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Effects of caffeine on development and behavior in infancy and childhood: a review of the published literature

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Abstract

The Medline literature on the behavioral effects of caffeine in infants and children are reviewed. There has been little recent work in this area. Generally, caffeine is well tolerated in usual dietary amounts, and there is evidence that individuals differ in their susceptibility to caffeine-related adverse effects, which in turn may influence their consumption. Overall, the effects of caffeine in children seem to be modest and typically innocuous. © 2002 Published by Elsevier Science Ltd.

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1. Introduction

Convictions about the behavioral effects of foods in children inspire strong reactions and, among other substances, caffeine continues to receive considerable attention. Among the various issues of concern have been the potential effects of prenatal exposure to caffeine on infant behavior and development, and adverse and possibly beneficial effects of dietary caffeine on normal and abnormal behavior in children. This paper is a review and update on the systematic research that has addressed the effects of caffeine on development and behavior in pediatric subjects.

It is beyond the scope of this review to cover caffeine consumption in children, or to address the effect of intake of caffeine containing foods on other dietary intake (e.g. see Guenther, 1986). As a frame of reference, however, it should be noted that caffeine intake is estimated to be (in mg/kg/day) 0.3 for infants, 1.0 for children in the 1–5 year age range, and 0.7 for children of 6–17 years (Barone and Roberts, 1996). However, individual variation is considerable, as evidenced from a report on infants for whom the daily caffeine intake from tea was closer to 5 mg/kg (Tang et al., 1989).

A review of the literature indexed in Medline found a small number of studies on the behavioral correlates of caffeine consumption by children. These are summarized in a series of tables below. Studies were only included if they used appropriate methodology and sample size. The focus of this brief review is to describe contributions made by recent studies.

2. Caffeine and infant development and behavior

The metabolic half-life of caffeine in neonates is prolonged, with a mean in one study of 82 h, with a range from 31 to 132 h (Parsons and Neims, 1981). As summarized by Leviton (1992), a number of claims for neonatal abstinence syndrome attributed to caffeine have been made.

As seen from Table 1, systematic studies have detected only minimal effects of maternal caffeine ingestion on neonatal behavior (Barr et al., 1984; Jacobson et al., 1984; Emory et al., 1988; Barr and Streissguth, 1991). However, cases of caffeine withdrawal have been documented in individual case studies where there has been unusually high maternal caffeine ingestion (over 800 mg/day) (McGowan et al., 1988). In one case in which the mother drank up to 24 cups of coffee per day during pregnancy, apnea in her prematurely born infant was ascribed to caffeine withdrawal when serum caffeine concentration was found to be 40.3 mcg/ml 4 days after birth (Khanna and Somani, 1984). However, even in this case, there was no abnormality detected in subsequent

Abbreviations: ADHD; Attention-Deficit/Hyperactivity Disorder; NIMH; National Institute of Mental Health; SIDS; sudden infant death syndrome.

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Table 1
Prenatal effects of caffeine on behavior and development in infancy and childhood

Study	Dose	Subjects (no., sex, age)	Design	Outcome measure	Effect/comments
Jacobsen et al., 1984	Mean maternal gestational caffeine ingestion: 121 mg/day range 0–500+ mg	173 newborns	Correlative, correcting for nicotine and alcohol exposure	Brazelton Neonatal Behavioral Assessment Scale (NBAS) irritability and arousal clusters; Ballard Examination for Neonatal Maturity	Caffeine during pregnancy related to shorter gestation and poorer neuromuscular development. Caffeine intake prior to pregnancy associated with greater irritability, greater arousal, and poorer orientation.
McGowan et al., 1988	Maternal caffeine ingestion 200–1100 mg/day during pregnancy	8 newborns	Descriptive case report during post-natal + days 1–12	Withdrawal symptoms of vomiting, jitteriness, bradycardia, tachypnea noted	Maternal caffeine ingestion estimated to range from 200 to 1800 mg/day.
Emory et al., 1988	NA	40 full term 1–2 day neonates, all breast-fed	Correlative (with salivary caffeine)	Number of state changes, rating of consolability during NBAS	Salivary caffeine level correlated with greater state lability ($r = 0.28$, $P = 0.05$) and with decreased consolability ($r = 0.27$, $P = 0.05$). Many neonatal behaviors not correlated with caffeine level.
Streissguth et al., 1980 Barr and Streissguth, 1991	Maternal gestational ingestion 193 mg/day early in pregnancy 152 mg/day mid pregnancy	1529 pregnancies followed prospectively	Descriptive, correlative and multiple regression analyses. examinations at day 1, 8 months 4 and 7 years	NBAS; Bayley Scales of Infant Development (BSID); Wechsler Preschool and Primary Scale of Intelligence (IQ); fine and gross motor test; battery of vigilance tests	Minimal newborn and 8 month effects No effects of prenatal caffeine exposure on IQ at 4 or 7 or motor abilities or alertness in general. At age 4 years, high maternal caffeine associated with more errors but faster correction during a motor task.
Engle et al., 1999	Mean caffeine consumption estimated to be 9 mg/kg/day introduced about age 7 months	132 children 12–24 months of age who drank coffee daily for over 2 months	Randomized discontinuation trial for 5 months; stratified by iron deficiency	Hemoglobin, hematocrit and an indicator of red blood cell protoporphyrin; dietary and coffee intake logs; maternal sleep recall on home visits; BSID rated blindly.	Replacement of coffee had no effect on any BSID scores; children drinking coffee substitute slept significantly more by visit 10. Maternal coffee drinking during pregnancy was significantly negatively associated with Emotional Regulation scale, Orientation and Engagement scale, and Total Behavior Rating Scales score. Coffee gestational effects likely mediated by children's iron status.

clinical course or later growth and development. A population-based case-control study of 1205 mothers interviewed within 24 h of delivery found no effects of prenatal maternal caffeine ingestion on low birth weight, preterm births, or intrauterine growth retardation (Santos et al., 1998).

The greatest concern associated with caffeine relates to its potential effects during gestation. Significant, though modest, effects were found in 173 newborns of maternal caffeine intake prior to and during pregnancy (Jacobson et al., 1984). The measure most affected was neuromuscular and motoric functioning. However, a larger study of 462 infants detected no deleterious effects of caffeine on mental or motor scores on the Bayley Scales of Infant Mental and Motor Development when maternal alcohol, nicotine, gestational age, maternal education and parity were controlled (Streissguth et al., 1980). Likewise, a 7-year prospective follow-up of 482 children led to the "general conclusion that the long-term consequences of prenatal caffeine in this cohort are nil" (Barr and Streissguth, 1991). Similarly, other authors have also concluded that "in utero caffeine exposure does not seem to translate into long-term effects on neurobehavioral development in the human child, even if the child's behavior may be transiently disturbed in the perinatal period as a consequence of heavy maternal caffeine consumption during pregnancy" (Nehlig and Debry, 1994).

Heavy caffeine intake, defined as 400 mg/day or more, was found to be significantly associated with an increased risk of sudden infant death syndrome (SIDS) in a nationwide case-control study performed in New Zealand (Ford et al., 1998). The accompanying commentary advised a cautious interpretation of this first report of an association between gestational caffeine intake and SIDS because of the retrospective design, the lack of a dose–response relationship, the substantial effect of the confounders that were quantified, and the possibility that the effect would have disappeared had other confounders been measured more accurately. For example, maternal smoking was only recorded during the last 2 weeks of pregnancy, and then only as yes or no. The subsequent Nordic epidemiological SIDS case control study found that after adjustment for maternal smoking in first trimester, maternal age, education and parity, no significant effect of caffeine during or after pregnancy remained even with caffeine consumption over 800 mg/day (Alm et al., 1999).

Maternal coffee drinking during pregnancy was significantly negatively associated with emotional regulation, orientation and engagement in 132 children aged 12–24 months who themselves were daily drinkers of coffee for over 2 months (Engle et al., 1999). The effects of gestational coffee drinking were even more strongly linked to a measure of iron deficiency in the children, leading the authors to conclude that prenatal coffee intake may have influenced behavioral ratings in the offspring through affecting fetal iron status. Interestingly, randomized discontinuation of coffee intake for 5 months had no behavioral effects in the children, regardless of iron deficiency, except to increase hours slept by about 30 min per night.

2.1. Caffeine effects on hyperactive children

Beginning with an open case series reporting robust efficacy of caffeinated coffee in hyperkinetic children (Schnackenberg, 1973), the possibility of avoiding scheduled medications has motivated a number of studies of caffeine in Attention-Deficit/Hyperactivity Disorder (ADHD) and its predecessor diagnoses, as shown in Table 2. Overall, controlled studies have not shown convincing evidence of benefit (Gross, 1975; Huestis et al., 1975; Reichard and Elder, 1977; Arnold et al., 1978; Firestone et al., 1978a,b). The exceptions have been one small study ($n = 6$) that was limited to simple and choice reaction time tasks (Reichard and Elder, 1977), and another small study ($n = 6$) in which low-dose (158 mg/day) but not high-dose caffeine significantly improved behavior alone, and in combination with 10 mg methylphenidate (Garfinkel et al., 1981). These small studies have not had substantial impact on altering clinicians' treatment strategies despite the fact that they have not been systematically refuted. The consensus in the field is that for the treatment of ADHD, adjunctive caffeine is not contraindicated, but it is also not a viable replacement for the stimulants.

Besides the question of possible efficacy in ADHD, controlled studies of caffeine in children could have been useful in determining potential differential adverse effects in children. Unfortunately, the early studies listed in Table 2 did not adequately address this issue, though adverse effects were typically described as "minimal" (Firestone et al., 1978a). Despite the overall absence of quantification, some studies did report expected adverse effects such as dose-dependent insomnia in a few children (Gross, 1975; Firestone et al., 1978a), and statistically significant but clinically minor group increases in blood pressure and heart rate (Arnold et al., 1978).

2.2. Effects of caffeine in normal children

Because of possible confounding between psychiatric diagnosis and caffeine effects, questions of adverse effects and possible "benefits" are best addressed in controlled studies with screened healthy children. Rapoport and colleagues conducted a number of controlled trials on the effects of caffeine in normal children at the National Institute of Mental Health (NIMH), as shown in Table 3. In acute single dose studies (Elkins et al., 1981; Rapoport et al., 1981b), "low doses" (3 mg/kg) had negligible effects in normal children. High doses

Table 2
Effects of caffeine on behavior in hyperactive (ADHD) children

Study	Caffeine daily dose (mg)	Subjects	Design	Outcome measure	Effect/comments
Gross, 1975	Mean 249 mg (range 100–400)	25 (sex unspecified) hyperkinetic children; mean age 9.2	Single blind cross-over trial of placebo followed by caffeine	Teacher and parent reports	No benefit in any subject; adverse effects not quantified but listed. One patient had insomnia, two had excessive urination. "More noisy," "jumpy," "silly," and "more wound up" reported.
Huestis et al., 1975	"At least 300 mg" (mean, range not provided)	18 (6 females) hyperkinetic minimal brain dysfunction (MBD); mean age 8.5	Single blind placebo lead in; double-blind cross-over of caffeine, d-amphetamine, methylphenidate	Parent and teacher standard ratings	No significant improvement on caffeine; caffeine adverse effects (other than loss of stimulant efficacy) not reported explicitly.
Kupietz and Winsberg, 1977	300 mg, single dose	10 reading disordered boys; mean age 9.9	Open cross-over comparison with placebo	Auditory continuous performance test errors	No difference between caffeine and placebo. Adverse effects not reported.
Reichard and Elder, 1977	6 mg/kg (maximum 200 mg)	6 hyperkinetic children (1 female); mean age 9.3; 6 normal controls, matched for age and intelligence score	Double-blind cross-over comparison of fruit drink with caffeine, with placebo, and session without fruit drink	Simple and choice reaction time tasks	Caffeine significantly improved accuracy in hyperkinetic children after the first of six blocks. No significant effects on normal group performance. Adverse effects not reported.
Arnold et al., 1978	Mean 320 mg (12 mg/kg)	29 hyperkinetic MBD, (7 females), includes subjects reported by Huestis et al., 1975; mean age 8 years	Single blind placebo lead-in, followed by double-blind cross-over caffeine, d-amphetamine, methylphenidate	Parent and teacher standard ratings; vital signs and weight.	Caffeine indistinguishable from placebo except for significant increases in systolic blood pressure (6 mmHg), heart rate (8 bpm). Weight loss of 0.48 kg probably due to design; weight loss significantly greater on both other stimulants.
Firestone et al., 1978a	300 mg (150 mg/dose)	20 hyperactive males, mean 9.3 years	Double-blind cross-over of placebo and caffeine	Parent and teacher standard ratings and cognitive measures	Significant caffeine benefits detected on one parent rating and one cognitive measure out of 9. "The children did not show any negative side effects, as determined by informal parental reports."
Garfinkel et al., 1981	158 and 308 mg (divided in two doses)	6 boys with attention deficit disorder between ages 6 and 10 years	Double-blind cross-over of caffeine at two doses, and placebo, with each combined with methylphenidate 10 mg	Standard ratings by teachers and staff in day hospital	Low-dose caffeine significantly improved behavior compared to placebo and to high-dose caffeine. Low-dose caffeine combined with methylphenidate was best. No consistent or significant effects on anxiety or sociability. Adverse effects not addressesd.

Table 3
Effects of caffeine on behavior in normal children

Study	Subjects	Design	Dose	Outcome measure	Effect/comment
Elkins et al., 1981	19 prepubertal boys; mean age 10.6 years	Double-blind cross-over of placebo, and two doses of caffeine; acute study	Low dose mean = 110 mg (3 mg/kg); High dose mean = 369 mg (10 mg/kg).	Vigilance, cognitive, and motor activity measures; ratings of mood, behavior and adverse effects; urinary epinephrine and norepinephrine	No significant effects on low dose. High dose significantly improved vigilance, increased activity, and increased ratings of fidgetiness, along with trend ($P = 0.10$) to worsening of free recall. "Jumpiness" on caffeine compared to restlessness accompanying anxiety.
Rapoport et al., 1981a	19 prepubertal boys (age 10.6 years) and 20 adult men (age 21.7 years). Adults selected as low consumers ($n = 12$; 26 mg/day) or high consumers ($n = 8$; 565 mg/day) of caffeine.	Double-blind cross-over of placebo, and two doses of caffeine; acute study	Low dose = 3 mg/kg High dose = 10 mg/kg	Vigilance, cognitive, speech rate, skin conductance, and motor activity measures; vital signs; ratings ofmood, behavior and adverse effects	In children, low dose significantly increased diastolic BP, lowered heart rate, and increased spontaneous skin conductance responses. High dose significantly decreased heart rate, increased activity and speech rate, improved vigilance, increased skin conductance responses and level, and increased ratings of "nervous/ jittery." There were no effects on self-reported anxiety. Compared with adults, children reported fewer adverse effects, and exhibited greater objective changes in activity and task performance.
Rapoport et al., 1981b	19 prepubertal boys (age 9.8); 10 were low consumers (1 mg/kg/day), 9 were high consumers (11 mg/kg/day).	Double-blind cross-over of placebo (quinine) and caffeine for 2 weeks each after 1 week baseline	5 mg/kg/dose twice a day	Vigilance, skin conductance measures; vital signs, ratings of mood, behavior and adverse effects	Low caffeine consumers reported significantly greater adverse effects ($P = 0.002$) and had significantly increased skin conductance responses. Mothers' ratings of adverse effects were significantly greater on caffeine for the total group. There were no "beneficial effects" on cognitive measures and no effects on vital signs. Evidence of "caffeinism" imputed.
Rapoport et al., 1984	19 high consumers (10.3 years old) and 19 matched low consumers obtained from 800 grade school children surveyed for baseline caffeine usage.	Double-blind cross-over of placebo (quinine) and caffeine for 2 weeks each after 1 week baseline and 2 weeks on low-caffeine diet	5 mg/kg/dose twice a day (mean daily dose 377 mg)	Vigilance, skin conductance measures; vital signs; ratings of mood, behavior and adverse effects; salivary caffeine levels	At baseline, high consumers reported significantly greater anxiety symptoms and were significantly more likely to be described as "disobedient" by parents. On caffeine, low consumers had significantly greater ratings of restless and fidgety behavior, greater adverse effects (headache, stomachache,

(*continued on next page*)

Table 3 (*continued*)

Study	Subjects	Design	Dose	Outcome measure	Effect/comment
					nausea, feeling faint, flushed, difficulty sleeping, decreased appetite). High consumers differed significantly from low consumers only in showing less restless and fidgety behavior on caffeine. High consumers had no significant caffeine effects, except for "normalization" of skin conductance response. There were no effects on vital signs, and only a minor significant improvement on vigilance in the combined group.
Baer, 1987	6 preschool children (5 years old, 2 girls)	Blind within-subject reversal of caffeinated and caffeine-free Diet Coke® (alternating sequences ABA or BAB counter-balanced) for several weeks	25 mg/day (1.6 to 2.5 mg/kg)	Blinded ratings of activity and behavior, actometer, vigilance and learning tasks	No consistent effects noticed in this small naturalistic study. Dose was much smaller than in prior studies, but more consistent with likely intake in preschool-age children. Caffeine condition terminated after 2 weeks in one child due to complaint of stomach pains.
Bernstein et al., 1994	21 prepubertal children (10.6 years), 9 female	Double-blind cross-over after baseline of placebo and two acute doses of caffeine	2.5 mg/kg and 5 mg/kg (maximum 250 mg)	Vigilance, cognitive, motor tasks, ratings of anxiety and of adverse effects; saliva caffeine levels	Dose-dependent significant improvements on vigilance task, and manual dexterity found. No effect on cognitive tasks. Self-reported current anxiety increased ($P = 0.1$) on one scale (linearly related to dose, $P = 0.03$), with no change in two other anxiety scales. Rating of "sluggish, slowed down" significantly decreased on caffeine.
Goldstein and Wallace, 1997	289 fifth- and sixth-grade children	Open-label pilot. Children logged habitual caffeine consumption on Day 1 and abstained from caffeine on Day 2	Low consumption group (10 mg/day or less) and high consumption group (50 mg/day or more) compared	Caffeine consumption; Modified Profile of Moods Scale	Median daily consumption was 28 mg; 17% consumed 100 mg/day or more. High-consumption group reported more stimulation on Day 1 and more dysphoric symptoms during abstinence on Day 2. Results considered preliminary since design open.
Bernstein et al., 1998	30 prepubertal children (mean ages not available).	Baseline (on normal intake), single-blind re-testing on 150 mg/day, continuation on caffeine for 2 weeks, with re-testing 24 h after discontinuation, and again on normal intake (mean 38.5 mg/day)	150 mg/day	Vigilance test and ratings of adverse effects	At 24 h after cessation of 13 days of caffeine, subjects were significantly worse on increase in response time and its variability. Deterioration persisted 1 week later even after resumption of pre-trial caffeine intake. Authors conclude that caffeine physical dependence and withdrawal effects likely demonstrated for this dose, and call for replication with more usual doses.

(10 mg/kg) tended to show significant improvements in tasks related to vigilance, and interestingly, significant increases in locomotor activity were also detected, whether measured objectively or by observer ratings. Also elevated by high doses of caffeine were ratings of being "nervous/jittery," although self-reported anxiety was not affected (Rapoport et al., 1981b). Compared with adults, children reported fewer adverse effects while exhibiting greater objective changes in activity and task performance.

One difficulty in studying effects of caffeine is that individuals may differ greatly in their usual intake and exposure. In subsequent studies also conducted at NIMH, children were stratified by prior caffeine dietary history. High or low consumers were administered caffeine chronically at doses of 10 mg/kg/day (Rapoport et al., 1981a, 1984). Low consumers of caffeine reported significantly greater adverse effects suggesting possible "caffeinism" in these subjects (Rapoport et al., 1981a). High consumers had no significant caffeine effects except for "normalization" of a skin conductance response (Rapoport et al., 1984). Adverse effects reported by the children and significantly associated with caffeine were headache, stomachache and nausea. The symptoms of "feeling faint" and "flushed" were decreased in high consumers and increased in low consumers. Parents reported that children were significantly more "nervous and jittery" and had more headaches on caffeine, with effects more pronounced for low consumers. Only parents of low caffeine consumers reported significant increases for symptoms of "difficulty sleeping," "appetite decreased" and "feeling faint." The authors concluded, "children, like adults, may self-select dietary caffeine in a more systematic way than is generally supposed" (Rapoport et al., 1984). It should also be noted that the doses of caffeine administered (5 mg/kg/dose, twice a day) are substantial.

A small study using six preschool children attempted to parallel actual usage patterns by administering 25-mg doses of caffeine repeatedly in alternation with caffeine-free Diet Coke® (Baer, 1987). This modest dose (<2.5 mg/kg/day) was chosen because it was the largest amount the children would consistently drink at one time (8 oz), and it produced no consistent effects, except for one child who complained of stomachaches when given caffeine. Baer emphasized the limitations of her small study, but concluded "restriction of children's caffeine intake, although possibly wise for medical reasons, probably will have little effect on children's behavior in the classroom".

The effects of caffeine have been relatively recently studied by Bernstein and colleagues (1994, 1998). In an acute dosing study, 20 children completed a double-blind cross-over of placebo and two doses of caffeine after an initial baseline test session. Caffeine produced dose-dependent improvements on a vigilance task (Test of Variables of Attention) and on a test of manual dexterity (Grooved Pegboard Test), but no change on two other cognitive tasks. A modest and non-significant relationship was found between caffeine and self-reported current anxiety ($P=0.1$), with regression analysis demonstrating a significant linear relationship between current anxiety (on only one of three ratings) and caffeine salivary levels ($P=0.03$) (Bernstein et al., 1994).

A follow-up study examined the possible magnitude of caffeine withdrawal in children (Bernstein et al., 1998). Thirty children were tested four times on the same vigilance task: at baseline, while taking 150 mg/day of caffeine, 24 h after discontinuing 13 days of daily caffeine doses (150 mg/day), and 1 week later after having resumed their usual caffeine intake (mean 38.5 mg/day). The authors reported that significant slowing in response time and increase in its variability was detected upon caffeine withdrawal, and that this remained 1 week later. They concluded that caffeine physical dependence and withdrawal were probably demonstrated when children were asked to consume approximately four times their habitual intake, and they called for future replication with more usual doses.

3. Discussion

This review has found that while there may continue to be public concern about caffeine and its effects on children, scientific interest on this question has been slight, especially in the past decade. This has led to the conclusion that, "in the absence of more precise data and to avoid any fetotoxic risk, women should be advised to moderate their consumption of coffee during pregnancy and above all, to avoid tobacco and alcohol as well as vasoconstricting medications", although "the number of studies in humans is still too sparse to be conclusive on the neurobehavioral development of children born of caffeine-drinking mothers" (Nehlig and Debry, 1994).

In children, a recent meta-analysis of caffeine based on nine studies using 193 children (96 with ADHD and 97 normal children) showed a beneficial effect on parental ratings of "externalizing behaviors" (aggressive or disruptive behaviors) with an extraordinary mean effect size of 1.53. However, mean effect sizes for measures of attention, and teacher reports of behavior were near 0, and the inter-study variability was so substantial that the apparent improvement on parent ratings of aggressive and disruptive behaviors was not statistically reliable (Stein et al., 1996). However, there was also no evidence of any deleterious effects from these studies.

Overall, there continues to be little evidence that would warrant grave concern about the use of moderate doses of caffeine in most situations. There is evidence that individuals differ in their susceptibility to caffeine-related

adverse effects, and that this may influence their usage patterns (Rapoport et al., 1984).

The effects of caffeine in children seem to be modest and generally innocuous. However, differential susceptibility is likely to be the rule, and studies of the effects of caffeine in children with anxiety disorders will be useful to further delineate the potential benefits and risks from this commonly ingested substance. Furthermore, the marketing of higher caffeine-containing soft drinks should motivate studies that would attempt to replicate the finding of the development of caffeine physical dependence and tolerance in children. If replicated, the clinical and public health implications should also be explored.

References

Alm, B., Wennergren, G., Norvenius, G., Skjaerven, R., Oyen, N., Helweg-Larsen, K., Lagercrantz, H., Irgens, L.M., 1999. Caffeine and alcohol as risk factors for sudden infant death syndrome. Nordic Epidemiological SIDS Study. Archives of Disease in Childhood 81, 107–111.

Arnold, L.E., Christopher, J., Huestis, R., Smeltzer, D.J., 1978. Methylphenidate vs dextroamphetamine vs caffeine in minimal brain dysfunction: controlled comparison by placebo washout design with Bayes' analysis. Archives of General Psychiatry 35, 463–473.

Baer, R.A., 1987. Effects of caffeine on classroom behavior, sustained attention, and a memory task in preschool children. Journal of Applied Behavior Analysis 20, 225–234.

Barone, J.J., Roberts, H.R., 1996. Caffeine consumption. Food and Chemical Toxicology 34, 119–129.

Barr, H.M., Streissguth, A.P., 1991. Caffeine use during pregnancy and child outcome: a 7-year prospective study. Neurotoxicology and Teratology 13, 441–448.

Barr, H.M., Streissguth, A.P., Martin, D.C., Herman, C.S., 1984. Infant size at 8 months of age: relationship to maternal use of alcohol, nicotine, and caffeine during pregnancy. Pediatrics 74, 336–341.

Bernstein, G.A., Carroll, M.E., Crosby, R.D., Perwien, A.R., Go, F.S., Benowitz, N.L., 1994. Caffeine effects on learning, performance, and anxiety in normal school-age children. Journal of the American Academy of Child and Adolescent Psychiatry 33, 407–415.

Bernstein, G.A., Carroll, M.E., Dean, N.W., Crosby, R.D., Perwien, A.R., Benowitz, N.L., 1998. Caffeine withdrawal in normal school-age children. Journal of the American Academy of Child and Adolescent Psychiatry 37, 858–865.

Elkins, R.N., Rapoport, J.L., Zahn, T.P., Buchsbaum, M.S., Weingartner, H., Kopin, I.J., Langer, D., Johnson, C., 1981. Acute effects of caffeine in normal prepubertal boys. American Journal of Psychiatry 138, 178–183.

Emory, E.K., Konopka, S., Hronsky, S., Tuggey, R., Dave, R., 1988. Salivary caffeine and neonatal behavior: assay modification and functional significance. Psychopharmacology (Berlin) 94, 64–68.

Engle, P.L., VasDias, T., Howard, I., Romero-Abal, M.E., Quan de Serrano, J., Bulux, J., Solomons, N.W., Dewey, K.G., 1999. Effects of discontinuing coffee intake on iron deficient Guatemalan toddlers' cognitive development and sleep. Early Human Development 53, 251–269.

Firestone, P., Davey, J., Goodman, J.T., Peters, S., 1978a. The effects of caffeine and methylphenidate on hyperactive children. Journal of the American Academy of Child Psychiatry 17, 445–456.

Firestone, P., Poitras-Wright, H., Douglas, V.I., 1978b. The effects of caffeine on hyperactive children. Journal of Learning Disabilities 11, 133–141.

Ford, R.P., Schluter, P.J., Mitchell, E.A., Taylor, B.J., Scragg, R., Stewart, A.W., 1998. Heavy caffeine intake in pregnancy and sudden infant death syndrome. New Zealand Cot Death Study Group. Archives of Disease in Childhood 78, 9–13.

Garfinkel, B.D., Webster, C.D., Sloman, L., 1981. Responses to methylphenidate and varied doses of caffeine in children with attention deficit disorder. Canadian Journal of Psychiatry 26, 395–401.

Goldstein, A., Wallace, M.E., 1997. Caffeine dependence in schoolchildren? Experimental and Clinical Psychopharmacology 5, 388–392.

Gross, M.D., 1975. Caffeine in the treatment of children with minimal brain dysfunction or hyperkinetic syndrome. Psychosomatics 16, 26–27.

Guenther, P.M., 1986. Beverages in the diets of American teenagers. Journal of the American Dietetic Association 86, 493–499.

Huestis, R.D., Arnold, L.E., Smeltzer, D.J., 1975. Caffeine versus methylphenidate and d-amphetamine in minimal brain dysfunction: a double-blind comparison. American Journal of Psychiatry 132, 868–870.

Jacobson, S.W., Fein, G.G., Jacobson, J.L., Schwartz, P.M., Dowler, J.K., 1984. Neonatal correlates of prenatal exposure to smoking, caffeine, and alcohol. Infant Behavior and Development 7, 253–265.

Khanna, N.N., Somani, S.M., 1984. Maternal coffee drinking and unusually high concentrations of caffeine in the newborn. Journal of Toxicology. Clinical Toxicology 22, 473–483.

Kupietz, S.S., Winsberg, B.G., 1977. Caffeine and inattentiveness in reading-disabled children. Perceptual and Motor Skills 44, 1238.

Leviton, A., 1992. Behavioral correlates of caffeine consumption by children. Clinical Pediatrics (Philadelphia) 31, 742–750.

McGowan, J.D., Altman, R.E., Kanto, W.P.J., 1988. Neonatal withdrawal symptoms after chronic maternal ingestion of caffeine. Southern Medical Journal 81, 1092–1094.

Nehlig, A., Debry, G., 1994. Potential teratogenic and neurodevelopmental consequences of coffee and caffeine exposure: a review on human and animal data. Neurotoxicology and Teratology 16, 531–543.

Parsons, W.D., Neims, A.H., 1981. Prolonged half-life of caffeine in healthy term newborn infants. Journal of Pediatrics 98, 640–641.

Rapoport, J.L., Berg, C.J., Ismond, D.R., Zahn, T.P., Neims, A., 1984. Behavioral effects of caffeine in children. Relationship between dietary choice and effects of caffeine challenge. Archives of General Psychiatry 41, 1073–1079.

Rapoport, J.L., Elkins, R., Neims, A., Zahn, T., Berg, C.J., 1981a. Behavioral and autonomic effects of caffeine in normal boys. Developmental Pharmacology and Therapeutics 3, 74–82.

Rapoport, J.L., Jensvold, M., Elkins, R., Buchsbaum, M.S., Weingartner, H., Ludlow, C., Zahn, T.P., Berg, C.J., Neims, A.H., 1981b. Behavioral and cognitive effects of caffeine in boys and adult males. Journal of Nervous and Mental Disease 169, 726–732.

Reichard, C.C., Elder, S.T., 1977. The effects of caffeine on reaction time in hyperkinetic and normal children. American Journal of Psychiatry 134, 144–148.

Santos, I.S., Victora, C.G., Huttly, S., Carvalhal, J.B., 1998. Caffeine intake and low birth weight: a population-based case-control study. American Journal of Epidemiology 147, 620–627.

Schnackenberg, R.C., 1973. Caffeine as a substitute for schedule II stimulants in hyperkinetic children. American Journal of Psychiatry 130, 796–798.

Stein, M.A., Krasowski, M., Leventhal, B.L., Phillips, W., Bender, B.G., 1996. Behavioral and cognitive effects of methylxanthines. A meta-analysis of theophylline and caffeine. Archives of Pediatric and Adolescent Medicine 150, 284–288.

Streissguth, A.P., Barr, H.M., Martin, D.C., Herman, C.S., 1980. Effects of maternal alcohol, nicotine, and caffeine use during pregnancy on infant mental and motor development at eight months. Alcoholism, Clinical and Experimental Research 4, 152–164.

Tang, D., Lowry, M.F., Williams, D.G., 1989. Caffeine and babies [Letter]. British Medical Journal 299, 121.