Neurobehavioral Outcomes 11 Years After Neonatal Caffeine Therapy for Apnea of Prematurity

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abstract

BACKGROUND AND OBJECTIVES: Caffeine is effective in the treatment of apnea of prematurity. Although caffeine therapy has a benefit on gross motor skills in school-aged children, effects on neurobehavioral outcomes are not fully understood. We aimed to investigate effects of neonatal caffeine therapy in very low birth weight (500–1250 g) infants on neurobehavioral outcomes in 11-year-old participants of the Caffeine for Apnea of Prematurity trial.

METHODS: Thirteen academic hospitals in Canada, Australia, Great Britain, and Sweden participated in this part of the 11-year follow-up of the double-blind, randomized, placebo-controlled trial. Measures of general intelligence, attention, executive function, visuomotor integration and perception, and behavior were obtained in up to 870 children. The effects of caffeine therapy were assessed by using regression models.

RESULTS: Neurobehavioral outcomes were generally similar for both the caffeine and placebo group. The caffeine group performed better than the placebo group in fine motor coordination (mean difference [MD] = 2.9; 95% confidence interval [CI]: 0.7 to 5.1; $P = .01$), visuomotor integration (MD = 1.8; 95% CI: 0.0 to 3.7; $P < .05$), visual perception (MD = 2.0; 95% CI: 0.3 to 3.8; $P = .02$), and visuospatial organization (MD = 1.2; 95% CI: 0.4 to 2.0; $P = .003$).

CONCLUSIONS: Neonatal caffeine therapy for apnea of prematurity improved visuomotor, visuoperceptual, and visuospatial abilities at age 11 years. General intelligence, attention, and behavior were not adversely affected by caffeine, which highlights the long-term safety of caffeine therapy for apnea of prematurity in very low birth weight neonates.

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WHAT'S KNOWN ON THIS SUBJECT: Caffeine is effective in the treatment of apnea of prematurity. It increases the rate of survival without neurodevelopmental disability, reduces the rates of cerebral palsy and cognitive impairment in toddlers, and has benefits on gross motor skills in school-aged children.

WHAT THIS STUDY ADDS: Neonatal caffeine therapy improved visuomotor, visuoperceptual, and visuospatial abilities at age 11 years. Adverse outcomes were not shown for neurobehavioral outcomes such as general intelligence, attention, executive function, and behavior.

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Apnea of prematurity occurs in over 50% of preterm neonates[1] and is most commonly treated with respiratory stimulants such as caffeine. However, short- and long-term effects of caffeine on the central nervous system are not clearly understood, with both neuroprotective[2] and neurotoxic[3] effects being reported in experimental evidence. In addition, caffeine may be indirectly associated with better developmental outcomes by reducing apnea and the duration of mechanical ventilation.[4,5]

Researchers of the Caffeine for Apnea of Prematurity (CAP) trial investigated the safety and effectiveness of caffeine therapy.[6] This international, randomized, placebo-controlled trial has revealed that caffeine therapy reduced the rate of bronchopulmonary dysplasia and severe retinopathy of prematurity (ROP) before discharge.[7,8] At 18 to 21 months' corrected age, caffeine therapy increased the rate of survival without neurodevelopmental disability and reduced the rates of cerebral palsy and cognitive impairment.[8] At the age of 5 years, evidence for the reduction in the rate of cerebral palsy with caffeine treatment was weaker, but improved motor function[9] and a reduced risk of developmental coordination disorder (DCD) were demonstrated.[10] Neonatal caffeine therapy did not affect functional impairment when assessed as a composite of poor academic performance, motor impairment, and behavior problems in 11-year-old children, but it reduced the risk of motor impairment.[4]

Although rates of cognitive impairment did not differ between the caffeine and placebo groups at 5 years of age,[9] long-term effects of caffeine therapy on specific neurobehavioral outcomes such as general intelligence, attention, executive function, visuomotor integration and perception, and behavior are still to be determined. Our aim in this study was to investigate the effects of neonatal caffeine therapy in very low birth weight infants (500–1250 g) on these neurobehavioral outcomes in 11-year-old participants of the CAP trial.

METHODS

Infants with a birth weight of 500 to 1250 g were eligible for the CAP trial if they were considered to be candidates for methylxanthine therapy by their clinicians during the first 10 days of life; 2006 infants in 35 academic hospitals and 9 countries were enrolled in this double-blind trial between October 1999 and October 2004. Infants were randomly assigned to receive caffeine citrate or normal saline placebo until treatment of apnea of prematurity was no longer needed. Exclusion criteria, randomization procedures, and use of the study drug have been described previously.[7] In short, exclusion criteria were (1) previous treatment with methylxanthines, (2) congenital abnormalities, and (3) likely unavailability for follow-up. Randomization was stratified according to the study center and was balanced in random blocks of 2 or 4 patients. A loading dose of 20 mg of caffeine citrate per kilogram of body weight was followed by a daily maintenance dose of 5 mg/kg. If apnea persisted, the dose could be increased to a maximum of 10 mg/kg per day. Infants received their first dose of the study drug at a median age of 3 days and were weaned off the study drug before reaching a median postmenstrual age of 35 weeks. Infants in the control group were treated with an equivalent volume of normal saline.

The primary outcome of the initial study was death before 18 months' corrected age or survival with at least 1 of the following conditions: cerebral palsy, cognitive delay, severe hearing loss, or bilateral blindness. Caffeine reduced the rate of the combined outcome (adjusted odds ratio [OR]: 0.77; 95% confidence interval [CI]: 0.64 to 0.93).[8] At 5-year follow-up, the evidence used to support a caffeine effect on the rate of survival without disability was weak, but secondary and post hoc analyses revealed lasting benefits of caffeine on motor performance.[9,10]

Fourteen centers participated in the 11-year follow-up and provided data for the primary outcome (n = 457 participants in the caffeine group, n = 463 participants in the placebo group), which was a composite measure of functional impairment in at least 1 of the following 3 domains: academic performance, behavior, and motor skills. A 15th center in Sweden provided partial data for components of the primary outcome.[4] The present analysis includes secondary outcomes of general intelligence, attention, executive function, visuomotor integration and perception, and behavior. Two centers administered only the 3 primary outcome measures, whereas the remaining 13 centers administered combinations of secondary outcome measures, depending on local resources. Consequently, the denominators vary among outcomes.

The 11-year follow-up was conducted between May 2011 and May 2016, and the target window for assessments was the year between the child's 11th and 12th birthday. Efforts to locate and examine the children continued beyond this age when necessary.

Each phase of the study was approved by the relevant institutional ethics boards. Written informed consent was obtained from a parent or guardian of each child, and at the 11-year follow-up, assent was obtained from the child when appropriate. The children, their families, and all clinicians and researchers involved in the

care of the participants and in the assessments of their outcomes remained unaware of the neonatal random assignments to caffeine or placebo treatment. Assessors were blinded to treatment allocation at all stages.

Eleven-Year Neurobehavioral Outcomes

General intelligence was estimated with the full-scale IQ from the 4-subtest version of the Wechsler Abbreviated Scale of Intelligence–II (WASI-II).[11] The scale also generates a verbal comprehension index (a measure of verbal acquired knowledge and verbal reasoning abilities) and a perceptual reasoning index (a measure of visual perception organization and reasoning skills). The indices are age standardized (mean = 100; SD = 15), with higher scores reflecting higher intelligence. Cognitive impairment was defined as a full-scale IQ < 85 (<1 SD relative to the normative mean). Children who could not be assessed because of severe intellectual impairment or severe autism were coded as having a severe cognitive impairment.

Visuomotor integration, visual perception, and fine motor coordination were assessed with the Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI), sixth edition[12] (mean = 100; SD = 15). The digit span subtest of the Wechsler Intelligence Scale for Children–IV (WISC-IV)[13] was administered to assess working memory (mean = 7; SD = 3). Attention was assessed by using subtests from the Test of Everyday Attention for Children (TEA-Ch; mean = 7; SD = 3),[14] including Sky Search (selective attention), Score! (sustained attention), Creature Counting (shifting attention), and Sky Search Dual Task (divided attention). The Rey complex figure test (RCF) was administered to assess planning and organizational aspects of executive function,[15] with performance assessed according to accuracy and organizational strategy.[16] The RCF delayed recall test was administered to assess the child's capacity to remember a drawn figure without cues after a 20- to 30-minute interval. Higher scores reflected better functional outcome in all of the abovementioned measures. Age standardized scores were used with the exception of the RCF, for which reliable norms are not available. Impairment in visuomotor integration, visual perception, fine motor coordination, working memory, attention, and executive function was defined as a performance <1 SD relative to the normative mean of the respective test.

The Behavior Rating Inventory of Executive Function (BRIEF), a parent-completed rating scale, was used to assess the everyday behavioral manifestations of children's executive control functions.[17] The Global Executive Composite (GEC), Behavioral Regulation Index (BRI), and Metacognition Index scores were reported. Parents also completed the Conners 3 Attention-Deficit/Hyperactivity Disorder (ADHD) Index,[18] which consists of 10 items that best differentiate children with ADHD from the general population. Age-standardized T-scores (mean = 50; SD = 10) are generated for both of these parent-reported behavior questionnaires, with elevated scores indicating greater problematic behaviors. Behavioral impairment was defined as a score >1 SD compared with the mean of the normative sample.

Statistical Analyses

Because randomization was stratified according to study center, the analyses were adjusted with the use of a multiple linear regression model that included terms for treatment and center (results from smaller centers were combined). The regression coefficient associated with treatment in the fitted model yielded a point estimate and a 95% CI for the treatment effect expressed as the mean difference (MD) between the study groups. Impairment rates were analyzed with equivalent logistic regression models, with the adjusted treatment effect expressed as an OR. The quotient of the estimated coefficient of the treatment effect and its SE were used as a *z*-test statistic for the null hypothesis of no treatment effect. After a reviewer's comment was received, a post hoc analysis was conducted to examine the contribution of severe ROP to visuomotor performance. A linear regression model was used with an interaction term to test for the consistency of the caffeine effect between children with and without severe ROP. All *P* values were 2-sided and considered significant if $P < .05$. No adjustments were made for multiple comparisons. SAS version 9.4 was used (SAS Institute, Inc, Cary, NC).

RESULTS

Study Participants

In Fig 1, we show the number of infants who were enrolled in the original trial, the number of children who were eligible for the current study in 13 sites, and the number of children who completed each of the outcome measures. A total of 870 children contributed data for at least 1 measurement instrument. Characteristics of these 870 children and their families are given in Table 1. Groups were comparable in age and school attendance at follow-up, as well as the characteristics of their primary caregivers and families.

Neurobehavioral Outcomes

Neurobehavioral outcomes were broadly similar between the caffeine and placebo groups, although mean scores were higher on most scales in the caffeine group. Evidence for group differences was strongest

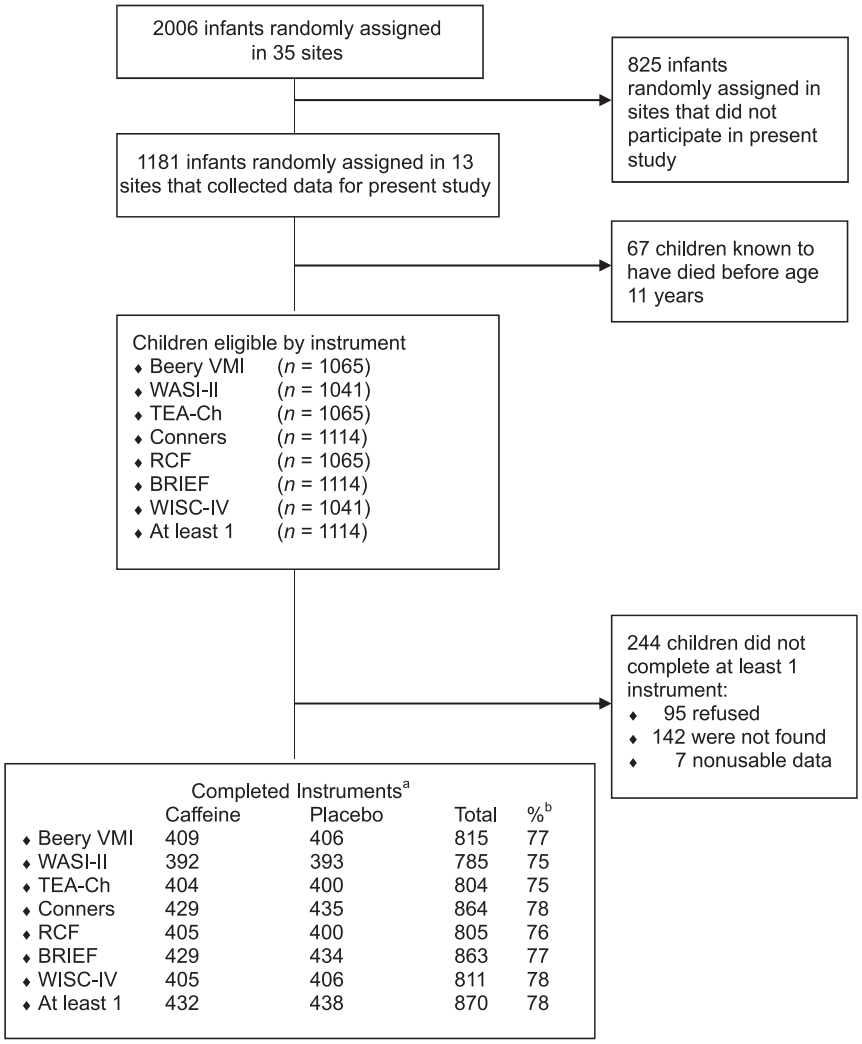

FIGURE 1
Instrument completion rates. [a]Primary score available. [b]Completion rate by instrument.

for visuomotor integration (MD = 1.8; 95% CI: 0.0 to 3.7; $P < .05$), visual perception (MD = 2.0; 95% CI: 0.3 to 3.8; $P = .02$), fine motor coordination (MD = 2.9; 95% CI: 0.7 to 5.1; $P = .01$), and RCF copy accuracy (MD = 1.2; 95% CI: 0.4 to 2.0; $P = .003$). For the parent-rated behavior questionnaires, there was little evidence for group differences (Table 2).

Differences of impairment rates between groups revealed a similar pattern, with lower odds of impairment in the caffeine group for visuomotor integration (OR = 0.74; 95% CI: 0.55 to 0.99; $P = .04$), visual perception (OR = 0.63; 95% CI: 0.43 to 0.92; $P = .02$), and fine motor coordination (OR = 0.69; 95% CI: 0.52 to 0.92; $P = .01$) compared with the placebo group (Table 3).

In the post hoc analysis conducted to examine the contribution of the indirect effect of caffeine on the visuomotor domain through the reduction of severe ROP, children with severe ROP showed significantly worse performance in all Beery subscales (Beery VMI: no severe ROP mean = 90.1, severe ROP mean = 84.3). However, when severe ROP was included in the regression model (Table 2), the observed reduction in severe ROP associated with caffeine explained only a small percentage (between 4.1% and 6.5%, depending on the subscale) of the overall caffeine effect on the visuomotor abilities at 11 years of age. When an interaction term was included in an additional model to test for the consistency of the caffeine effect between children with and without severe ROP, no significant subgroup interaction was shown.

DISCUSSION

Neonatal caffeine citrate therapy is one of the most common therapies in neonatal medicine,[20] and it is essential that the long-term benefits and risks of this therapy are understood. In this study, in which we examined the effects of neonatal caffeine therapy on neurobehavioral outcomes, we demonstrated that caffeine therapy had specific long-term benefits for fine motor coordination, visuomotor integration, visual perception, and visuospatial organization. There was little evidence for differences between the caffeine and placebo groups on tests of general intelligence, attention, executive function, and behavior. Thus, we found specific benefits of neonatal caffeine therapy in the visuomotor domain and no evidence of harmful effects on neurobehavioral outcomes up to 11 years of age.

The caffeine benefit we observed in fine motor coordination and visuomotor integration is consistent with our previously reported associations of neonatal caffeine therapy with a reduced risk for motor impairment at 18 months,[8] 5 years,[9] and 11[4] years, improved fine motor coordination at 5 years,[9] and lower rates of DCD at 5 years.[10] The positive effect of caffeine therapy on motor development for very preterm and very low birth weight infants is important clinically because this population is ~10 times more likely to develop cerebral palsy[21] and 3 to 4 times more likely to develop DCD than term

TABLE 1 Characteristics of the Children and Their Families

Characteristics	Caffeine Group (n = 432)	Placebo Group (n = 438)	P
Children at birth			
Mean birth wt (SD), g	967 (181)	956 (182)	.39
Mean gestational age (SD), wk	27.3 (1.7)	27.3 (1.8)	.48
Female sex, No. (%)	222 (51.4)	199 (45.4)	.08
Birth wt <10th percentile for gestational age, No. (%)[a]	59 (13.7)	67 (15.3)	.49
Exposure to antenatal corticosteroids, No. (%)	390 (90.3)	394 (90.0)	.95
Singleton birth, No. (%)	297 (68.8)	315 (71.9)	.31
Outcomes at 18 mo			
Disability, No./total No. (%)[b]	122/418 (29.2)	153/424 (36.1)	.03
Cerebral palsy, No./total No. (%)	14/427 (3.3)	27/433 (6.2)	.04
Moderate cognitive delay, No./total No. (%)[c]	113/416 (27.2)	133/423 (31.4)	.17
Severe cognitive delay, No./total No. (%)[d]	38/416 (9.1)	52/423 (12.3)	.14
Severe ROP, No./total No. (%)[e]	18/432 (4.2)	26/438 (5.9)	.23
Outcomes at 5 y			
Disability, No./total No. (%)[f]	56/415 (13.5)	72/411 (17.5)	.11
Motor impairment, No./total No. (%)[g]	5/424 (1.2)	13/425 (3.1)	.06
Cognitive impairment, No./total No. (%)[h]	18/417 (4.3)	12/421 (2.9)	.25
Full-scale IQ, mean (SD)	100 (16)	99 (15)	.10
Behavior problem, No./total No. (%)[i]	23/415 (5.5)	29/413 (7.0)	.38
11-y follow-up			
Median age (IQR), y	11.4 (11.1, 11.8)	11.4 (11.1, 11.8)	.88
Schooling			
Mainstream school (public or private), No. (%)	418 (96.8)	424 (96.8)	.63
Special education facility, No. (%)	10 (2.3)	11 (2.5)	
Homeschool, No. (%)	4 (0.9)	2 (0.5)	
Hospital or chronic care facility, No. (%)	0 (0.0)	1 (0.2)	
Primary caregivers and family arrangements at follow-up			
Relationship to child			
Biological mother, No. (%)	369 (85.4)	379 (86.5)	.23
Biological father, No. (%)	47 (10.9)	51 (11.6)	
Other or unknown, No. (%)	16 (3.7)	8 (1.8)	
Race			
White, No. (%)	350 (81.0)	355 (81.1)	.70
Black, No. (%)	14 (3.2)	18 (4.1)	
Asian, No. (%)	45 (10.4)	44 (10.0)	
Indigenous, No. (%)	11 (2.5)	14 (3.2)	
Other or unknown, No. (%)	12 (2.8)	7 (1.6)	
Level of caregiver education			
Did not finish high school or Eq, No. (%)	83 (19.2)	89 (20.3)	.53
Completed high school or Eq, No. (%)	86 (19.9)	91 (20.8)	
Some college or university, No. (%)	75 (17.4)	60 (13.7)	
College or university graduate, No. (%)	188 (43.5)	198 (45.2)	
Family arrangement			
Single parent, No. (%)	56 (13.0)	52 (11.9)	.44
Single parent with partner closely involved, No. (%)	39 (9.0)	28 (6.4)	
2-parent family, No. (%)	319 (73.8)	341 (77.9)	
Other or unknown, No. (%)	18 (4.2)	17 (3.9)	
Other children <18 y old living in the household, median (IQR)	1 (1, 2)	1 (1, 2)	.61
Family's main source of financial support			
Earnings from employment or self-employment, No. (%)	374 (86.6)	390 (89.0)	.12
Government benefits (excluding pensions), No. (%)	41 (9.5)	37 (8.4)	
Other, No. (%)	10 (2.3)	2 (0.5)	

These data are for the 870 children who completed data for at least one measurement instrument. Percentages may not sum to 100 because of rounding. Eq, equivalent.

[a] The 10th percentile for gestational age in a normal population was reported by Kramer et al.[19]

[b] Disability at 18 mo was defined as at least 1 of cerebral palsy, moderate cognitive delay, deafness, or blindness.

[c] Moderate cognitive delay was defined as a Mental Development Index score of <85 on the Bayley Scales of Infant Development, second edition.

[d] Severe cognitive delay was defined as a Mental Development Index score of <70 on the Bayley Scales of Infant Development, second edition.

[e] Severe ROP was defined as unilateral or bilateral stage 4 or 5 disease or as receipt of retinal therapy in at least 1 eye.

[f] Disability at 5 y of age was defined as at least 1 of motor impairment, cognitive impairment, behavior problems, poor general health, deafness, or blindness.

[g] Motor impairment was defined as a Gross Motor Function Classification System level of >2.

[h] Cognitive impairment was defined as a full-scale IQ of <70 on the Wechsler Preschool and Primary Scale of Intelligence–III.

[i] A behavior problem was defined as a Total Problem T score of >69 on the Child Behavior Checklist.

TABLE 2 Neurobehavioral Outcomes

Outcome	Max *n*[a]	Caffeine Group		Placebo Group		Unadjusted MD (95% CI)	MD Adjusted for Center (95% CI)	*P*	MD Adjusted for Center and Patient Characteristics (95% CI)[b]
		n	Mean ± SD	*n*	Mean ± SD				
Fine motor skills	1065								
Beery VMI		409	90.7 ± 13.1	406	88.9 ± 13.8	1.8 (−0.1 to 3.6)	1.8 (0.0 to 3.7)	< .05	1.5 (−0.3 to 3.3)
Visual perception		407	97.7 ± 12.9	397	95.6 ± 13.4	2.1 (0.2 to 3.9)	2.0 (0.3 to 3.8)	.02	1.9 (0.1 to 3.6)
Motor coordination		406	90.8 ± 15.8	397	88.0 ± 17.0	2.9 (0.6 to 5.2)	2.9 (0.7 to 5.1)	.01	2.3 (0.1 to 4.4)
General intelligence (WASI-II)	1041								
Full-scale IQ		392	97.0 ± 14.9	393	95.5 ± 14.7	1.5 (−0.5 to 3.6)	1.6 (−0.5 to 3.6)	.14	1.4 (−0.6 to 3.3)
Verbal comprehension		392	97.8 ± 15.5	394	97.0 ± 14.9	0.9 (−1.3 to 3.0)	0.9 (−1.2 to 3.0)	.39	0.7 (−1.4 to 2.7)
Perceptional reasoning		392	96.8 ± 14.9	395	95.2 ± 14.9	1.6 (−0.5 to 3.7)	1.6 (−0.5 to 3.6)	.13	1.4 (−0.6 to 3.4)
Attention									
TEA-Ch	1065								
Selective, Sky Search		404	10.8 ± 3.1	400	10.8 ± 3.1	0.0 (−0.4 to 0.4)	0.0 (−0.4 to 0.4)	.96	0.0 (−0.5 to 0.4)
Sustained, Score!		402	8.5 ± 3.6	399	8.2 ± 3.6	0.3 (−0.2 to 0.8)	0.3 (−0.2 to 0.8)	.21	0.2 (−0.2 to 0.7)
Divided, Sky Search DT		395	6.8 ± 3.3	390	6.5 ± 3.4	0.2 (−0.2 to 0.7)	0.2 (−0.2 to 0.7)	.36	0.1 (−0.3 to 0.6)
Task decrement shifting, Creature Counting		396	9.3 ± 3.2	393	9.2 ± 3.3	0.1 (−0.3 to 0.6)	0.1 (−0.3, 0.5)	.65	0.0 (−0.4 to 0.5)
Conners ADHD index	1114								
T-score		429	61.5 ± 18.2	435	60.7 ± 18.4	0.7 (−1.7 to 3.2)	0.6 (−1.8 to 3.0)	.61	1.2 (−1.2 to 3.5)
Probability score		429	45.2 ± 33.5	435	43.6 ± 33.5	1.6 (−2.9 to 6.0)	1.3 (−3.1 to 5.8)	.56	2.4 (−1.9 to 6.7)
Executive function									
RCF	1065								
Copy score		405	22.8 ± 5.3	400	21.6 ± 6.1	1.1 (0.4 to 1.9)	1.2 (0.4 to 2.0)	.003	1.1 (0.3 to 1.8)
Recall score		406	12.6 ± 5.1	399	12.0 ± 5.8	0.5 (−0.2 to 1.3)	0.6 (−0.1 to 1.3)	.11	0.5 (−0.3 to 1.2)
Strategy score		392	4.0 ± 1.0	387	4.0 ± 1.1	0.0 (−0.1 to 0.2)	0.0 (−0.1 to 0.2)	.56	0.0 (−0.1 to 0.2)
BRIEF parent T-scores	1114								
GEC		429	55.9 ± 12.5	434	54.8 ± 12.3	1.2 (−0.5 to 2.8)	1.1 (−0.5 to 2.8)	.18	1.4 (−0.3 to 3.0)
Metacognition index		429	55.8 ± 11.7	434	54.7 ± 11.6	1.1 (−0.5 to 2.7)	1.1 (−0.5 to 2.6)	.19	1.2 (−0.3 to 2.7)
BRI		431	54.9 ± 13.6	436	53.9 ± 13.2	1.0 (−0.8 to 2.8)	1.0 (−0.8 to 2.7)	.30	1.3 (−0.5 to 3.0)
WISC-IV digit span	1041								
Digit span forward		405	8.8 ± 3.4	406	8.6 ± 3.3	0.2 (−0.2 to 0.7)	0.3 (−0.1 to 0.7)	.16	0.2 (−0.2 to 0.6)
Digit span backward		405	8.4 ± 2.9	406	8.2 ± 2.9	0.2 (−0.2 to 0.6)	0.2 (−0.2 to 0.6)	.27	0.2 (−0.2 to 0.6)

DT, Dual Task

[a] Number of randomly assigned children not known to have died before follow-up who were eligible for assessment with the designated instrument.

[b] The MD was adjusted for the gestational age and sex of the child, antenatal administration of corticosteroids, multiple births, and the primary caregiver's education at the time of the assessment.

TABLE 3 Rates of Impairment in Neurobehavioral Outcome

Outcome	Threshold Score[a]	No./Total No. (%)		OR (95% CI)			
		Caffeine Group Impairment Rate	Placebo Group Impairment Rate	Unadjusted	Adjusted for Center	*P*	Adjusted for Center and Patient Characteristics[b]
Fine motor skills							
Beery VMI	<85	108/409 (26.4)	133/406 (32.8)	0.74 (0.54 to 1.00)	0.74 (0.55 to 0.99)	.04	0.77 (0.57 to 1.04)
Visual perception	<85	54/407 (13.3)	77/397 (19.4)	0.64 (0.44 to 0.93)	0.63 (0.43 to 0.92)	.02	0.64 (0.43 to 0.95)
Motor coordination	<85	122/406 (30.0)	151/397 (38.0)	0.70 (0.52 to 0.94)	0.69 (0.52 to 0.92)	.01	0.73 (0.54 to 0.98)
General intelligence (WASI-II)							
Full-scale IQ	<85	76/392 (19.4)	86/393 (21.9)	0.86 (0.61 to 1.21)	0.87 (0.61 to 1.23)	.43	0.89 (0.62 to 1.27)
Verbal comprehension	<85	72/392 (18.4)	69/394 (17.5)	1.06 (0.74 to 1.53)	1.11 (0.77 to 1.59)	.59	1.13 (0.77 to 1.64)
Perceptional reasoning	<85	79/392 (20.2)	95/395 (24.1)	0.80 (0.57 to 1.12)	0.78 (0.55 to 1.10)	.16	0.80 (0.56 to 1.13)
Attention							
TEA-Ch							
Selective, Sky Search	<7	36/404 (8.9)	37/400 (9.3)	0.96 (0.59 to 1.55)	0.97 (0.59 to 1.58)	.89	1.02 (0.62 to 1.67)
Sustained, Score!	<7	125/402 (31.1)	141/399 (35.3)	0.83 (0.62 to 1.11)	0.84 (0.62 to 1.12)	.23	0.87 (0.64 to 1.16)
Divided, Sky Search DT	<7	146/395 (37.0)	152/390 (39.0)	0.92 (0.69 to 1.23)	0.93 (0.69 to 1.24)	.61	0.97 (0.72 to 1.31)
Shifting, creature counting	<7	84/396 (21.2)	86/393 (21.9)	0.96 (0.68 to 1.35)	0.99 (0.70 to 1.41)	.96	1.08 (0.75 to 1.56)
Conners ADHD index							
T-score	>80	178/429 (41.5)	170/435 (39.1)	1.11 (0.84 to 1.45)	1.08 (0.82 to 1.41)	.60	1.15 (0.87 to 1.53)
Probability score	>80	144/429 (33.6)	143/435 (32.9)	1.03 (0.78 to 1.37)	1.00 (0.75 to 1.31)	.98	1.05 (0.79 to 1.40)
Executive function							
RCF							
Copy score	<1 SD[c]	385/405 (95.1)	383/400 (95.8)	0.85 (0.44 to 1.66)	0.83 (0.43 to 1.62)	.59	0.82 (0.42 to 1.61)
Recall score	<1 SD[c]	296/406 (72.9)	296/399 (74.2)	0.94 (0.68 to 1.28)	0.91 (0.67 to 1.25)	.57	0.96 (0.70 to 1.31)
BRIEF parent T-scores							
GEC	>60	137/429 (31.9)	130/434 (30.0)	1.10 (0.82 to 1.46)	1.08 (0.80 to 1.45)	.62	1.11 (0.82 to 1.51)
Metacognition index	>60	144/429 (33.6)	125/434 (28.8)	1.25 (0.94 to 1.67)	1.23 (0.92 to 1.65)	.16	1.29 (0.95 to 1.73)
BRI	>60	125/431 (29.0)	112/436 (25.7)	1.18 (0.88 to 1.59)	1.18 (0.87 to 1.60)	.29	1.24 (0.90 to 1.69)
WISC-IV digit span							
Digit span forward	<7	118/405 (29.1)	125/406 (30.8)	0.92 (0.68 to 1.25)	0.90 (0.65 to 1.23)	.50	0.92 (0.67 to 1.28)
Digit span backward	<7	112/405 (27.7)	126/406 (31.0)	0.85 (0.63 to 1.15)	0.83 (0.61 to 1.14)	.25	0.86 (0.63 to 1.18)

DT, Dual Task.

[a] Threshold score used to define impairment for the respective instrument. For all tests, this corresponded to 1 SD below or above the mean of the normative sample, depending on the test.

[b] The OR was adjusted for the gestational age and sex of the child, antenatal administration of corticosteroids, multiple births, and the primary caregiver's education at the time of the assessment.

[c] Threshold scores are age-dependent.

newborns.[22] It is well established that motor impairment is associated with behavioral difficulties, low self-esteem, poor social skills, and academic underachievement[23]; however, we found no evidence that neonatal caffeine therapy benefits behavior or academic achievement.[4] It is possible that the modest motor gains observed in the caffeine group were not sufficient to influence academic achievement and behavioral outcomes or that different mechanisms are involved. Gains in other domains, such as self-esteem and social skills, are possible but need further study.

An astute comment from a reviewer and the evidence of improved visuomotor integration, visual perception, and visuospatial organization in the caffeine group prompted us to consider the contribution of severe ROP. Consistent with previous reports,[24–26] children with severe ROP were at increased risk for visuomotor difficulties compared with children without severe ROP. However, in our post hoc analysis, it was indicated that only a small proportion of the overall beneficial caffeine effect on visuomotor performance could be attributed to the reduction of severe ROP by caffeine.

It is possible that improved visual perception and organization after caffeine therapy is related to the lower number of children with DCD in the caffeine group[10] because DCD has been associated with decreased visual perception and visuomotor integration.[27] We have previously described reduced diffusion in cerebral white matter in the newborn brain at term-equivalent age in infants treated with caffeine compared with infants in the placebo group,[28] and thus an alternative possibility is that white matter changes are restricted to early mature cortical regions and sensory functions.

Caffeine may have a neuroprotective effect,[2] which leads to specific functional improvements, although the short- and long-term effects of caffeine on the central nervous system are not clearly understood.[29] Methylxanthines have been described to inhibit adenosine receptors, thereby compromising the role of adenosine as an important neuromodulator.[30] In addition, rodent studies revealed altered astrocytogenesis in neonates after caffeine treatment.[31] However, caffeine has been shown to potentiate neural plasticity at the level of N-methyl-D-aspartate receptors, resulting in altered morphology of neural synapses and increased size of dendritic spines.[32,33] Moreover, caffeine administration in hypoxia-exposed neonatal pups was associated with enhanced myelination and reduced ventriculomegaly.[34,35] This is consistent with our neonatal MRI study in which reduced diffusion in cerebral white matter was demonstrated, reflecting improved white matter microstructural development.[28]

No other study has been conducted in which researchers assessed the long-term effects of caffeine therapy on general intelligence, attention, executive function, visuoperception, and behavior. Conducting this 11-year follow-up was challenging, given the large number of centers in the trial and the different languages spoken by participants. Thirteen centers provided data for the present secondary analyses in addition to the primary composite outcome. This resulted in an ascertainment rate of 78% (870 of 1114 potentially eligible surviving children) for the neurobehavioral outcomes. Despite this less than ideal ascertainment rate, the main birth characteristics and childhood outcomes were comparable between the group that was assessed at 11 years and the larger cohort assessed at earlier stages. Therefore, we are confident that the outcomes of the whole cohort are reflected in the present results with sufficient accuracy.

CONCLUSIONS

Neonatal caffeine therapy was associated with better visuomotor, visuoperceptual, and visuospatial abilities at 11 years of age in children born at very low birth weight. None of the secondary outcomes reported in this study were adversely affected by caffeine. This highlights the long-term safety and efficacy of caffeine therapy for apnea of prematurity in very low birth weight neonates.

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ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
BRI: Behavioral Regulation Index
BRIEF: Behavior Rating Inventory of Executive Function
CAP: Caffeine for Apnea of Prematurity
CI: confidence interval
DCD: developmental coordination disorder
GEC: Global Executive Composite
MD: mean difference
OR: odds ratio
RCF: Rey complex figure test
ROP: retinopathy of prematurity
TEA-Ch: Test of Everyday Attention for Children
VMI: visual-motor integration
WASI-II: Wechsler Abbreviated Scale of Intelligence–II
WISC-IV: Wechsler Intelligence Scale for Children–IV

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REFERENCES

1. Finer NN, Higgins R, Kattwinkel J, Martin RJ. Summary proceedings from the apnea-of-prematurity group. *Pediatrics*. 2006;117(3, pt 2):S47–S51
2. Abdel-Hady H, Nasef N, Shabaan AE, Nour I. Caffeine therapy in preterm infants. *World J Clin Pediatr*. 2015;4(4):81–93
3. Dunwiddie TV, Masino SA. The role and regulation of adenosine in the central nervous system. *Annu Rev Neurosci*. 2001;24(1):31–55
4. Schmidt B, Roberts RS, Anderson PJ, et al; Caffeine for Apnea of Prematurity (CAP) Trial Group. Academic performance, motor function, and behavior 11 years after neonatal caffeine citrate therapy for apnea of prematurity: an 11-year follow-up of the CAP randomized clinical trial. *JAMA Pediatr*. 2017;171(6):564–572
5. Walsh MC, Morris BH, Wrage LA, et al; National Institutes of Child Health and Human Development Neonatal Research Network. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr*. 2005;146(6):798–804
6. Schmidt B. Methylxanthine therapy in premature infants: sound practice, disaster, or fruitless byway? *J Pediatr*. 1999;135(4):526–528
7. Schmidt B, Roberts RS, Davis P, et al; Caffeine for Apnea of Prematurity Trial Group. Caffeine therapy for apnea of prematurity. *N Engl J Med*. 2006;354(20):2112–2121
8. Schmidt B, Roberts RS, Davis P, et al; Caffeine for Apnea of Prematurity Trial Group. Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med*. 2007;357(19):1893–1902
9. Schmidt B, Anderson PJ, Doyle LW, et al; Caffeine for Apnea of Prematurity (CAP) Trial Investigators. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. *JAMA*. 2012;307(3):275–282
10. Doyle LW, Schmidt B, Anderson PJ, et al; Caffeine for Apnea of Prematurity Trial investigators. Reduction in developmental coordination disorder with neonatal caffeine therapy. *J Pediatr*. 2014;165(2):356–359.e2
11. Wechsler D. *Wechsler Abbreviated Scale of Intelligence–Second Edition (WASI-II)*. San Antonio, TX: NCS Pearson; 2011
12. Beery KE, Beery NA. *The Beery-Buktenica Developmental Test of Visual-Motor Integration: Administration, Scoring, and Teaching Manual*. 6th ed. Minneapolis, MN: NCS Pearson; 2010
13. Wechsler D. *Wechsler Intelligence Scale for Children*. 4th ed. San Antonio, TX: Pearson Assessment; 2003
14. Manly T, Robertson IH, Anderson V, Nimmo-Smith I. *TEA-Ch: The Test of Everyday Attention for Children Manual*. Bury St. Edmunds, United Kingdom: Thames Valley Test Company Limited; 1999
15. Rey A. L'examen clinique en psychologique dans les cas d'encephalopathic traumatique. *Arch Psychol*. 1941;28:286–340
16. Anderson P, Anderson V, Garth J. Assessment and development of organizational ability: the Rey Complex Figure Organizational Strategy Score (RCF-OSS). *Clin Neuropsychol*. 2001;15(1):81–94
17. Gioia GA, Isquith PK, Retzlaff PD, Espy KA. Confirmatory factor analysis of the Behavior Rating Inventory of Executive Function (BRIEF) in a clinical sample. *Child Neuropsychol*. 2002;8(4):249–257
18. Conners CK. *Conners 3rd Edition Manual*. Toronto, ON: Multi-Health Systems; 2008
19. Kramer MS, Platt RW, Wen SW, et al; Fetal/Infant Health Study Group of the Canadian Perinatal Surveillance System. A new and improved population-based Canadian reference for birth weight for gestational age. *Pediatrics*. 2001;108(2). Available at: www.pediatrics.org/cgi/content/full/108/2/e35
20. Robertson CMT, Watt MJ, Dinu IA. Outcomes for the extremely premature infant: what is new? And where are we going? *Pediatr Neurol*. 2009;40(3):189–196
21. Vincer MJ, Allen AC, Allen VM, Baskett TF, O'Connell CM. Trends in the prevalence of cerebral palsy among very preterm infants (<31 weeks' gestational age). *Paediatr Child Health*. 2014;19(4):185–189
22. Williams J, Lee KJ, Anderson PJ. Prevalence of motor-skill impairment in preterm children who do not develop cerebral palsy: a systematic review. *Dev Med Child Neurol*. 2010;52(3):232–237
23. Roberts G, Anderson PJ, Davis N, De Luca C, Cheong J, Doyle LW; Victorian Infant Collaborative Study Group. Developmental coordination disorder in geographic cohorts of 8-year-old children born extremely preterm or extremely low birthweight in the 1990s. *Dev Med Child Neurol*. 2011;53(1):55–60
24. Molloy CS, Anderson PJ, Anderson VA, Doyle LW. The long-term outcome of extremely preterm (<28 weeks' gestational age) infants with and without severe retinopathy of prematurity. *J Neuropsychol*. 2016;10(2):276–294
25. Schmidt B, Davis PG, Asztalos EV, Solimano A, Roberts RS. Association between severe retinopathy of prematurity and nonvisual disabilities at age 5 years. *JAMA*. 2014;311(5):523–525
26. Msall ME, Phelps DL, DiGaudio KM, et al; on behalf of the Cryotherapy for Retinopathy of Prematurity Cooperative Group. Severity of neonatal retinopathy of prematurity is predictive of neurodevelopmental functional outcome at age 5.5 years. *Pediatrics*. 2000;106(5):998–1005

27. Van Waelvelde H, De Weerdt W, De Cock P, Smits-Engelsman BC. Association between visual perceptual deficits and motor deficits in children with developmental coordination disorder. *Dev Med Child Neurol*. 2004;46(10):661–666

28. Doyle LW, Cheong J, Hunt RW, et al. Caffeine and brain development in very preterm infants. *Ann Neurol*. 2010;68(5):734–742

29. Atik A, Harding R, De Matteo R, et al. Caffeine for apnea of prematurity: effects on the developing brain. *Neurotoxicology*. 2017;58:94–102

30. Millar D, Schmidt B. Controversies surrounding xanthine therapy. *Semin Neonatol*. 2004;9(3):239–244

31. Desfrere L, Olivier P, Schwendimann L, Verney C, Gressens P. Transient inhibition of astrocytogenesis in developing mouse brain following postnatal caffeine exposure. *Pediatr Res*. 2007;62(5):604–609

32. Yoshimura H. The potential of caffeine for functional modification from cortical synapses to neuron networks in the brain. *Curr Neuropharmacol*. 2005;3(4):309–316

33. Connolly S, Kingsbury TJ. Caffeine modulates CREB-dependent gene expression in developing cortical neurons. *Biochem Biophys Res Commun*. 2010;397(2):152–156

34. Rivkees SA, Wendler CC. Adverse and protective influences of adenosine on the newborn and embryo: implications for preterm white matter injury and embryo protection. *Pediatr Res*. 2011;69(4):271–278

35. Back SA, Craig A, Luo NL, et al. Protective effects of caffeine on chronic hypoxia-induced perinatal white matter injury. *Ann Neurol*. 2006;60(6):696–705

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