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Effects of Acute Caffeine Administration on Adolescents

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Acute caffeine administration has physiological, behavioral, and subjective effects. Despite its widespread use, few studies have described the impact of caffeine consumption in children and adolescents. The purpose of this study was to investigate the effects of acute caffeine administration in adolescents. We measured cardiovascular responses and snack food intake after acute administration of 0 mg, 50 mg, 100 mg, and 200 mg of caffeine. We also compared usual food intake and subjective effects of caffeine between high- and low-caffeine consumers. Finally, we conducted a detailed analysis of caffeine sources and consumption levels. We found main effects of caffeine dose on heart rate (HR) and diastolic blood pressure (DBP), with HR decreasing and DBP increasing with increasing caffeine dose. There were significant interactions among gender, caffeine use, and time on DBP. High caffeine consumers (>50 mg/day) reported using caffeine to stay awake and drinking coffee, tea, soda, and energy drinks more than low consumers (<50 mg/day). Boys were more likely than girls to report using getting a rush, more energy, or improved athletic performance from caffeine. Finally, when we examined energy and macronutrient intake, we found that caffeine consumption was positively associated with laboratory energy intake, specifically from high-sugar, low-fat foods and also positively associated with protein and fat consumption outside of the laboratory. When taken together, these data suggest that acute caffeine administration has a broad range of effects in adolescents and that the magnitude of these effects is moderated by gender and chronic caffeine consumption.

Keywords: caffeine, drugs, adolescents, eating, gender differences

Caffeine is the most widely used stimulant in the world (Nehlig, 1999). While generally recognized as safe, most of the evidence supporting caffeine safety comes from studies conducted in adults. Given that children ages 12 to 17 are among the fastest-growing segment of the population for caffeine use (Frary, Johnson, & Wang, 2005; Harnack, Stang, & Story, 1999), it is imperative that more empirical data be collected in children and adolescents to understand how acute and chronic caffeine use affect the physiology and behavior of this population. In addition, given the recent attention being paid to caffeine-containing beverages, such as soda and energy drinks, and their relationship to obesity and sleep loss in children, it is important to understand the mechanisms that underlie these associations.

Acute caffeine has dose-dependent effects on subjective response, attention, and physiology in adults and children. For example, moderate doses of caffeine (200–350 mg) decrease heart rate and increase blood pressure in adults (Bender, Donnerstein, Samson, Zhu, & Goldberg, 1997; Lane & Williams, 1987; Sung et al., 1994; Waring, Goudsmit, Marwick, Webb, & Maxwell, 2003). In addition, these same doses of caffeine produce enhanced feelings of well-being, improve concentration, and increase arousal and energy (Garrett & Griffiths, 1997; Griffiths et al., 1990). High doses (>400 mg), however, lead to feelings of anxiety, nausea, jitteriness, and nervousness (Garrett & Griffiths, 1997). Studies in children and adolescents have shown that acute caffeine administration has similar cardiovascular and subjective effects to those described in adults. Doses of caffeine ranging from 100 to 400 mg led to increased reports of nervousness, jitteriness, fidgetiness, and decreased reports of sluggishness in children and adolescents (Bernstein et al., 1994; Elkins et al., 1981; Rapoport et al., 1981). Similar to adults, acute caffeine administration to children and adolescents increases ambulatory blood pressure in a dose dependent manner (Savoca, Evans, Wilson, Harshfield, & Ludwig, 2004; Savoca et al., 2005). Withdrawal from caffeine also produces similar effects in a subset of adolescent caffeine users as those seen in adults, such as headache, drowsiness, and fatigue (Bernstein, Carroll, Thuras, Cosgrove, & Roth, 2002; Hale, Hughes, Oliveto, & Higgins, 1995). However, these effects are seen in fewer children and are more inconsistent than what is typically observed in adult caffeine users (Rapoport et al., 1981). These differences may be because of the amount, type, and pattern of caffeine intake among children and adolescents compared with adults.

Consumption of caffeine-containing beverages in children and adolescents is associated with greater body mass index (BMI; Johnson & Kennedy, 2000; Ludwig, Peterson, & Gortmaker, 2001), greater intake of unhealthy foods, and

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lower intake of healthy foods, such as fruits, vegetables, and milk (Harnack et al., 1999). In children, the primary vehicle for caffeine is soda, which also contains 40 g of sugar per 12-ounce can (Frary et al., 2005; Harnack et al., 1999; Smiciklas-Wright, Mitchell, Mickle, Goldman, & Cook, 2003). Therefore, it is possible that one reason for the association between soda consumption and consumption of less healthy foods is that repeated pairings of sugar and caffeine facilitates the development of enhanced preference for foods and beverages containing added sugar. Sugar is a known "natural reward" that activates similar reward pathways as drugs of abuse, such as cocaine, amphetamine, and nicotine (Robinson & Berridge, 2000). Intermittent access to sugar in food-deprived rats leads to both behavioral and neurochemical (Avena & Hoebel, 2003; Colantuoni et al., 2001) similarities to drug addiction. Because of the well-established similarities between sugar and drugs of abuse (reviewed in Avena, Rada, & Hoebel, 2008), the possibility exists that caffeine can potentiate sensitivity to, liking of, and consumption of sugar, just as it does with nicotine (Jones & Griffiths, 2003; Puccio, McPhillips, Barrett-Connor, & Ganiats, 1990; Swanson, Lee, & Hopp, 1994). In addition, because caffeine can also activated the dopaminergic system (Fuxe et al., 2003; Kudlacek et al., 2003; Salim et al., 2000), caffeine paired with high levels of added sugar in foods and beverages may act synergistically to release dopamine and, as a consequence, increase the reinforcing properties of sweetened foods and beverages. To date, there have been no studies examining potential links between sugar consumption and caffeine use in children.

A previous study from our laboratory found that boys found caffeinated soda more reinforcing than did girls after a 2-week exposure period using a double-blind, placebo-controlled design (Temple, Bulkley, Briatico, & Dewey, 2009). To our knowledge, this was the first study to report a gender difference in response to caffeine in adolescents. In adults, some gender differences have been reported. For example, caffeine reduces the risk of Parkinson's disease in men only (Ascherio et al., 2004; Ascherio et al., 2001; Benedetti et al., 2000; Ross et al., 2000), suggesting that there are gender differences in neurobiological responses to caffeine. Similar gender differences have been reported for subjective effects of caffeine. For example, one study examining the effects of acute caffeine administration on subjective state showed greater effects in men than women (Adan, Prat, Fabbri, & Sanchez-Turet, 2008). This was despite the fact that all participants were given the same dose of caffeine (100 mg), resulting in a higher mg/kg dose in girls. It is possible that gender differences in responses to caffeine administration are mediated by differences in circulating steroid hormones. This hypothesis is supported by studies showing that caffeine consumption (Kotsopoulos, Eliassen, Missmer, Hankinson, & Tworoger, 2009) and subjective responses to caffeine (Terner & de Wit, 2006) vary across the menstrual cycle. These gender differences in subjective and reinforcing effects of caffeine may mediate differences in intake patterns and motivations for caffeine usage.

The purpose of this study was to investigate the dose dependent effects of acute caffeine administration in relation to level of chronic caffeine use in adolescent boys and girls. We used a double-blind, placebo controlled design to test cardiovascular and subjective responses to caffeine as well as acute snack food ingestion. This is among the first studies to examine the effects of acute caffeine administration in this age group. The data from this study will help determine the effects of acute and chronic caffeine use in adolescents and add to the growing body of literature on gender differences in drug responses.

Method

Participants and Recruitment

Adolescents, ages 12 to 17 years old, were recruited through direct mailings, flyers distributed at local middle and high schools, as well as flyers posted around the University at Buffalo and the surrounding community. Eligibility criteria included the following: previous experience with caffeine with no adverse reactions, not using hormone-based contraceptives, not smoking, not on any medication that could have adverse interactions with caffeine (e.g., methylphenidate), and willing to visit the laboratory on four occasions for 90 min each time. Stratification of usual caffeine consumption was estimated based on the participant's self-report of daily or weekly intake of caffeine from all major sources, including tea (40 mg/5 oz), soda (40 mg/12 oz), coffee (100 mg/5 oz), energy drinks ($\sim$150 mg/12 oz), chocolate (10 mg/oz), and caffeine-containing pills (Excedrin or No-Doze, 130–200 mg/pill). These estimates of caffeine content are based on information published by the U.S. Department of Nutritional Services. An equal number of children were recruited within each of the following caffeine consumption groups: 0–25 mg/day, 25–50 mg/day, 50–75 mg/day, $>$75 mg/day. This was done to have a sample that was balanced for typical caffeine use. We began with a total of 55 participants. We had one drop out before the study was completed and data from two individuals were removed because they had salivary caffeine levels indicative of recent usage. This left us with a total of 52 participants (26 boys, 26 girls).

Telephone Screening

Interested participants called our laboratory or completed an online survey to provide basic information, including names of parent and child, address, telephone number, child's date of birth, child's height and weight, any medications or health problems in the child, including dietary restrictions, latex allergies, and neurological disorders. Then we spoke to the child about amount and sources of caffeine consumption to attain an estimate of typical usage. If the child met the above eligibility criteria and was interested in participating, he or she was scheduled for four laboratory visits. Parents and participants were also instructed prior to each visit that the participant needed to abstain from consumption of caffeine for 24-hr and to not eat or drink anything other than water for 2 hours.

General Experimental Procedures

All questionnaires and measurement procedures are described in more detail below. Upon arrival to the laboratory, parents and participants were given consent and assent forms to read and sign. To remove subject expectations about the effects of caffeine, participants were told that "the purpose of the study is to determine how substances commonly found in soft drinks affect mood and physiological measurements, such as heart rate and blood pressure" and that the beverage they would be consuming "may have levels of one or more of the following substances manipulated: sugar, aspartame, Splenda, caffeine, or artificial coloring. The levels of these substances will not exceed what is considered safe by the Food and Drug Administration." This deception was considered acceptable because it involved no greater than minimal risk, and was necessary to prevent potential preconceptions of caffeine's effects from altering experimental results. Participants then completed a 24-hr dietary and physical activity recall while the parent completed a demographic questionnaire. Parents were then escorted from the room and participants provided a 3-ml saliva sample into a sterile tube that was analyzed for caffeine and steroid hormones. The participant then completed the Behavioral Checklist Questionnaire. He or she then had baseline blood pressure and heart rate readings taken. Then, the participants consumed a drink containing 0 mg, 50 mg, 100 mg, or 200 mg of caffeine. Each dose was administered on a separate visit and the order in which they were administered was counterbalanced. Blood pressure and heart rate measurements were then taken every 10 min for a total of 60 min. During the hour, participants viewed a National Geographic Video of their choice. After 1 hr, participants completed the Behavioral Checklist a second time and an ad libitum snack food eating session.

The participant returned to the laboratory for three more visits following identical procedures. In between visits, participants were asked to complete the Block Kids Food Frequency Questionnaire (described below). After the final session, participants had their height and weight measured. Both the participant and their parent were debriefed and compensated for participation. All study procedures were conducted in accordance with National Institutes of Health (NIH) guidelines for the use of humans in research and with the approval of the University at Buffalo Social and Behavioral Sciences Institutional Review Board.

Caffeine and Beverage Preparation

Caffeine and placebo treatments were prepared by an experimenter who was not involved in the data collection for this study. Caffeine at each concentration (50 mg, 100 mg, or 200 mg) was dissolved in flattened Sprite to facilitate masking of the bitter taste of the caffeine. Sprite was flattened by heating it to 140°C and stirring it at a speed of 50 rpm for 25 min. Flattened Sprite without the added caffeine was used as the placebo. The caffeine or placebo solutions were then aliquoted into 14-ml vials labeled A–D and frozen. On the day of the visit, the appropriate dose was thawed for 1 to 2 hr at room temperature. To remove expectancies about caffeine, participants were able to choose to drink orange juice, lemonade, or Sprite, which are all caffeine-free. On the first laboratory visit, participants were provided 2-oz samples of each beverage and were asked to rate how much they liked them using a 7-point Likert scale anchored with 1 = *not at all* and 7 = *extremely*. The drink with the highest rating was chosen. While the participant was providing a saliva sample and completing questionnaires, the researcher prepared 288 ml of the selected drink, to which 12 ml of placebo of caffeine (A, B, C, or D) were added.

Salivary Caffeine Measurement

Saliva collection was conducted at the beginning of each laboratory visit. Participants were instructed to expectorate into a tube with a funnel attached. They provided 3 ml of saliva, without air bubbles. This line was indicated for them on the outside of the sterile vile with a sticker labeled with participant number and visit letter. Participants were given a piece of wax which they could chew to facilitate saliva production.

To verify 24-hr caffeine abstinence, the saliva sample provided on the visit where the participant received the placebo beverage was analyzed. Samples were stored at −20 °C until analyzed. Analyses of caffeine content was conducted by LabStat (Kitchner, Ontario) using a standard gas chromatography method with a structural analogue of caffeine used as an internal standard (Liguori, Hughes, Goldberg, & Callas, 1997). Participants were considered abstinent if caffeine levels fell below 0.85 μg/ml, which is consistent with overnight caffeine abstinence (Evans, Critchfield, & Griffiths, 1994; Griffiths & Woodson, 1988; Liguori et al., 1997).

Cardiovascular Responses

An automated heart rate and blood pressure monitor (Tango; SunTech Medical, Inc., Morrisville, NC) was used to collect cardiovascular measurements. The participants were seated in reclined position and instructed to relax. The nondominant arm was slipped into the blood pressure cuff, with the microphone placed over the brachial artery, between the bicep and tricep muscles. The cuff was wrapped around the participants arm. Electrodes were placed on each forearm and on the chest above the heart. A baseline reading was conducted prior to consumption of the test beverage. Then readings were taken every 10 min for 60 min. In between readings, participants watched a video. One minute prior to each reading, the video was shut off and the participant was instructed to sit in silence and relax. The video resumed after the reading was recorded.

Measurements

Weight, height, BMI. Participant weight was assessed by use of a digital scale (SECA; Hanover, MD). Height was assessed using a SECA stadiometer. On the basis of the height and weight data BMI was calculated according to the following formula: BMI = kg/m^2.

Behavioral checklist. A questionnaire containing 31 adjectives describing mood and physiological symptoms was presented to the participants at the beginning and end of each session. The participants were asked to rate how they felt "right now" on a 9-point Likert-type scale anchored by 1 = "*not at all*" and 9 = "*extremely*." This questionnaire has been used by multiple investigators (Richardson, Rogers, & Elliman, 1996; Yeomans, Pryke, & Durlach, 2002) and is sensitive to caffeine use (Richardson, Rogers, Elliman, & O'Dell, 1995). The participant rated their subjective experience of each adjective on a 9-point Likert-type anchored by 1 = "*not at all*" and 9 = "*extremely*" (Hughes et al., 1991). The items on the list were as follows: anxious, alert, content, depressed, dizzy, drowsy, fatigued, frequent urination, headache, insomnia, irregular heartbeat, diarrhea, impatient, hungry, irritable, motivated to work, well-being, mood swings, muscle twitches, talkative, nausea, palpitation, restlessness, ringing in ears, energetic, stomachache, vigorous, perspiration, tremor, sleepy, and tired. Participants were told to indicate how they felt at that exact moment. This questionnaire was completed on a lap top using Survey Monkey.

24-hr food and exercise recall. The participant (with the assistance of the parent) recalled his or her dietary intake and physical activity for the previous 24 hr. Any participant who had not complied with the study protocol (caffeine abstinence for 24 hr) would have been rescheduled, but we did not have anyone who was not compliant based on self-report.

Ad libitum snack food eating. Participants were given access to a variety of snack foods differing in fat and sugar content along with water ad libitum. The foods were provided in 300 kcal portions and were as follows: Skittles and Smarties (high sugar/low fat), potato chips and Doritos (low sugar/high fat), and M&Ms and Twix (high sugar/high fat). Participants were told that they were completing a taste test and that they needed to sample each food and rate its liking using a 7-point Likert scale anchored with 1 = "*not at all*" and 7 = "*extremely*." They were told that they could eat as much as they wanted of each food because it would have to be discarded after the session. We have used this procedure previously in adults (Epstein et al., 2007).

Block Kids Food Frequency Questionnaire (2004). A 77-item Food Frequency Questionnaire developed for use in 8- to 17-year-olds was issued to assess food intake patterns. This questionnaire asks how many times in the past week they have consumed certain foods. For each food, participants chose from among the following: None, 1 day, 2 days, 3–4 days, 5 to 6 days, every day. Once they selected how many times food were consumed, they indicated typical portion sizes using pictures to help with their selections.

Caffeine use questionnaire. This questionnaire was adapted from Miller (Miller, 2008) and was designed to assess sources, amounts, and frequency of caffeinated food and beverage intake as well as reasons why adolescents use and/or do not use caffeine. Individuals were asked to report whether they ever drink caffeinated beverages, reasons for drinking caffeinated beverages, and the types and frequency of caffeinated beverages they normally drink.

Demographic questionnaire. While the participant was reading over the assent form and being explained the study procedures, parents filled out a demographic questionnaire. They were informed that this was for research purposes only and if they did not feel comfortable answering some/any of the questions, they were not required to do so. Information on this sheet included: who currently lived in the household where the participant resided, the marital status of the primary caregiver of the child, which households the participant spent time in and how much time was spent in them, the highest level of education completed by the primary caregiver and their spouse, the occupation of the primary caregiver and their spouse, the employment status of the primary caregiver and their spouse, where the total household income was derived from, the amount of the total household income, and the parent and participant's ethnicity and race.

Analytic Plan

The potential differences between subjects were analyzed using a one-way analysis of variance (ANOVA), with gender and caffeine use group (low vs. high) as the between subjects factors. Caffeine use group was determined using a median split for caffeine use with anyone consuming <50 mg/day considered a low user and anyone consuming ≥ 50 mg/day being considered a high user. This is consistent with our previous study (Temple et al., 2009) in which that average caffeine consumption of our sample was found to be 52 mg/day. Potential differences in categorical variables, such as race, household income, and parental education, were analyzed using χ^2. The pattern of diastolic and systolic blood pressure and heart rate were analyzed using mixed effects regression models with gender, caffeine use (mg/day), and BMI as time invariant predictors and time and drug dose as time variant predictors and baseline blood pressure and heart rate as covariates. Answers on the behavioral checklist were analyzed using a mixed effects regression model with gender, caffeine use (mg/day), and BMI as time invariant predictors and drug dose and pre/post as time variant predictors. Energy intake was analyzed using a mixed-effects regression model with usual caffeine consumption (mg/day), gender, and BMI as time invariant predictors and acute caffeine dose as the time variant predictor. All data were considered significantly different if $p < .05$ and data analyses were conducted using SYSTAT 11.0 (Chicago).

Results

Participants

Participants were male ($n = 28$) and female ($n = 26$) 12- to 17-year-olds. Data from two high-consuming boys were eliminated from analyses because they had salivary caffeine levels indicative of recent usage. This left us with 26 boys (9 low consumers and 17 high consumers) and 26 girls (17 low consumers and 9 high consumers) for the remaining

analysis. At the time of screening, participants were placed into groups based on their self-reported caffeine use during the phone interview and at this time, the groups were balanced for age and gender. After the participants completed the caffeine use questionnaire, which was considerably more detailed than what we used for our telephone screening, we recalculated their daily usage and some participants were reassigned to different groups. This is why we ended up with an unequal distribution of participants in each caffeine consumption group. When we analyzed participant characteristics by gender and caffeine consumption group, we found no relationships between caffeine use group or gender and BMI, parental education, household income, or race ($p > .05$). There was a significant relationship between caffeine use group and the amount of caffeine consumed, $F(1, 48) = 26.3$; $d = 1.6$; $r = .62$; $p < .0001$, and age, $F(1, 48) = 7.6$; $d = 0.65$; $r = .31$; $p = .04$. These data are shown in Table 1.

Caffeine Sources and Reasons for Consumption

We found that the majority of participants in this study reported consuming caffeine at least occasionally (96%) and that the single largest source of caffeine for the majority of participants was soda (92%; Table 2). There was a significant difference in the proportion of low- and high-caffeine consumers that drink coffee, $\chi^2(1) = 5.13$; $p = .02$; soda, $\chi^2(1) = 4.0$; $p = .045$; and energy drinks, $\chi^2(1) = 11.9$; $p = .001$, with a larger proportion of high consumers than low consumers drinking these beverages. There was also a difference in daily total caffeine consumption, $F(1, 48) = 26.3$; $d = 1.59$; $r = .62$; $p < .0001$; and daily caffeine consumed from coffee, $F(1, 48) = 10.00$; $d = 0.97$; $r = .44$; $p = .003$; tea, $F(1, 48) = 6.3$; $d = 0.76$; $r = .36$; $p = .015$; soda, $F(1, 48) = 11.66$; $d = 0.96$; $r = .43$; $p = .001$; and energy drinks, $F(1, 48) = 5.99$; $d = 0.84$; $r = .39$; $p = .018$, as a function of caffeine consumption group (Table 2).

There were gender differences in the proportion of participants consuming caffeine from different sources. A larger proportion of boys than girls reported consuming energy drinks, $\chi^2(1) = 4.3$; $p = .04$, and a larger proportion of girls consume tea than boys, $\chi^2(1) = 6.2$; $p = .01$. There were also gender differences in average daily caffeine consumption, $F(1, 50) = 5.02$; $d = 0.62$; $r = .297$; $p = .03$, as well as amount of caffeine from energy drinks, $F(1, 50) = 4.97$; $d = 0.62$; $r = .296$; $p = .03$, with boys consuming more than girls. In terms of reasons for caffeine consumption, boys were more likely than girls to report using caffeine for energy, $F(1, 48) = 6.2$; $d = 0.88$; $r = .40$; $p = .02$; to get a rush, $F(1, 48) = 11.06$; $d = 1.12$; $r = .49$; $p < .0001$; or to enhance athletic performance, $F(1, 48) = 12.2$; $d = 1.08$; $r = .48$; $p = .001$; Figure 1).

Blood Pressure and Heart Rate

There were main effects of drug dose on HR ($\beta = -0.015$; $SE = 0.005$; $Z = -3.34$; $p = .001$; Figure 2a) and DBP ($\beta = 0.04$; $SE = 0.005$; $Z = 7.2$; $p < .0001$; Figure 2b). There were also main effects of baseline readings on HR ($\beta = 0.82$; $SE = 0.04$; $Z = 20.71$; $p < .0001$), DBP ($\beta = 0.75$; $SE = 0.052$; $Z = 14.5$; $p < .0001$), and SBP (all $p < .0001$). There was an interaction of gender, caffeine use (mg/day), and time on DBP ($\beta = -0.001$; $SE < 0.0001$; $Z = -2.3$; $p = .02$), but no interactions for SBP or HR (all $p \geq .34$). When this interaction was probed by examining each caffeine use group separately, we found that, in low consumers, there were main effects of time ($\beta = 0.07$; $SE = 0.02$; $Z = 4.1$; $p < .0001$) and baseline DBP

Table 1
Participant Characteristics Shown by Gender and Caffeine Use Group

	Male		Female	
	Low ($n = 9$)	High ($n = 17$)	Low ($n = 17$)	High ($n = 9$)
	Mean ± *SEM*			
Age	13.4 ± 0.4	14.7 ± 0.3[a]	13.8 ± 0.3	14.4 ± 0.4[a]
Body mass index	21.7 ± 1.7	22.1 ± 0.7	21.3 ± 1.0	21.3 ± 1.8
	N (%)			
Race				
Caucasian	6 (67)	12 (71)	15 (88)	7 (78)
African American	2 (22)	4 (24)	1 (6)	1 (11)
Asian	1 (11)	0 (0)	0 (0)	0 (0)
Other	0	1 (6)	1 (6)	1 (11)
Parental education				
High school	1 (11)	1 (6)	1 (6)	2 (22)
College	7 (78)	11 (65)	10 (59)	6 (67)
Graduate school	1 (11)	5 (29)	6 (35)	1 (11)
Household income				
<$30,000	1 (11)	6 (35)	2 (12)	0 (0)
$30,000–$50,000	2 (23)	3 (18)	3 (18)	1 (11)
$50,000–$70,000	3 (33)	1 (6)	5 (29)	3 (33)
$70,000	3 (33)	7 (41)	7 (41)	5 (56)

[a] Significant differences as a function of caffeine use ($p < .05$).

Table 2
Caffeine Usage From Different Sources in Male and Female Adolescents With Different Levels of Caffeine Use

	Males				Females			
	Low (n = 9)		High (n = 17)		Low (n = 17)		High (n = 9)	
Drink caffeine	8 (89)		17 (100)		16 (94)		9 (100)	
Daily consumption (mg)	22.86[a]	5.1	145.5	26.2	21.5[a,b]	3.4	108.3[b]	14.0
Coffee	0 (0)[a]		7 (41)		5 (29)[a]		5 (56)	
Daily consumption (mg)	1.6[a]	1.6	25.2	7.5	4.6[a]	2.2	16.7	6.7
Tea	4 (44)		5 (29)		12 (71)[b]		6 (67)[b]	
Daily consumption (mg)	9.8[a]	4.4	30.6	10.8	7.4[a]	2.4	26.9	10.7
Soda	7 (78)[a]		17 (100)		15 (88)[a]		9 (100)	
Daily consumption (mg)	9.1[a]	1.7	32.9	7.1	8.2[a]	2.8	46.2	12.9
Energy drinks	1 (11)[a]		11 (65)		2 (12)[a,b]		3 (33)[b]	
Daily consumption (mg)	2.4[a]	7.1	56.7	18.9	1.3[a]	1.3	18.5	16.5

Note. For each category, the top set of numbers is the number of participants who reported at least occasional consumption of each of the caffeine sources, n(%), and underneath the numbers is the mean and SE of the mean daily consumption (mg) of caffeine from each of these sources. Proportions of users were analyzed using χ^2 across caffeine consumption group and gender. Differences in the amount of daily caffeine use were analyzed using a one-way analysis of variance with gender and caffeine consumption group as the between subjects variables.
[a] Significant differences as a function of caffeine consumption group. [b] Significant differences as a function of gender.

(β = 0.73; SE = 0.07 Z = 11.03; $p < .0001$), but no interactions or effects of gender. In high consumers, there were main effects of gender (β = 3.98; SE = 1.97; Z = 2.02; $p = .043$), drug dose (β = 0.025; SE = 0.008; Z = 3.13; $p = .002$), time (β = 0.07; SE = 0.025; Z = 2.63; $p = .009$), and baseline DBP (β = 0.774; SE = 0.08; Z = 9.73; $p < .0001$). There were also interactions between gender and time ($\beta = -0.073$; SE = 0.028; Z = −2.58; $p = .01$) and gender and drug dose ($\beta = -0.037$; SE = 0.008; Z = −4.74; $p < .0001$). When this interaction was probed by examining each gender separately, we found main effects of drug dose (β = 0.029; SE = 0.0089 Z = 3.15; $p = .02$), time (β = 0.117; SE = 0.03; Z = 4.01; $p < .0001$), and baseline DBP (β = 0.76; SE = 0.08; Z = 10.00; $p < .0001$) as well as an interaction of caffeine consumption (mg/day) and time ($\beta < -0.0001$; SE <0.0001; Z = −2.17; $p = .03$) in boys (Figure 3A). In girls, there was a main effect of baseline DBP (β = 0.72; SE = 0.08; Z = 9.4; $p < .0001$), but no other main effects or interactions were observed (all $p \geq .15$; Figure 3B).

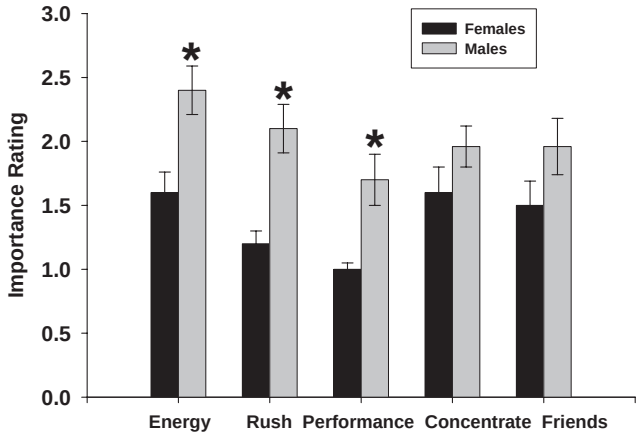


Figure 1. Mean ± *SEM* importance rating for a series of reasons why people may use caffeine in boys (gray bars) and girls (black bars). Participants were asked to indicate how important each reason was for why they consume caffeine on a 4-point scale, where 1 = *very unimportant*, 2 = *moderately unimportant*, 3 = *moderately important*, and 4 = *very important.* Boys rated energy, getting a rush, and athletic performance as more important than did girls, but there was no difference in ratings of importance for concentration or because friends are consuming caffeine. The data were analyzed using an analysis of variance with gender and caffeine consumption group as between-subjects factors. * $p < .05$.

Caffeine Consumption and Laboratory Snack Food Intake

There was a relationship between usual caffeine consumption and energy from high-sugar/low-fat foods (β = 0.59; SE = 0.15; Z = 3.97; $p < .0001$; Figure 4), with higher caffeine consumption associated with greater intake of energy from high-sugar foods. There were no differences as a function of caffeine consumption group for intake of high-sugar/high-fat or low-sugar/low-fat foods (both $p > .10$). There were main effects of BMI on total energy consumption (β = 30.74; SE = 14.4; Z = 2.13; $p = .03$) and consumption of high-sugar/high-fat foods (β = 10.54; SE = 4.0; Z = 2.64; $p = .008$), but there were no interactions between BMI and any of the other predictors in the model (all $p > .20$). There were no effects of gender or acute caffeine dose (all $p > .05$) on snack food intake.

Caffeine Consumption and Usual Nutrient Intake

When we analyzed the data from the food frequency questionnaire, we found a significant main effect of caffeine consumption group on total daily intake of energy, $F(1, 45) = 4.1$; d = 0.67; r = .32; $p = .049$; energy intake from protein, $F(1, 45) = 5.1$; d = 0.71; r = .33; $p = .029$; and energy intake from fat , $F(1, 45) = 4.1$; d = 0.66; r = .31;

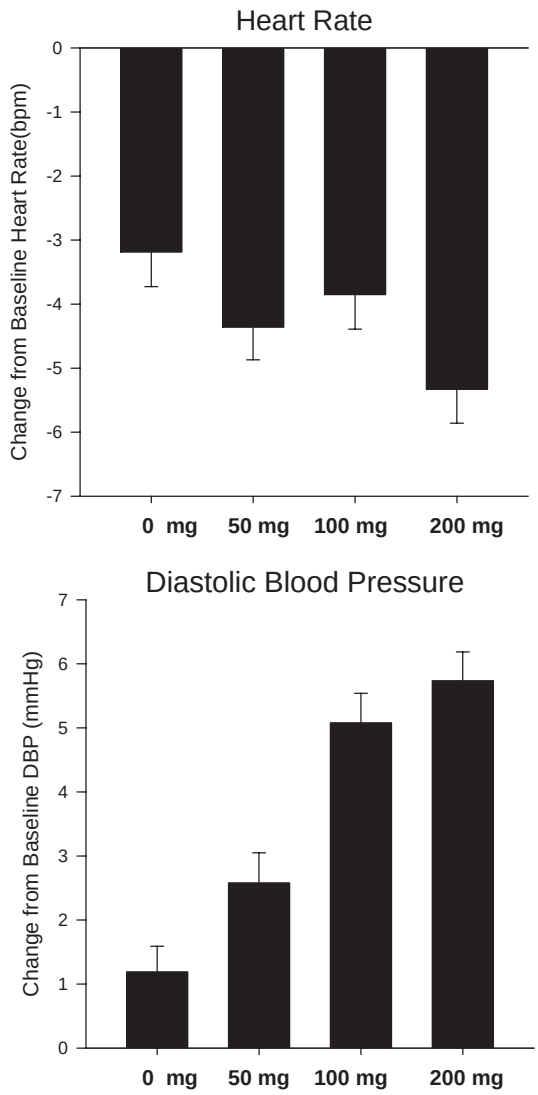


Figure 2. Mean ± *SEM* change from baseline heart rate (top) and diastolic blood pressure (bottom) after administration of placebo (0 mg) or 50, 100, or 200 mg of caffeine. We found a main effect of drug dose on each of these measures, with a dose-dependent decrease in heart rate ($p = .001$) and a dose-dependent increase in diastolic blood pressure ($p < .0001$).

$p = .048$, with high-caffeine consumers having higher consumption of total energy, protein, and fat compared with low-caffeine consumers. When we examined the percentage of energy from the various macronutrient sources, there were no differences as a function of caffeine or gender. In addition, there were no differences as a function of caffeine consumption group or gender on the number of servings of vegetables, grains, fruit, or fat. There was a significant effect of caffeine consumption group on daily servings of meat, $F(1, 45) = 6.2$; $d = 0.81$; $r = .37$; $p = .017$, with high-caffeine consumers reporting greater meat consumption than low-caffeine consumers. There was also a gender by group interaction on daily servings of dairy, $F(1, 45) = 5.6$; $p = .02$, with male dairy intake decreasing as caffeine consumption increased and female dairy consumption increasing as caffeine consumption increased.

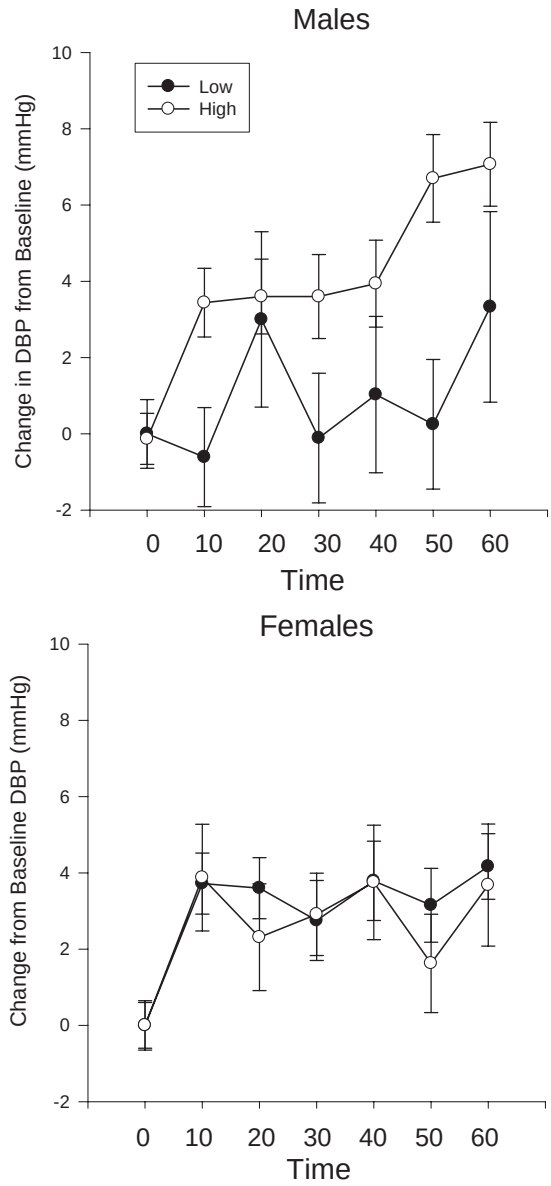


Figure 3. Mean ± *SEM* change from baseline diastolic blood pressure at baseline and every 10 minutes after administration of caffeine in male (top) and female (bottom) low-caffeine consumers (<50 mg/day; black circles) and high-caffeine consumers (>50 mg/day; white circles). We found a three-way interaction of caffeine use, gender, and time ($p = .008$) on diastolic blood pressure. When this interaction was probed by examining each gender differently, we found main effects of drug dose ($p = .002$), time ($p < .0001$), and baseline diastolic blood pressure ($p < .0001$), as well as an interaction of caffeine consumption (mg/day) and time ($p = .03$) in boys. In girls, there was a main effect of baseline diastolic blood pressure ($p < .0001$), but no other main effects or interactions were observed.

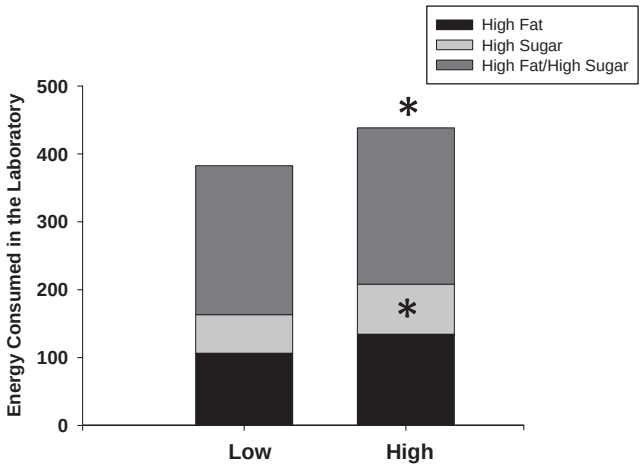


Figure 4. Laboratory energy intake from high-fat/low-sugar (black), high-sugar/low-fat (light gray) and high-sugar/high-fat (dark gray) snack foods in low- (left) and high-caffeine (right) consumers. Each participant was given 300 kcal portions of two foods in each macronutrient category and allowed to consume as little or as much as they wanted. The data were analyzed using an analysis of variance with gender and caffeine consumption group as between subjects factors. * $p < .05$. High-caffeine consumers ate more total energy than low consumers ($p = .003$). This was because of differences in intake of high-sugar/low-fat foods ($p = .01$).

Behavioral Checklist

When we examined the behavioral checklist data, we found effects on only a subset of the adjectives. There were main effects of pre/post on alertness ($\beta = -0.614$; $SE = 0.19$; $Z = -3.26$; $p = .001$), contentment ($\beta = -0.46$; $SE = 0.22$; $Z = -2.08$; $p = .037$), motivation to work ($\beta = -0.48$; $SE = 0.182$; $Z = -2.64$; $p = .008$), muscle twitches ($\beta = 0.35$; $SE = 0.097$; $Z = 3.59$; $p < .0001$), talkative ($\beta = -0.68$; $SE = 0.197$; $Z = -3.45$; $p = .001$), and energy ($\beta = -0.586$; $SE = 0.20$; $Z = -2.95$; $p = .003$). There were main effects of gender on contentment ($\beta = 1.29$; $SE = 0.645$; $Z = 2.00$; $p = .045$) and heart palpitations ($\beta = -0.177$; $SE = 0.084$; $Z = -2.11$; $p = .035$). There were main effects of usual caffeine consumption on anxiety ($\beta = 0.005$; $SE = 0.002$; $Z = 2.12$; $p = .034$). There were interactions of caffeine use and drug dose on fatigue ($\beta < -0.0001$; $SE < 0.0001$; $Z = -2.07$; $p = .038$) and stomachache ($\beta < 0.0001$; $SE < 0.0001$; $Z = 3.49$; $p < .0001$). There were three-way interactions of sex, drug dose, and pre/post on ($\beta = 0.006$; $SE = 0.002$; $Z = 2.59$; $p = .01$) and on tremor ($\beta = 0.002$; $SE = 0.001$; $Z = 1.98$; $p = .047$). There were three-way interactions of usual caffeine consumption, drug dose and pre/post on fatigue ($\beta < 0.0001$; $SE < 0.0001$; $Z = 2.802$; $p = .005$), energy ($\beta < 0.0001$; $SE < 0.0001$; $Z = 2.03$; $p = .043$), and stomach ($\beta < -0.0001$; $SE < 0.0001$; $Z = -2.56$; $p = .011$). There was also a three-way interaction of usual caffeine consumption, drug dose and pre/post on anxiety ($\beta < -0.0001$; $SE < 0.0001$; $Z = 2.013$; $p = .044$).

Discussion

This study investigated the relationship between acute and chronic caffeine consumption and cardiovascular effects, subjective responses, and ingestive behavior in adolescents. In order to accomplish this, we conducted a double-blind, placebo controlled, dose-response study in 12- to 17-year-olds. Consistent with previous studies, we found dose-dependent increases in DBP and decreases in HR. We found no relationship between typical caffeine consumption and DBP in response to acute caffeine consumption in girls, but in boys, high-caffeine consumers showed greater increases in DBP over time than did low-consuming boys. Boys also rated "to get energy," "to get a rush," and "athletic performance" as more important reasons for using caffeine compared with ratings from girls. When taken together, these findings suggest that boys and girls differ in their responses to caffeine. When we examined ingestive behavior as a function of chronic and acute caffeine use, we found that high- and low-caffeine consumers differed in macronutrient intake, with high consumers having more energy, protein, and fat in their typical diet and consuming more high-sugar snack foods in the laboratory compared with low-caffeine consumers. More studies need to be conducted to determine the mechanism that underlies these gender differences in response to caffeine.

In adults (Bender et al., 1997; Lane & Williams, 1987; Sung et al., 1994; Waring et al., 2003) and adolescents (Bernstein et al., 2002; Savoca et al., 2004; Savoca et al., 2005) acute administration of caffeine increases BP and decreases HR in a dose-dependent manner. Consistent with these findings, we demonstrated a dose-dependent decrease in HR after caffeine administration that was independent of gender and level of habitual caffeine consumption. We also showed a main effect of drug dose on DBP, but this effect was moderated by gender and level of chronic caffeine consumption. Specifically, both high- and low-consuming boys showed increases in DBP over time after caffeine administration, but the magnitude of the increase was greater in high-consuming boys than in low-consuming boys. In girls, there was an increase in DBP after 10 min, but then no further increases after that and no difference in responses as a function of chronic caffeine use. When taken together, our data demonstrate that boys and girls respond differently to acute caffeine administration.

In addition to gender differences in cardiovascular responses to acute caffeine administration, gender was associated with the types, amount, and motivations for caffeine consumption. Boys reported consuming more energy drinks and girls reported consuming more tea. Energy drinks have significantly more caffeine than tea. Perhaps boys enjoy or require larger doses of caffeine than girls. Alternatively, energy drink consumption may be elevated in boys because of energy drink marketing directly to adolescent and young adult males (Reissig, Strain, & Griffiths, 2009). Boys were also more likely than girls to report using caffeine for energy, to get a rush, or to enhance performance. These subjective effects of caffeine are more likely to occur after ingestion of higher acute doses of caffeine, which could also

explain the differences in the type of caffeinated drinks consumed. We are not the first to report gender differences in caffeinated beverage consumption. Kathleen Miller has reported that male college students are significantly more likely to consume energy drinks than girls (Miller, 2008). The question remains, are girls consuming energy drinks less frequently because they do not experience the positive subjective effects of caffeine or are they not experiencing the positive subjective effects of caffeine because they are less likely to consume energy drinks?

Gender differences have been reported for subjective and physiological responses to other drugs of abuse. For example, work from Harriet de Wit's laboratory has demonstrated that boys and girls have different subjective responses to drugs such as amphetamine. In addition, within girls, subjective responses to amphetamine change across the menstrual cycle (Terner & de Wit, 2006). One potential mechanism for gender differences in response to acute caffeine administration is that estradiol is known to decrease the metabolism of caffeine (Pollock et al., 1999). This affects the half-life of the caffeine and could affect the maximal blood level by lengthening the dose response curve (Granfors, Backman, Laitila, & Neuvonen, 2005). It is also possible that there are differences in caffeine use between boys and girls that lead to differential responses. For example, in our study, there was a trend for boys in the high-consuming group to consume more caffeine than girls in the same group (146 mg/day vs. 108 mg/day; $p = .07$). While we might predict that if boys are consuming more caffeine than girls, they would be more likely to develop tolerance and would, therefore, have reduced effects of caffeine. Conversely, it is possible that girls consume less because they do not experience the positive, stimulating effects that the boys appear to find reinforcing (Temple et al., 2009). It is also possible that boys sensitize to the effects of acute caffeine administration. We found that the increase in DBP after acute caffeine administration was greater in high-consuming boys than in low-consuming boys. To our knowledge, no previous studies have reported sensitization to the effects of caffeine, and our results are too preliminary to draw any conclusions about sensitization. However, sensitization occurs to many other drugs and it would be important to determine if there are gender differences in sensitization to the effects of caffeine.

In contrast to gender differences in cardiovascular and subjective effects of caffeine, we did not find gender differences in the relationship between caffeine use and energy or macronutrient intake. We did, however, find a relationship between usual caffeine consumption and energy and macronutrient intake. Specifically, high-caffeine consumers ate more energy both in the laboratory (as assessed by snack food intake) as well as outside of the laboratory (as assessed by food frequency questionnaire) compared with low consumers. In addition, high consumers ate more high-sugar, low-fat foods in the laboratory and consumed more protein and fat outside of the laboratory. This suggests an association between chronic caffeine use and intake of higher energy density foods. Previous studies have report and association between caffeine consumption and intake of other types of foods. Harnack and colleagues reported that soda consumption is inversely correlated with fruit, vegetable, milk intake and positively correlated with intake of "junk food" (Harnack et al., 1999). In addition, children who consume soda on a regular basis are at higher risk for obesity (Johnson & Kennedy, 2000) and for every additional serving of sugar-sweetened beverages consumed daily, there is a 60% increase in the odds of becoming obese (Ludwig et al., 2001). Therefore, the relationship between soda consumption and weight may be mediated by poor diet. Despite finding a relationship between caffeine consumption and energy intake, we did not find a similar relationship with BMI or body weight. It is possible that gender mediated the relationship between caffeine use and energy intake because boys consumed more caffeine and boys have greater energy needs compared with girls at this age. Another possibility is that because we limited or study population to nonoverweight adolescents that we were missing the heaviest children. If overweight children were included in the study, we may have observed a relationship between BMI and caffeine consumption.

We had several findings from the Behavioral Checklist. The most consistently observed finding was that acute caffeine administration altered responses on this questionnaire, including increases in alertness, contentment, motivation to work, talkative, and energy and decreases in muscle twitches. None of the pre/post effects were moderated by usual caffeine use, suggesting that, at least for a subset of the adjectives on this questionnaire, there was no evidence of tolerance. In addition, similar to effects of acute caffeine administration on food intake in the laboratory, there were no interactions with gender and any other factors on Behavioral Checklist responses, suggesting that subjective physiological and mood changes may be less susceptible to moderation by steroid hormones or other gender-related factors. A previous study in adolescent caffeine users reported that acute caffeine use decreased reports of depression, sleepiness, and fatigue and increased reports of irregular heartbeat and talkative (Hale et al., 1995). Although the study population in this study was 11- to 15-year-olds that consumed at least one can of soda per day, the findings are similar to ours in that, at least for some subjective measures, chronic caffeine use does not eliminate the acute effects of caffeine, suggesting that tolerance to these effects is minimal. It is, however, important to consider that in our study and in the Hale et al. study, participants were overnight withdrawn from caffeine. Therefore, the acute effects of caffeine may have been because of withdrawal reversal as opposed to positive stimulating effects. This distinction is important, as there are many studies suggesting that the majority of the positive effects of caffeine in chronic caffeine users are merely the result of removal of the negative effects of caffeine abstinence (James & Rogers, 2005; Rogers, Martin, Smith, Heatherley, & Smit, 2003; Yeomans, Ripley, Davies, Rusted, & Rogers, 2002).

This study had several strengths, including a double-blind, placebo controlled, within-subjects, dose-response design, biological confirmation of caffeine abstinence, and efforts to conceal the nature of the study. In addition, children and

adolescents are an understudied population in terms of caffeine use. This study adds to the small, but growing body of literature on the effects of caffeine in this population. This study was not without limitations. First, although we stratified for caffeine consumption in order to get a wide range of caffeine consumers, we did not recruit many very high-caffeine consumers (>200 mg/day). Therefore, we may be missing the population that is the most dependent on caffeine. Second, our sample was small and very homogeneous in terms of race, income, and education. This limits the generalizability of our findings to largely white, upper-middle class populations. Third, by instructing participants to abstain from caffeine use prior to their visits to the laboratory, we may have increased their awareness that caffeine was being manipulated. Because this was a dose-response study and placebo was administered on one of the visits, we were more concerned with achieving caffeine abstinence than we were with expectancy effects. However, it would have been better if we could have controlled for both. Finally, although we recruited a sample balanced for gender and caffeine use based on a telephone interview, when participants completed our extensive caffeine use questionnaire, we did a more complete analysis of typical caffeine intake and regrouped participants. This led to a higher proportion of boys and a lower proportion of girls in the high-consuming group.

In sum, this study was the first to demonstrate gender differences in physiological response to acute caffeine administration in adolescents. In addition, we found gender differences in caffeine sources and motivations for caffeine consumption. Finally, we demonstrated an association between caffeine use and macronutrient and energy intake. Adolescents are among the fastest growing consumers of caffeine and yet very few empirical studies have focused on this population. It is imperative that we understand the impact of caffeine use on adolescents. Our data may shed light on the effects of caffeine use on adolescent physiology and behavior as well as uncover potential mechanisms that underlie gender differences in drug responses.

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