
Sleep latency (min)**	16.2 (18.6)	17.7 (18.4)	-1.5* (-6.8,3.8) P=0.57	-2.1* (-7.4,3.1) P=0.43
Wake after sleep onset (min)**	33.4 (23.0)	29.9 (20.4)	3.5* (-2.7,9.7) P=0.27	3.2* (-3.2,9.7) P=0.33
Stage N1 (% TST)**	5.2 (2.1)	4.7 (1.8)	0.5* (-0.1,1.0) P=0.10	0.4* (-0.2,1.0) P=0.18
Stage N2 (% TST)**	38.2 (7.1)	38.9 (6.8)	-0.7* (-2.7,1.3) P=0.51	-0.4* (-2.5,1.6) P=0.69
Stage N3 (% TST)**	33.0 (6.4)	33.9 (7.1)	-0.9* (-2.8,1.0) P=0.36	-1.0* (-3.0,1.0) P=0.33
Rapid eye movement sleep (% TST)**	23.6 (4.9)	22.5 (4.5)	1.1* (-0.2,2.5) P=0.11	1.0* (-0.1,2.4) P=0.14
Arousal index (N/hr)	9.1 (7.7,10.4)	9.4 (7.6,10.6)	1.02§ (0.95,1.10) P=0.57	1.03§ (0.95,1.11) P=0.47
Ventilation				
Subjects with obstructive apnea hypopnea index ≥ 2/hr	8 (8.2%)	11 (11.0%)	0.73† (0.28,1.89) P=0.51	0.51† (0.18,1.48) P=0.22
Subjects with obstructive	23	29	0.76† (0.40,1.44)	0.73† (0.38,1.42)

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apnea hypopnea index ≥ 2/hr and/or history of adenoidectomy/tonsillectomy	(23.7%)	(29.0%)	P=0.40	P=0.35
Central apnea index (N/hr)	0.3 (0.1,0.6)	0.3 (0.1,0.7)	1.20§ (0.91,1.59) P=0.19	1.16§ (0.88,1.55) P=0.29
Periodic breathing (% TST)	0.2 (0.5)	0.1 (0.3)	0.06* (-0.05,0.17) P=0.30	0.06* (-0.05,0.18) P=0.29
SpO$_2$ nadir (%)	91.8 (2.4)	91.3 (3.5)	0.5* (-0.3,1.4) P=0.21	0.6* (-0.3,1.4) P= 0.19
Time with SpO$_2$ < 90% (% TST)	0.0 (0.1)	0.3 (1.7)	-0.23* (-0.57,0.11) P=0.18	-0.16* (-0.51,0.19) P=0.37
Limb movements				
Periodic limb movement index (N/hr)	0.7 (0.0,7.4)	0.6 (0.0,1.8)	1.56§ (1.01,2.39) P=0.043	1.47§ (0.98,2.21) P=0.066
Subjects with periodic limb movement index >5/hr	17 (17.5%)	11 (11.0%)	1.72† (0.76,3.89) P=0.19	1.62† (0.69,3.85) P=0.27

‡ Covariates: Center, age at assessment, gender, race, maternal education

* Quantitative data shown as caffeine-placebo mean difference, estimated by a multiple linear regression model.

§ Indices are shown as rate ratios caffeine/placebo, estimated by a Poisson regression model.

† Dichotomized data shown as odds ratios caffeine/placebo, estimated by a logistic regression model.

¶ SD provided in minutes

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** N=95 for caffeine and 96 for placebo as data from several subjects with short total recording

times due to power or child-related issues were excluded from sleep architecture analyses.

Table 4: Questionnaire Results

Variable	Unadjusted Results			Adjusted for covariates‡
	Caffeine Mean (SD) or N(%)	Placebo Mean (SD) or N(%)	Mean difference* rate ratio§ or Odds Ratio† (95% CI) P	Mean difference rate ratio§ or Odds Ratio† (95% CI) P
Pediatric Sleep Questionnaire Sleep Related Breathing Disorder Scale: N	94	99		
Result	0.23 (0.19)	0.27 (0.20)	-0.03* (-0.09, 0.02) P=0.23	-0.04* (-0.10, 0.02) P=0.15
Restless Legs Syndrome Questionnaire N†	87	82		
Result	3.7 (4.0)	4.5 (5.0)	-0.8* (-2.2, 0.5) P=0.23	-1.0* (-2.3, 0.4) P=0.17

§ Indices are shown as rate ratios caffeine/placebo, estimated by a Poisson regression model.

* Quantitative data shown as caffeine-placebo mean difference, estimated by a multiple linear regression model.

† The Restless Legs Syndrome questionnaire was added later in the study, resulting in a lower N.

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Figure 1: Study enrollment


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        ┌─────────────────────────────────────┐
        │ 793 Infants randomized to caffeine or │
        │     placebo at the 4 study sites      │
        └─────────────────────────────────────┘
                          │
                          │──────────────▶ ┌──────────────────────────┐
                          │                │ 48 Died before age 5 years │
                          │                └──────────────────────────┘
                          ▼
        ┌─────────────────────────────────────┐
        │ 745  Potentially available for this study │
        └─────────────────────────────────────┘
```

| 373 Had been assigned to the caffeine group | 372 Had been assigned to the placebo group |

| 176 Approached | 172 Approached |

| 74 No parental consent
4 Consent but not enrolled | 66 No parental consent
3 Consent but not enrolled |

| 98 Children underwent polysomnography and actigraphy:

97 Had successful polysomnography
94 Had successful actigraphy | 103 Children underwent polysomnography and actigraphy:

100 Had successful polysomnography
97 Had successful actigraphy |

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ONLINE DATA SUPPLEMENT

LONG-TERM EFFECTS OF CAFFEINE THERAPY FOR APNEA OF PREMATURITY ON SLEEP AT SCHOOL-AGE

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METHODS

This was a prospective follow-up study of the CAP trial. Due to the intensive monitoring

required for this study, a subsample of the original CAP sites was selected based on recruitment

and retention rates and geographic clustering close to a pediatric sleep medicine facility. Thus,

two sites in Canada and two sites in Australia were chosen. The Neonatal Trials Group at

McMaster University was the Data Coordinating Center. The research ethics board at each

institution approved the study, and written informed consent was obtained from

parents/guardians. The study was registered at ClinicalTrials.gov (NCT01020357). Children

underwent two weeks of actigraphy and one night of comprehensive ambulatory home

polysomnography, with actigraphy spanning the polysomnography night. Actigraphic and

polysomnographic data were scored and interpreted centrally by one technologist (JT) and one of

two pediatric sleep medicine specialists (LJM for actigraphy and CLM for polysomnography),

respectively. The children's caregivers completed sleep diaries and sleep questionnaires. All

investigators and subjects/families remained blinded as to whether the subject had received

caffeine or placebo as a neonate. The co-primary outcomes for the study were the subject's

average total sleep time based on multiple nights of actigraphy, and the obstructive apnea

hypopnea index (AHI) from polysomnography.

Study population

Children from the CAP trial were studied at age 5-12 years. Subjects were born prematurely,

weighed 500-1,250 g at birth, did not have major congenital anomalies or syndromes, were

considered by their clinicians to be candidates for methylxanthine therapy during the first 10

2

days of life, and were randomized to either caffeine or placebo for a median duration of 6 weeks during the neonatal period.[E1]

Study procedures

Actigraphy was performed for two weeks (Actiwatch 2, Philips Respironics, Bend, OR). Actigraphy is a validated technique for measuring sleep *vs* wakefulness based on movement, using a wristwatch-like device, and was used primarily to assess sleep quality and quantity during normal daily life. The actigraph was worn on the non-dominant wrist. Caregivers completed a sleep diary which was used to identify bedtime and wake time, as well as to identify when the device was removed or when there was artifact. Subjects with <5 nights of recordings were excluded. The Actiwatch 2 has been validated compared to in-lab polysomnography in this age group.[E2, 3] However, further validation was performed by an epoch-by-epoch comparison of actigraphy and simultaneous ambulatory polysomnography in a random sample of 20 subjects, using methods previously described.[E2]

Subjects underwent one night of full, unattended, ambulatory polysomnography. The primary purpose of polysomnography was to detect sleep-related medical conditions, such as OSAS, rather than sleep quality, as sleep quality may be affected by the instrumentation. Details of the polysomnography technique and quality have been published elsewhere.[E4] In brief, technologists went to the home to apply and remove monitoring leads at the child's usual bed/wake times. Electroencephalograms, electrooculograms, submental and tibial electromyograms, chest and abdominal wall movement (inductance plethysmography), ECG, airflow (nasal pressure and oronasal thermistor) and arterial oxygen saturation with pulse waveform were monitored (Siesta

802, Compumedics, Charlotte, NC). Studies were scored using standard pediatric rules.[E5]

Periodic limb movements during sleep (PLMS) were not scored if associated with respiratory

events.[E5]

The caregiver completed an abbreviated form of the National Sleep Foundation 2004 Sleep In

America questionnaire[E6], a comprehensive review of children's sleep habits, and the Pediatric

Sleep Questionnaire Sleep Related Breathing Disorder Scale, an assessment of symptoms of

OSAS (scores range from 0-1, with a score >0.33 suggestive of OSAS).[E7] After several early

subjects showed evidence of PLMS on polysomnography, a restless legs syndrome questionnaire

was added (score ranging from 0-26, with a higher score indicating more symptoms of restless

legs syndrome).[E8]

Race was categorized based on maternal race in the original CAP database. Height and weight

were not obtained at the time of study, but were obtained from the closest CAP follow-up visit.

Statistical Methods

AHI was compared between groups using a Poisson regression model incorporating adjustment

for the pre-specified covariates of center, age at assessment, gender, race, and maternal

education.[E9] The model assumed Poisson variance for the count of total apnea and hypopnea

episodes, included a log link function and logged total observation time as an offset variable, and

allowed for potential over-dispersion (additional between-subject variation). The treatment

effect and associated confidence interval were expressed as rate ratios. The protocol called for

14 nights of actigraphy but the actual number varied between subjects. Average total sleep time

4

was compared between treatments with a weighted (inverse variance) regression model[E10] with

adjustment for the same covariates as above, but with the addition of the number of weekend

nights and season (winter/summer). Secondary outcomes were analyzed using similar methods

depending on whether they were rate-based or quantitative. Analyses were also performed on

dichotomous secondary outcomes using equivalent logistic regression models. Baseline

comparisons of descriptive information were compared between treatment groups using

Student's t-tests (or equivalent non-parametric tests) for quantitative data and chi-squared tests

for categorical data. All statistical calculations were performed with SAS version 9.3; p-values

are two-sided and considered significant if <0.05. The target sample size of 200 was anticipated

to yield 90% power for a 2.5% decrease in actigraphic mean sleep time (0.21 hours, which was

considered clinically meaningful) and 80% power to detect a mean difference in AHI of 1.5

events/hr.

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