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Prenatal caffeine exposure: association with neurodevelopmental outcomes in 9- to 11-year-old children

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Background: Despite the widespread use of caffeine including consumption during pregnancy, the effect of prenatal caffeine exposure on child brain development and behavior is unclear. **Methods:** To address this, we used data from the Adolescent Brain and Cognitive Development Study (n = 11,875 children aged 9–11 years from 22 sites across the United States). We explored the associations between prenatal caffeine exposure and various developmental outcomes including birth outcomes, physical health, behavior problems, cognition, substance use and brain structure in children, and evaluated dose effects. **Results:** Among 9,978 children (4,745 females) who had valid data for prenatal caffeine exposure and whose mothers did not use drugs of abuse after knowing of pregnancy, 4,170 (41.79%) had no prenatal caffeine exposure, 2,292 (22.97%) had daily, 1,933 (19.37%) had weekly, and 1,583 (15.86%) had less than weekly exposures. Prenatal caffeine exposure including the widely recommended 'safe' dose was associated with greater externalizing problems, whereas greater BMI and soda consumption were only observed in children with high dose exposures (3+ per day). Notably, the effect size for association of externalizing problems with prenatal caffeine exposure was comparable with that reported for prenatal alcohol (*The American Journal of Psychiatry*, 177, 2020 and 1060) and prenatal cannabis (*JAMA Psychiatry*, 78, 2020 and 64) exposures from previous ABCD publications. Additionally, prenatal caffeine exposure was associated with brain structural changes that included greater posterior and lower frontal cortical thickness and altered parietooccipital sulcal depth. **Conclusions:** The recommended 'safe' dose of caffeine during pregnancy should be carefully studied to assess whether the behavioral and brain correlates observed here are clinically relevant and determine whether it needs adjustment. Because of the high prevalence of caffeine use in the general population, studies on prenatal exposure to drugs of abuse should include prenatal caffeine use as a covariate. **Keywords:** Prenatal caffeine exposure; psychopathology; brain structural development; childhood outcomes; ABCD study; childhood obesity.

Introduction

Caffeine is the most commonly used stimulant in the United States and worldwide (Fredholm, Bättig, Holmén, Nehlig, & Zvartau, 1999). Caffeine blocks adenosine A_1 and A_{2A} receptors increasing alertness and cognitive performance while regulating mood and disrupting sleep (van Dam, Hu, & Willett, 2020). Though caffeine is widely used by many pregnant women worldwide, the consequences of prenatal caffeine exposure to neurocognitive development during childhood are poorly understood (van Dam et al., 2020). During pregnancy, caffeine metabolism is markedly reduced and its half-life can be up to 15 hr in the third trimester (van Dam et al., 2020). Fetal and newborn capacity to metabolize caffeine is extremely limited (van Dam et al., 2020; Pearlman, Duran, Wood, Maisels, & Berlin, 1989). Thus, maternal caffeine intake during pregnancy likely leads to accumulation of caffeine in the fetus's brain, which might affect early development and later childhood outcomes.

In laboratory animals, caffeine exposure during pregnancy results in downregulation of adenosine A1 receptors (Lorenzo et al., 2010), loss of neurons, and cognitive deficits in offspring (Li et al., 2018; Silva et al., 2013). Most of the population studies on prenatal caffeine exposure have focused on negative pregnancy outcomes including miscarriage, stillbirth, low birth weight, and/or small gestational age and preterm birth (Jacobson, Fein, Jacobson, Schwartz, & Dowler, 1984) and a few have focused on childhood outcomes including overweight, obesity (James, 2020), cognition and behavior (Galéra et al., 2016; Jacobson et al., 1984; Loomans et al., 2012; Mikkelsen, Obel, Olsen, Niclasen, & Bech, 2017). Some reported associations between prenatal caffeine exposure and low birth weight (Modzelewska et al., 2019), excess weight in childhood (Papadopoulou et al., 2018), externalizing problems (Bekkhus, Skjøthaug, Nordhagen, & Borge, 2010; Mikkelsen et al., 2017), and impaired cognitive development (Galéra et al., 2016), whereas others found no evidence of adverse effects (Linnet et al., 2009; Loomans et al., 2012). Doses and gestation stages when caffeine exposures occurred may account for discrepant findings, as high-dose exposures during the last trimester were associated with increased risk of adverse outcomes in the offspring compared with low doses or to earlier gestational

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exposures (Bakker et al., 2010; Chen et al., 2014; Klebanoff & Keim, 2015). Methodological issues may also account for the inconsistent findings, particularly lack of statistical power for the studies done in small samples and insufficient control of confounders such as familial psychopathology and co-use of drugs of abuse during pregnancy (Linnet et al., 2003). Moreover, no studies to our knowledge have evaluated prenatal caffeine exposure-related brain changes in the offspring.

The large sample size in the Adolescent Brain Cognitive Development (ABCD) study provides the opportunity to assess the effects of prenatal caffeine exposure while controlling for confounds. Furthermore, the broad range of neurodevelopmental measures including imaging in the ABCD study provides a unique opportunity to explore behavioral as well as brain correlates of prenatal caffeine exposure. Using ABCD data, we therefore aimed to (a) Investigate childhood outcomes associated with prenatal caffeine exposure including birth outcomes, physical health, cognition, behavior problems, substance use, and brain development. The outcome variables were chosen based on previous findings (Bekkhus et al., 2010; Galéra et al., 2016; Mikkelsen et al., 2017; Modzelewska et al., 2019; Papadopoulou et al., 2018) but expanded to additionally assess the association of in utero caffeine exposure with sleep problems and substance use and to fill the knowledge gap of its brain correlates in children; (b) examine whether the recommended safe dose of caffeine consumption during pregnancy (up to 200 mg per day) (European Food Safety Authority (EFSA), 2015) was associated with differences in brain structure and behavior; (c) examine the associations between behavioral and brain outcomes; (d) explore parental characteristics associated with caffeine consumption during pregnancy and how they affect the association between prenatal caffeine exposure and childhood outcomes.

Methods

Participants

The dataset used for this study was obtained from the ABCD 2.0.1 data release, which contains 11,875 children at age 9–11. Children who lacked English proficiency, had severe sensory, intellectual, medical, or neurological issues were not enrolled in the ABCD study. The full ABCD baseline assessments including the interviews, questionnaires, and MRI scans took about 6–7 hr and were performed in the first visit of parents and children and were completed in 1- or 2-day session. For the current analyses, we further excluded children who did not have valid data for prenatal caffeine exposure (i.e. missing data, conflicting report, and outliers) or whose mother used tobacco, alcohol, and illicit drugs after knowing of pregnancy (i.e. marijuana, cocaine, heroin/morphine, and oxycontin) (Appendix S1). As a result, data from 9,978 children were left for the analyses. Full written informed consent and verbal assent approved by a central institutional review board were obtained from caregivers and children, respectively. All analyses were rerun only including (a) children whose caregiver respondent was biological mother (9,063 of 9,978 [90.8%]), and (b) children who had never tried any tobacco, alcohol and/or illicit drugs (n = 9,915). All main results remained unchanged (see Appendix S2).

Assessments of prenatal caffeine exposure

The Developmental History Questionnaire was used to assess prenatal exposure to caffeine (coffee and tea) through parents' retrospective report (Barch et al., 2018). A categorical question 'Did you/biological mother have any caffeine during pregnancy (from conception until delivery)?' (0 = No, 1 = Yes—at least once a day; 2 = Yes—less than once a day but more than once a week; 3 = Yes—less than once a week) and follow-up questions 'During pregnancy, how much caffeine per day/week/month?' were asked. For analyses, we used the categorical variable for prenatal caffeine exposure (No/daily/weekly/less than weekly exposure) and for daily doses we separately assessed for the recommended 'safe' dose of caffeine (up to 2 cups per day) or higher doses (3+ cups per day), which we refer to here as 'overlimit' dose. The number of weeks before mother learned of her pregnancy was retrospectively reported in the questionnaire. On average, mothers learned of their pregnancy at 6.7 (*SD* 6.6) weeks.

Assessments of birth outcomes and physical health

Birth outcomes of children were characterized by weeks of prematurity and body weight at birth in the Developmental History Questionnaire. *Puberty status* was measured by the Pubertal Developmental Scale Parent (Petersen, Crockett, Richards, & Boxer, 1988). Children were categorized to prepuberty, early puberty, mid puberty, late puberty, and postpuberty based on their physical characteristics. Body Mass Index (BMI) was calculated from measured height and weight): $703 \times \text{weight}_{(\text{lbs})}/\text{height}_{(\text{in})}^2$ (https://www.cdc.gov/nccdphp/dnpao/growthcharts/training/bmiage/page5_2.html). The BMI of two participants were excluded due to impossible height measures (4 and 4.25 inches). *Waist circumference* was used as an additional variable to evaluate physical health. One participant was excluded due to impossible value (3.5 inches).

Assessments of behavioral outcomes

Sleep problems were assessed by the Sleep Disturbances Scale for Children (Bruni et al., 1996). It comprises 26 syndromes that relate to 6 different sleep disorders: disorders of initiating and maintaining sleep, sleep breathing disorders, disorder of arousal, sleep-wake transition disorder, disorders of excessive somnolence, and sleep hyperhidrosis. Higher scores indicate greater sleep disturbance. *Psychopathology and behavior problems* were assessed by the Child Behavior Checklist (*t*-scores) (Achenbach & Rescorla, 2004). It comprises eight empirically based syndrome scales: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior and two higher order factors: externalizing and internalizing problems. Additionally, there are six DSM5-oriented scales: depressive, anxiety, attention deficit hyperactivity (ADHD), oppositional defiant, conduct problems, and somatic complaints. The *t*-scores were used for the current analyses and higher scores indicate greater psychiatric problems. Cognition was assessed by various neurocognitive tasks (Luciana et al., 2018) including the NIH Toolbox Cognition Battery, Little Man Task for visual-spatial processing, Rey Auditory Verbal Learning for learning and memory, and Matrix Reasoning Task for fluid intelligence; and neuroimaging tasks (Casey et al., 2018) including Stop-Signal Task for inhibitory control and Monetary Incentive Delay for reward processing. Please see Appendix S1. Supplemental Methods for more detailed information. Substance use in children including

caffeine, alcohol and nicotine use was captured with the Youth Substance Use Interview. For caffeine intake, weekly and largest daily use in the past 6 months and the type of caffeinated beverage were assessed. If a youth endorsed hearing of any caffeinated beverages, they were then asked the typical number of caffeinated drinks consumed per week in the past 6 months covering coffee, espresso, tea with caffeine, soda with caffeine, and energy drinks. Typical serving sizes are provided (coffee = 8 oz; espresso = 1 shot; tea = 8 oz, soda = 12 oz; energy drink = 5 oz or 2 oz for 5-hr energy drink). Maximum dose in ounces (largest amount of a caffeinated beverage consumed in 1 day in the past 6 months) was also obtained. For drugs of abuse such as alcohol and nicotine use, the lifetime drug use as well as maximum and average drug use in the past 6 months were assessed (Lisdahl et al., 2018).

Structural imaging processing

A total of 9,699 of 9,978 participants had structural imaging data. All the imaging data were preprocessed by the ABCD data team using standardized processing pipelines (Hagler et al., 2019). Data from 382 subjects did not pass the FreeSurfer Quality Control measures and were removed. As a result, n = 9,317 were left for analyses. Morphometric measures from the preprocessing pipeline include cortical thickness (CT), surface area, gray matter volume (GMV), and sulcal depth of 68 cortical regions (Desikan et al., 2006) and volume of 40 subcortical regions (Fischl et al., 2002). For cortex, CT, surface area and sulcal depth of 68 cortical regions as well as structural components from principal component analyses (PCA) were used in the current analyses. We did not include cortical GMV in the analyses as in FreeSurfer an estimate of cortical volume is obtained by multiplying cortical area by thickness at each vertex. For subcortical regions, we examined the association between prenatal caffeine exposure and GMV in striatum (caudate, putamen, and accumbens), regions that are rich with adenosine receptors (Borea, Gessi, Merighi, Vincenzi, & Varani, 2018; Svenningsson, Le Moine, Fisone, & Fredholm, 1999) and controlled for intracranial volume.

Statistical analyses

Principal component analysis. To reduce dimensionality of cognitive variables and to identify shared patterns of variation in brain morphometry (joint structural components), we performed PCA with varimax rotation on cognitive performance (n = 4,965 with all cognitive measures) and on brain structural imaging data (n = 9,317).

Association analyses. A linear mixed-effect model (LME) was used to test the associations between prenatal caffeine exposure and various childhood outcomes. The childhood outcomes were modeled as dependent variables. The categorical variable of prenatal caffeine exposure and nuisance covariates, i.e. parents' psychopathology, household income, household marital status, parents' age at child's birth, highest household education, as well as child's age, sex, race/ethnicity were modeled as fixed effects and recruitment site was modeled as a random effect. The covariates remained the same for all analyses unless explicitly noted. Please see Appendix S3: Data files from ABCD study for information of data used in this study. We also reported the LME model without including covariates to examine how covariates affect the results. Two follow-up analyses were performed including (a) sibling status, (b) mothers' use of drugs of abuse before knowing of pregnancy (8% used tobacco, 21% used alcohol, 2.4% used marijuana, 0.1% used cocaine/crack, none used heroin/morphine, 3 mothers used oxycontin) as covariates in the models. All main results remained essentially unaltered (see Appendix S2). Furthermore, we investigated the effect of the recommended safe dose (200 mg per day, which roughly corresponds to two cups of coffee) (van Dam et al., 2020). We divided children with daily prenatal caffeine exposure into two groups: exposure to caffeine within the recommended safe dose (up to twice) (n = 1,829) versus above the recommended caffeine safe dose (3+ per day) (n = 221) and compared them with children without exposure (n = 4,170). All categorical variables were dummy coded. False discovery rate (FDR) was applied for multiple comparisons in imaging data and childhood outcomes. Bonferroni correction was applied for post hoc pairwise group comparisons. Furthermore, LMEs were performed to examine the association between brain structure and behavioral outcomes while adjusting for all covariates. The restricted maximum likelihood approach was used for missing values in all LMEs.

As preliminary analyses to assess whether brain structure mediates the effect of prenatal caffeine exposure on childhood outcomes, we performed 'mediation' (more appropriately termed 'indirect' analysis, for cross-sectional studies such as the current one) on the data from ABCD. Because mediation analyses cannot reveal the longitudinal mediation processes in cross-sectional data (Maxwell & Cole, 2007; O'Laughlin, Martin, & Ferrer, 2018), we included the related methods and results as preliminary in Appendix S2. In the future when the follow-up data becomes available from the ABCD study, it will be possible to determine whether our preliminary findings are corroborated by the longitudinal data.

To identify parental factors associated with caffeine intake during pregnancy, we performed one-way ANOVA for continuous factors (i.e. group differences in parents' age at child's birth, psychopathology and week when aware of being pregnant). Spearman's correlation was used to further explore the relationship between weeks of being pregnant and daily caffeine intake during pregnancy. For categorical (i.e. race/ethnicity of caregiver) and ordinal dependent variables (i.e. family income and highest household educational level), chi square tests, and Kruskal–Wallis H tests were performed, respectively. When significant, post-hoc tests were performed for pairwise group comparisons (two-sided and Bonferroni-corrected). All statistical analyses were implemented using SPSS 22 (IBM Corp., Armonk, NY).

Results

Children's demographic characteristics and prenatal caffeine exposure

In our sample, n = 4,170 (41.79%) had no caffeine exposure in utero, 2,292 (22.97%) had at least once per day caffeine exposures (0.25–10 units/day), 1,933 (19.37%) had more than once per week (0.5–24 units/week) but less than once per day and 1,583 (15.86%) had less than once per week (1–32 units/month). Children with different prenatal caffeine exposure did not significantly differ in age or sex. White children had the greatest amount of prenatal caffeine exposure whereas there were no significant differences between Black and Asian children (Table 1). Singleton, non-twin siblings, twin and triplet were not equally distributed in the four groups (Table 1), which was adjusted in LMEs.

Birth outcomes and physical health

Prenatal caffeine exposure was not related to adverse birth outcomes, pubertal development or waist

Table 1 children's demographic characteristics associated with prenatal caffeine exposure

	Prenatal caffeine exposure[a]					
	Daily (n = 2,292)	Weekly (n = 1,933)	Less than weekly (n = 1,583)	No (n = 4,170)	p[b]	Post hoc[c]
Age (month), mean (SD)	118.91 (7.4)	119.07 (7.5)	118.89 (7.4)	118.88 (7.5)	.83	
Female, *N* (%)	1,076 (46.9)	935 (48.4)	751 (47.4)	1,983 (47.6)	.28	
Race/Ethnicity, *N* (%)						
White	1,339 (25.1)	1,220 (22.9)	912 (17.1)	1,862 (34.9)	<.001	vs. Black/Asian/ Hispanic
Black	233 (17.2)	178 (13.2)	165 (12.2)	776 (57.4)		vs. White/Hispanic/ Other
Asian	41 (20.1)	18 (8.8)	30 (14.7)	115 (56.4)		vs. White/Other
Hispanic	439 (21.1)	306 (14.8)	309 (14.9)	1,016 (49.1)		vs. White/Black/ Other
Other	234 (23.3)	210 (20.9)	167 (16.6)	394 (39.2)		vs. Black/Asian/ Hispanic
Sibling status, No. (%)	Single 1,571 (68.5) Sibling 271 (11.8) Twin 444 (19.4) Triplet 6 (.3)	Single 1,301 (67.3) Sibling 262 (13.6) Twin 366 (18.9) Triplet 4 (.1)	Single 1,113 (70.3) Sibling 181 (11.4) Twin 289 (18.3) Triplet 0	Single 2,774 (66.5) Sibling 610 (14.6) Twin 766 (18.4) Triplet 20 (.5)	.001	

[a]Prenatal caffeine exposure No, No exposure; Daily, at least once a day; Weekly, less than once a day but more than once a week; Less than Weekly, less than once a week.
[b]p Value of F-test.
[c]All listed post-hoc results are two sided and Bonferroni-corrected $p < .05$. Nonsignificant comparisons are not listed in the table.

circumference. The association remained nonsignificant when we compared the groups with overlimit exposures (3+ per day) versus no exposure (all $|b| < 0.19$, all $p > .66$). No group differences were found in total sleep problems (Table 2). Compared with children without exposure, children with overlimit exposures (3+ per day) did not show sleep abnormalities ($b = 0.502$, $p > .99$). Children with daily or weekly exposures had higher BMI than children without exposure. However, post hoc pairwise comparisons did not reach significance after Bonferroni-correction (Table 2). Further analyses revealed that prenatal caffeine exposure was associated with higher BMI only when daily exposure was above the recommended 'safe' dose (vs. No exposure; $b = 0.717$, 95% CI [0.02, 1.41], $p = .04$).

Behavioral outcomes

Behavior problems. Compared with no exposure, daily prenatal caffeine exposure including the recommended 'safe' dose (vs. No exposure $b = 0.903$, 95% CI [0.27, 1.54], $p = .002$) was associated with greater externalizing but not internalizing problems in children (Table 2). Weekly prenatal caffeine exposure or less was not associated with greater symptoms. In terms of DSM-oriented scales, higher prenatal caffeine exposure was associated with greater somatic, oppositional defiant, and conduct problems. The 'safe' dose was associated with greater risk of all three psychiatric disorders (vs. No exposure all $|b| > .371$, all $p < .05$). As sex differences have been observed in neurodevelopmental disorders (May, Adesina, McGillivray, & Rinehart, 2019; Mowlem et al., 2019; Rucklidge, 2010), we further explored sex effects by conducting analyses separately in males and females. We found different forms of behavior problems associated with prenatal caffeine exposure in males and females (Table 2). Females showed greater somatic complaints and conduct problems, while males showed greater total scores for externalizing problems associated with prenatal caffeine exposure, which was also observed for 'safe' dose (compared with No exposure: $b = 1.233$, 95% CI [0.30, 2.17], $p = .005$). Furthermore, over-limit daily prenatal caffeine exposure (3+ cups) was associated with greater oppositional defiant (compared with No exposure: $b = 1.51$, 95% CI [0.24, 2.78], $p = .013$) and conduct problems (vs. No exposure $b = 1.52$, 95% CI [0.33, 2.70], $p = .007$) in males.

Cognitive performance. Three components obtained from PCA (Kaiser-Meyer-Olkin [KMO] = 0.753) explained more than 40% of the variance across all cognitive measures. The first component (reward processing) loaded heavily on the Monetary Incentive Delay task. The second component (learning/memory) loaded heavily on Rey Auditory Verbal Learning and various memory, vocabulary and reading tests from the NIH toolbox. The third component (Executive function) loaded heavily on pattern comparison processing speed, dimensional change card sort and flanker inhibitory

Table 2 Childhood outcomes associated with prenatal caffeine exposure after controlling for covariates

	Prenatal caffeine exposure[a] Estimated marginal mean (95% confidence interval) adjusted for covariates					
	Daily (n = 2,292)	Weekly (n = 1,933)	Less than Weekly (n = 1,583)	No (n = 4,170)	p[b]	Post hoc[c]
Birth outcomes and physical health						
Premature at birth (weeks)	0.85 (0.50-1.21)	0.85 (0.49-1.20)	0.70 (0.34-1.06)	0.86 (0.51-1.21)	.07	
Birth weight (lbs)	6.5 (6.24-6.81)	6.6 (6.27-6.83)	6.6 (6.30-6.86)	6.5 (6.22-6.77)	.18	
BMI	19.2 (18.84-19.54)	19.2 (18.86-19.57)	19 (18.64-19.37)	18.9 (18.59-19.25)	.02	n.s.
Waist (inches)	26.7 (26.18-27.11)	26.6 (26.14-27.10)	26.6 (26.09-27.05)	26.6 (26.13-27.03)	.94	
Puberty, No. (%)	Pre 332 (31.5)	Pre 303 (33.3)	Pre 242 (32.5)	Pre 608 (32)	.81	
Female	Early 273 (25.9)	Early 224 (24.6)	Early 181 (24.3)	Early 408 (21.5)		
	Mid 416 (39.5)	Mid 366 (40.2)	Mid 301 (40.5)	Mid 839 (44.1)		
	Late 31 (2.9)	Late 17 (1.9)	Late 20 (2.7)	Late 44 (2.3)		
	Post 2 (0.2)	Post 0	Post 0	Post 3 (0.2)		
Puberty, No. (%)	Pre 867 (73.1)	Pre 699 (71.8)	Pre 566 (70)	Pre 1,426 (68.7)	.30	
Male	Early 261 (22)	Early 235 (24.2)	Early 198 (24.5)	Early 497 (23.9)		
	Mid 51 (4.3)	Mid 37 (3.8)	Mid 42 (5.2)	Mid 138 (6.6)		
	Late 6 (.5)	Late 2 (.2)	Late 3 (.4)	Late 12 (.6)		
	Post 1 (0.1)	Post 0	Post 0	Post 3 (0.1)		
Sleep disturbance						
Total score	36.8 (36.16–37.36)	36.9 (36.31–37.55)	36.9 (36.29–37.55)	36.5 (35.96–37.09)	.11	
Initiating and maintaining sleep	11.6 (11.29–11.89)	11.6 (11.30–11.92)	11.6 (11.33–11.96)	11.5 (11.26–11.82)	.79	
Sleep breathing	3.8 (3.75–3.93)	3.9 (3.82–4.00)	3.9 (3.76–3.95)	3.9 (3.79–3.95)	.32	
Arousal	3.4 (3.38–3.51)	3.4 (3.35–3.48)	3.4 (3.36–3.49)	3.5 (3.40–3.51)	.27	
Sleep-Wake transition	8.3 (8.09–8.47)	8.4 (8.20–8.60)	8.5 (8.25–8.66)	8.2 (8.03–8.39)	.005	No < Less than Weekly
Excessive somnolence	7.1 (6.91–7.27)	7.1 (6.91–7.27)	7.0 (6.80–7.18)	7.0 (6.81–7.14)	.13	
Sleep Hyperhydrosis	2.5 (2.43–2.59)	2.5 (2.43–2.60)	2.5 (2.44–2.62)	2.5 (2.39–2.54)	.18	
Behavior problems						
Internalizing	47.8 (47.07–48.58)	48.0 (47.22–48.77)	48.0 (47.33–48.90)	47.9 (47.16–48.57)	.75	
Male	49.3 (48.31–50.24)	49.5 (48.45–50.45)	49.4 (48.38–50.41)	49.2 (48.33–50.10)	.913	
Female	46.3 (45.26–47.27)	46.4 (45.38–47.45)	46.7 (45.67–47.79)	46.5 (45.54–47.41)	.745	
Externalizing	45.7 (45.03–46.47)	45.1 (44.32–45.81)	45.0 (44.23–45.75)	44.7 (44.04–45.39)	<.001	Daily>No
Male	47.3 (46.32–48.28)	46.8 (45.74–47.77)	46.5 (45.51–47.58)	46.0 (45.10–46.90)	.003	Daily>No
Female	44.2 (43.22–45.07)	43.3 (42.35–44.27)	43.4 (42.44–44.40)	43.5 (42.66–44.38)	.120	
DSM5-Depressive	53.4 (52.96–53.76)	53.4 (52.97–53.80)	53.2 (52.75–53.59)	53.6 (53.21–53.95)	.06	
Male	53.9 (53.35–54.44)	54.0 (53.41–54.55)	53.6 (53.04–54.20)	54.0 (53.54–54.54)	.295	
Female	52.8 (52.29–53.33)	52.8 (52.28–53.36)	52.8 (52.22–53.33)	53.2 (52.71–53.67)	.087	
DSM5-Anxiety	53.4 (52.93–53.83)	53.2 (52.84–53.76)	53.3 (52.88–53.82)	53.6 (53.16–54.00)	.26	
Male	54.0 (53.37–54.57)	54.0 (53.34–54.58)	54.0 (53.36–54.62)	54.0 (53.48–54.58)	.988	
Female	52.7 (52.14–53.33)	52.6 (51.97–53.20)	52.7 (52.06–53.32)	53.2 (52.62–53.72)	.028	n.s.
DSM5-Somatic	55.5 (55.08–56.01)	55.6 (55.15–56.13)	55.5 (55.05–56.04)	55.0 (54.57–55.43)	<.001	No<other groups
Male	55.4 (54.76–56.04)	55.5 (55.84–56.17)	55.5 (54.78–56.14)	55.0 (54.40–55.57)	.101	
Female	55.7 (54.99–56.31)	55.7 (55.03–56.40)	55.6 (54.87–56.27)	55.0 (54.36–55.56)	.005	No < Daily/Weekly
DSM5-ADHD	53.4 (53.00–53.80)	53.2 (52.77–53.60)	53.1 (52.69–53.53)	53.1 (52.70–53.44)	.13	
Male	54.2 (53.64–54.80)	53.9 (53.30–54.51)	54.2 (53.60–54.83)	53.9 (53.32–54.39)	.208	
Female	52.5 (52.03–53.00)	52.4 (51.93–52.95)	52.0 (51.48–52.52)	52.3 (51.87–52.77)	.105	

(continued)

Table 2 (continued)

	Prenatal caffeine exposure[a] Estimated marginal mean (95% confidence interval) adjusted for covariates					
	Daily (n = 2,292)	Weekly (n = 1,933)	Less than Weekly (n = 1,583)	No (n = 4,170)	p[b]	Post hoc[c]
DSM5-Opposite	53.6 (53.18–53.93)	53.2 (52.85–53.62)	53.2 (52.84–53.64)	53.1 (52.76–53.45)	.01	Daily > No
Male	54.3 (53.74–54.84)	54.0 (53.45–54.60)	54.0 (53.45–54.62)	53.7 (53.24–54.25)	.064	
Female	52.8 (52.35–53.26)	52.5 (51.99–52.93)	52.5 (52.01–52.98)	52.6 (52.14–52.97)	.304	
DSM5-Conduct	53.4 (53.01–53.73)	52.8 (52.46–53.22)	52.9 (52.52–53.30)	52.9 (52.52–53.20)	<.001	Daily > other groups
Male	53.8 (53.33–54.35)	53.5 (52.98–54.04)	53.4 (52.90–53.98)	53.4 (52.88–53.82)	.068	
Female	52.9 (51.42–53.38)	52.2 (51.67–52.67)	52.4 (51.87–52.89)	52.4 (51.95–52.84)	.003	Daily > No/Weekly
Cognition						
Reward processing	0.01 (−0.10 to 0.12)	0.02 (−0.09 to 0.13)	0.04 (−0.08 to 0.15)	0.06 (−0.04 to 0.16)	.52	
Learning/Memory	−0.09 (−0.20 to 0.02)	−0.12 (−0.23 to 0.01)	−0.05 (−0.16 to 0.07)	−0.06 (−0.16 to 0.05)	.33	
Executive function	0.18 (0.07–0.30)	0.16 (0.04–0.28)	0.20 (0.08–0.32)	0.24 (0.13–0.35)	.18	
Substance use, N (%) of subjects used drugs						
Alcohol lifetime use	16 (0.1)					
Nicotine lifetime use	Cigarettes: 4 (<0.1); E–Cigarettes: 6 (<0.1); Cigars: 3 (<0.1); Hookah: 7 (0.1); Smokeless tobacco: 5 (<0.1); Pipes: 5 (<0.1); Nicotine replacement: 3 (<0.1)					
Caffeine intake, N (%) of subjects used drugs	Coffee: 1,405 (14.4); Espresso: 746 (7.5); Tea: 2,710 (27.2); Soda: 5,589 (56.1); Energy drink: 197 (2)					
Soda (per week in the past 6 months)	1.5 (1.10–1.81)	1.4 (1.05–1.79)	1.4 (1.06–1.81)	0.99 (0.65–1.32)	<.001	No < other groups

[a]Prenatal caffeine exposure No, No exposure; Daily, at least once a day; Weekly, less than once a day but more than once a week; Less than Weekly, less than once a week.
[b]p Value of F-test. Externalizing symptoms and soda use survived FDR-corrected $p < .05$.
[c]All listed post hoc results are two sided and Bonferroni-corrected $p < .05$. Nonsignificant comparisons are not listed in the table.

test from the NIH toolbox as well as the Little Man Task and Stop-Signal Task (Appendix S2). These three components obtained from PCA were not associated with prenatal caffeine exposure (Table 2). Even children with overlimit exposures (3+ per day) did not exhibit any significant cognitive differences compared with children without exposure (all $|b| < 0.173$, all $p > .33$).

Drug use in children. As the most frequently used drug in children was caffeine and the primary source was from soda, here we only focused on soda use in children (Table 2). Children with prenatal caffeine exposure consumed significantly more soda in the past 6 months than those without exposure (Table 2). Overlimit daily prenatal caffeine exposure (3+ cups) was associated with greater soda consumption (vs. No exposure $b = 1.59$, 95% CI [0.94, 2.25], $p < .001$; vs. 'safe' dose $b = 1.40$, 95% CI [0.73, 2.07], $p < .001$). Exposures within the recommended 'safe' dose did not differ from no exposure. Soda consumption was positively correlated with BMI in children (rho = .098, $p < .001$).

Brain structure

Five components for CT (KMO = 0.972; explaining 51.6% variance) and two components for surface area (KMO = 0.970; explaining 46.6% variance) were obtained from PCA (Appendix S2). For CT, Component 1 (35.7% variance) loaded on frontoparietal regions, especially supramarginal and inferior parietal cortex; Component 2 (5.8% variance) loaded heavily on insula, entorhinal and temporal regions; Component 3 (4.5% variance) loaded on occipital cortex: lingual, cuneus, and pericalcarine cortex; Component 4 (2.9% variance) loaded on frontal regions, particularly medial orbitofrontal and superior frontal cortex; and Component 5 (2.7% variance) loaded heavily on cingulate regions, especially the posterior part.

For surface area, Component 1 (42.7% variance) had strongest loading in frontotemporal regions; and Component 2 (3.9% variance) heavily loaded in occipital regions. As sulcal depth was not suitable for PCA (KMO = 0.408), we only used 68 ROIs.

LMEs revealed group differences in CT for Components 3 (occipital), 4 (frontal), and 5 (dorsal/posterior cingulate) after adjusting for all covariates and correcting for multiple comparisons (Figure 1 and Table 3). Post hoc comparisons showed that daily prenatal caffeine exposure was associated with greater CT in occipital and dorsal/posterior cingulate regions, while both daily and weekly exposure was associated with lower CT in frontal regions. Differences were also observed for 'safe' dose exposure (all $|b| > 0.01$, all Bonferroni-corrected $p < .01$) and were corroborated by ROI analyses showing brain correlates of lower CT in superior frontal gyrus and greater CT in occipital and posterior cingulate regions (Figure 1 and Table 3). For sulcal depth, prenatal caffeine exposure was associated with altered folding in posterior parietooccipital regions (Table 3) that for 'safe' dose included left cuneus, lingual, supramarginal and right pericalcarine cortex (all $|b| > 0.004$, all Bonferroni-corrected $p < .01$). All results remained the same after adjusting for sibling status (all $F > 4.2$, all $p < .03$). For cortical surface area (two components and 68 ROIs) and striatal GMV (controlled for intracranial volume), no group differences were found.

Association between brain structure and childhood outcomes

We examined the association between brain structure and childhood outcomes that were associated with prenatal caffeine exposure (i.e. CT and sulcal depth; externalizing problems, soda use and BMI). Externalizing problems in children were positively associated with CT Component 5 (dorsal/posterior cingulate cortex) ($F = 8.97$, $b = 0.289$, 95% CI [0.100, 0.478], FDR-corrected $p = .009$) and ROI left isthmus cingulate cortex ($F = 12.30$, $b = 1.83$, 95% CI [0.808, 2.856], FDR-corrected $p < .001$), while BMI was negatively associated with CT Component 4 (medial and superior frontal cortex) ($F = 187.78$, $b = -0.603$, 95% CI [−0.689, −0.516], FDR-corrected $p < .001$), ROI left superior frontal gyrus ($F = 89.82$, $b = -2.80$, 95% CI [−3.375, −2.218], FDR-corrected $p < .001$), left ($F = 21.93$, $b = -1.37$, 95% CI [−1.938, −0.794], FDR-corrected $p < .001$) and right cuneus ($F = 21.03$, $b = -1.27$, 95% CI [−1.814, −0.728], FDR-corrected $p < .001$) and left isthmus cingulate cortex ($F = 19.20$, $b = -1.00$, 95% CI [−1.454, −0.555], FDR-corrected $p < .001$) after adjustment for covariates. Soda use was negatively associated with CT Component 4 (medial and superior frontal cortex) (rho = −0.03, $p = .006$) but this finding was not significant after adjusting for covariates. The associations between sulcal depth and behavioral outcomes did not survive corrections for multiple comparisons and adjustment for covariates.

Parental factors associated with caffeine consumption during pregnancy

Older parents and parents with greater behavioral, emotional and social problems assessed by adult self-report (ASR) had greater caffeine intake during pregnancy. Mothers with weekly caffeine consumption during pregnancy were aware of being pregnant earlier than mothers who did not consume caffeine or consumed caffeine daily. Among daily caffeine users, earlier awareness of pregnancy was associated with a lower daily dose (rho = 0.14, $p < .001$). Lower alcohol and tobacco use before knowing of pregnancy was also associated with lower caffeine consumption after knowing of pregnancy (Table 4). Family income and parental educational level were

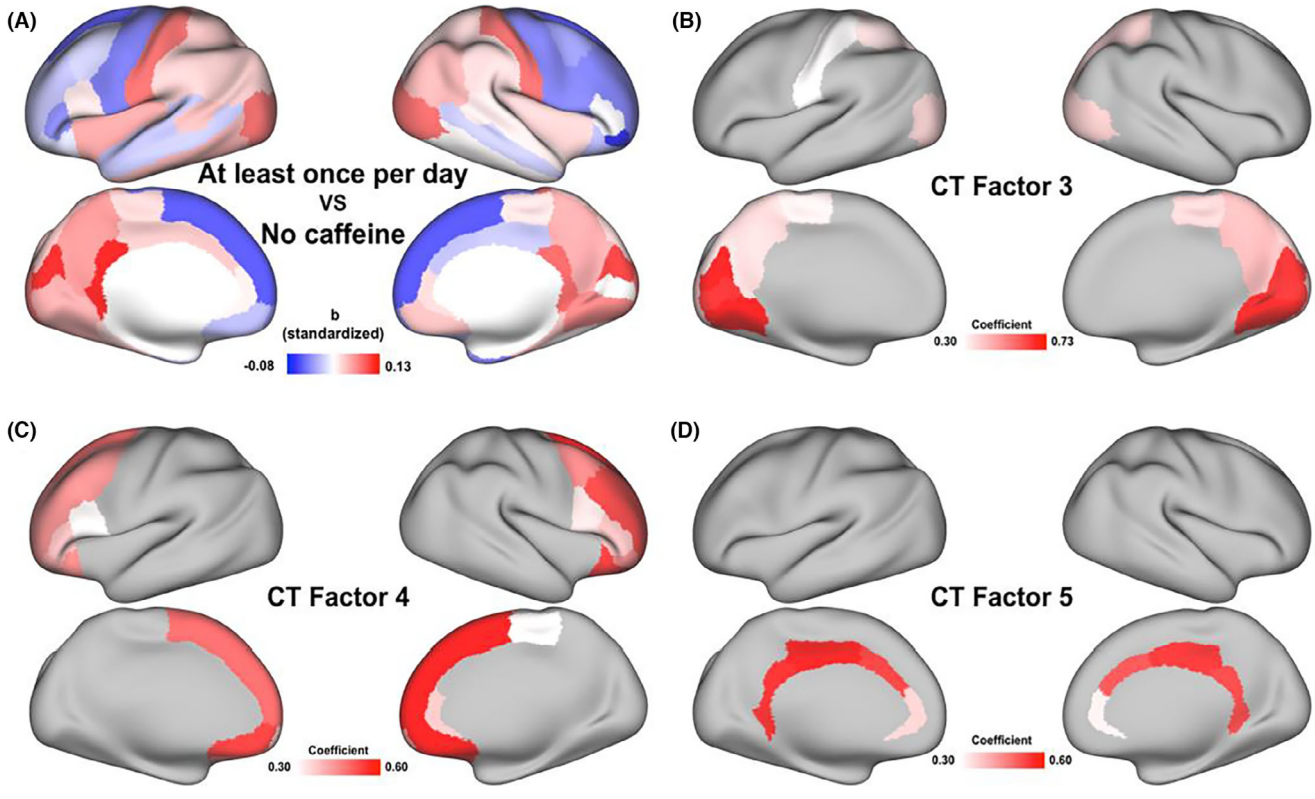

Figure 1 Cortical thickness, prenatal caffeine exposure, and childhood outcomes. (A) Cortical thickness (CT) association with prenatal caffeine exposure controlling for all covariates. Please see Methods for all covariates included in the analyses. Color bar represents the standardized coefficient, i.e. marginal mean differences between the group with daily prenatal caffeine exposure versus those with no exposure; (B–D) CT components from PCA that are associated with prenatal caffeine exposure. Only ROI regions with a coefficient value (loading) greater than 0.3 are presented. CT factor 4 is negatively associated with BMI, whereas CT factor 5 is positively associated with externalizing problems after adjusting for covariates

Table 3 Prenatal brain exposure and brain structure

	p (*F*-test)	Group pairwise comparisons[a,b]	Marginal mean difference (*b*)	*p* Bonferroni-corrected (pairwise)
Cortical thickness (Components)				
Comp 1	1.60E−01			n.s.
Comp 2	4.69E−01			n.s.
Comp 3	2.90E−05[c]	Daily > No/Less than Weekly	0.119/0.099	<.001/.008
Comp 4	1.00E−03[c]	No > Daily/Weekly	0.106/0.084	.001/.02
Comp 5	8.00E−03[c]	Daily > No	0.098	.004
Cortical thickness (ROIs)				
L_Cuneus	4.11E−06[c]	Daily/Weekly>No/Less than Weekly	All |*b*| > 0.013	All *p* < .03
R_Lateral occipital	4.43E−04[c]	Daily>other groups	All |*b*| > 0.012	All *p* < .03
R_Cuneus	4.64E−04[c]	Daily>No/Less than Weekly	0.018/0.017	<.001/.009
L_Lateral occipital	1.00E−03[c]	Daily>No/Less than Weekly	0.013/0.014	.002/.007
L_Isthmus cingulate	2.14E−04[c]	Daily>No	0.024	<.001
L_Superior frontal	2.00E−03[c]	No>Weekly	0.015	.003
Sulcal depth (ROIs)				
L_Cuneus	2.60E−05[c]	Daily>other groups	All |*b*| > 0.007	All *p* < .03
R_Cuneus	1.00E−03[c]			n.s.
R_Pericalcarine	2.00E−03[c]	No>Daily	0.009	.001
L_Lingual	2.00E−03[c]	Daily>other groups	All |*b*| > 0.004	All *p* < .05
L_inferiorparietal	1.00E−03[c]	Less than Weekly>No	0.005	.001
L_Supramarginal	3.00E−03	No>Daily/Less than Weekly	0.004/0.004	.01/.02

[a]Prenatal caffeine exposure No, No exposure; Daily, at least once a day; Weekly, less than once a day but more than once a week; Less than Weekly, less than once a week.
[b]All listed post hoc results are two sided and Bonferroni-corrected $p < .05$.
[c]All survived FDR correction for multiple comparisons.

higher in the group with less than one prenatal caffeine exposure per day compared to the group without exposure or the group with daily exposure. White, multiracial and/or non-Hispanic/Latino parents had more caffeine use during pregnancy than other groups (Table 4).

Covariates

Controlling for covariates decreased the associations between prenatal caffeine exposure and sleep disturbance, internalizing problems and male (but not female) pubertal development, which were significant before adjustment (Appendix S2). Among all covariates, parents' psychopathology, which correlated with caffeine use during pregnancy, had the strongest effect on both sleep disturbance and internalizing problems in children ($b = 0.32$ and 0.56, all $p < .001$), while household income strongly contributed to pubertal development in males ($b = 0.08$, $p < .001$).

Discussion

This study examined the association between prenatal caffeine exposure and various childhood neurobehavioral outcomes. Prenatal caffeine exposure was associated with greater externalizing problems, BMI and soda consumption in children in a dose-dependent manner such that the association with externalizing problems was observed even for the 'safe' dose (Safe dose vs. No exposure $b = 0.90$), while the associations with BMI (Overlimit vs. No exposure $b = .72$) and soda consumption (Overlimit vs. No exposure $b = 1.59$) were only seen with overlimit exposures (3+ per day). We found no associations between prenatal caffeine exposure and sleep problems, internalizing problems and boy's pubertal development after regressing out essential confounders (e.g. parents' psychopathology), nor did we find significant associations with birth outcomes or cognitive performance. As for brain structure, prenatal caffeine exposure was associated with greater CT in occipital and in dorsal and posterior cingulate and with lower CT in medial and superior frontal cortex (Daily vs. No exposure $b = 0.10$–0.12), and with altered sulcal depth in parietooccipital regions (Daily vs. No exposure $b = 0.04$–0.09). We found no association of caffeine exposure with surface area or striatal GMV. The meaning and practical relevance of the seemingly small effect size observed in an exceptionally large dataset like ABCD study are discussed later.

Several studies found that maternal caffeine consumption during pregnancy was dose dependently associated with higher BMI during the offspring's childhood, independent of birth weight (Chen, Murrin, Mehegan, Kelleher, & Phillips, 2019; Li, Ferber, & Odouli, 2015; Voerman et al., 2016). Furthermore, a prospective cohort study demonstrated a dose-by-age interaction effect on BMI in children, such that any in utero caffeine exposure was associated with higher risk of being overweight at age 3 and 5 years, whereas the association persisted at 8 years only for very high exposures (>200 mg/day) (Papadopoulou et al., 2018). In agreement with previous studies, we only observed higher BMI in children at age 9–11 years with daily prenatal caffeine exposures above the recommended 'safe' dose, independent of birth weight. The decreased association between prenatal caffeine exposure and BMI at older ages likely reflects the growing contribution of postnatal factors as children age. Notably, the association with BMI remained after controlling for a range of potential confounders including socioeconomic status and parental education and had also been observed in European samples, which indicates that the association emerges across different social and cultural contexts. However, we did not have available information on maternal BMI, weight or maternal weight gain during pregnancy, which could also be key variables, associated with our outcome measures. The vulnerability for a higher BMI with prenatal caffeine exposure may reflect epigenetic modifications in the hypothalamic-pituitary-adrenocortical axis that affect metabolism, perhaps via its antagonism of A_1 adenosine receptors, as suggested by preclinical studies (Buscariollo et al., 2014; Xu et al., 2012). Alternatively, it could also reflect the effects of prenatal caffeine in fat tissue via its antagonism of A_{2A} and A_{2B} receptors, which modulate fat metabolism and have been shown to counteract obesity (Gnad et al., 2014, 2020).

In line with previous studies, we found a small but significant association of prenatal caffeine exposure with externalizing but not with internalizing problems in children (Bekkhus et al., 2010; Mikkelsen et al., 2017). In animals, prenatal caffeine exposure increased locomotor activity and fearless behavior (Hughes & Beveridge, 1990). Importantly, in this study, males and females showed different profiles for externalizing problems associated with prenatal caffeine exposure such that males showed greater externalizing problems in general while females reported greater conduct problems specifically. This is consistent with previous findings that males with prenatal cocaine exposure had greater externalizing problems than females aged 8–10 (Bennett, Marini, Berzenski, Carmody, & Lewis, 2013). In contrast, females but not males with prenatal exposure had greater somatic complaints, one of the internalizing problems. The biological mechanism underlying these sex differences is unclear and requires further investigations (Beauchaine, Hong, & Marsh, 2008). Compared with previous findings in humans, the link observed in this study was only robust for syndromes related to conduct-oppositional disorders but not for ADHD. Furthermore, we did not find any associations between prenatal caffeine exposure and birth weight, cognitive performance or sleep

Table 4 Parents/caregivers' characteristics associated with prenatal caffeine exposure

	Prenatal caffeine exposure[a]					
	Daily (n = 2,292)	Weekly (n = 1,933)	Less than weekly (n = 1,583)	No (n = 4,170)	p[b]	Post hoc[c]
Age at birth of child, mean (*SD*)						
Mother's	30.2 (6.1)	29.8 (5.93)	29.6 (5.7)	29.4 (6.4)	<.001	Daily>Less than Weekly/No
Father's	32.58 (6.9)	32.1 (6.84)	31.7 (6.6)	31.7 (7.2)	<.001	Daily>Less than Weekly/No
Psychopathology, mean (*SD*)						
Total problem	44.2 (10.3)	43.0 (9.7)	43.0 (9.6)	41.0 (10.0)	All <.001	Daily > Weekly/Less than Weekly > No
Internalizing	49.2 (10.7)	48.0 (10.0)	47.9 (10.1)	46.3 (10.1)		
Externalizing	47.2 (9.8)	45.8 (9.2)	45.9 (9.2)	44.2 (9.4)		
Weeks of pregnancy knowledge	7.1 (6.9)	6.3 (5.3)	6.7 (6.6)	6.8 (6.9)	.003	Weekly<No/Daily
Family income[d] (past 12 months)	7.3 (2.39)	7.7 (1.96)	7.6 (2.19)	7.1 (2.56)	<.001	No < Daily < Weekly/ Less than Weekly
Current marital status, *N* (%)						
Married	1,605 (23)	1,458 (20.9)	1,159 (16.6)	2,744 (39.4)	<.001	vs. Divorced/Separated/ never married
Widowed	21 (31.8)	8 (12.1)	12 (18.2)	25 (37.9)		vs. never married
Divorced	212 (24.7)	147 (17.1)	126 (14.7)	374 (43.5)		vs. never married/ Married
Separated	108 (28.3)	62 (16.3)	52 (13.6)	159 (41.7)		vs. never married/with partner/married
Never married	218 (20)	141 (12.9)	138 (12.6)	594 (54.4)		vs. all others
With partner	112 (20.8)	113 (21)	89 (16.5)	224 (41.6)		vs. separated/never married
Education[e]	16.7 (2.77)	17.1 (2.27)	16.9 (2.49)	16.5 (2.94)	p < .001	No/daily < weekly/less than weekly
Race, *N* (%)						
Asian	66 (17.7)	44 (11.8)	66 (17.7)	197 (52.8)	<.001	vs. White/Mixed
Black	239 (17)	182 (12.9)	175 (12.4)	811 (57.6)		vs. White/Mixed/ Others
Others	117 (21.1)	64 (11.6)	89 (16.1)	284 (51.3)		vs. White/Mixed/Black
White	1,724 (24.8)	1,508 (21.7)	1,154 (16.6)	2,561 (36.9)		vs. Asian/Black/Others
Mixed	108 (22.8)	102 (21.5)	75 (15.8)	189 (39.9)		vs. Asian/Black/Others
Ethnicity, No. (%)						
Hispanic/Latino	376 (20.9)	234 (13)	266 (14.8)	919 (51.2)	<.001	
Non-Hispanic/Latino	1,908 (23.5)	1,695 (20.8)	1,314 (16.2)	3,218 (39.6)		
Use of drugs of abuse before knowing of pregnancy						
Tobacco (times/day)	0.93 (3.09)	0.55 (2.11)	0.45 (2.10)	0.32 (1.76)	<.001	No < daily/weekly; Daily > other groups
Alcohol (drinks/week)	1.06 (2.89)	0.95 (2.50)	0.89 (2.27)	0.57 (2.03)	<.001	No < other groups
Marijuana (times/day)	0.06 (.40)	0.05 (0.44)	0.04 (0.29)	0.04 (0.33)	.301	
Cocaine/Crack (times/day)	0.002 (0.07)	0.001 (0.02)	0.006 (0.18)	0.002 (0.07)	.398	
Heroin/Morphine (times/day)	0	0	0	0	–	
Oxycontin (times/day)	0.0017	0	0	0.0005	.378	

[a]Prenatal caffeine exposure No, No exposure; Daily, at least once a day; Weekly, less than once a day but more than once a week; Less than Weekly, less than once a week.
[b]p Value of F-test.
[c]All listed post hoc results are two sided and Bonferroni-corrected p < .05. Non-significant comparisons are not listed in the table.
[d]1 = Less than $5 K, 2 = $5–12 K, 3 = $12–16 K, 4 = $16–25 K, 5 = $25–35 K, 6 = $35–50 K, 7 = $50–75 K, 8 = $75–100 K, 9 = $100–200 K, 10 = greater than 200 K.
[e]1–14 = Up to high school degree, 15 = Some college, 16–17 = Associate degree, 18 = Bachelor, 19 = Master, 20–21 = MD/PhD.

(Bekkhus et al., 2010; Galéra et al., 2016; Mikkelsen et al., 2017; Modzelewska et al., 2019; Santos, Matijasevich, & Domingues, 2012). The discrepancy between current and previous human findings could be ascribed to doses of prenatal caffeine exposure and the age at which children were tested. Links between prenatal caffeine exposure and ADHD were observed with maternal coffee consumption of greater than 8 cups per day and in our sample only seven participants reported such high levels of prenatal caffeine exposure (Mikkelsen et al., 2017). For cognition and sleep, a significant association between prenatal caffeine exposure and IQ was reported in preschool age children (Galéra et al., 2016) and a prospective cohort study showed high maternal caffeine consumption increased infant nighttime waking but at a nonsignificant level (Santos et al., 2012). All our participants were school-

aged (9–11) children. There might be a potential dose-by-age interaction effect on cognition and sleep similar to BMI, which requires further investigation. The association between prenatal caffeine exposure, cognition and sleep might be dampened by school attendance, peer influences, and other social/environmental factors (Jirout et al., 2019). Additionally, timing of prenatal caffeine exposure can be critical as children's IQ is more strongly affected by caffeine exposure at the late compared with the early stage of the pregnancy (Klebanoff & Keim, 2015).

Because of very low use of drugs of abuse in children 9–10 years of age, we were only able to investigate soda consumption, which is the main source of caffeine intake for most children. In this study, we were not able to disentangle whether the association between child and maternal caffeine use is due to a biological 'programming' effect during pregnancy or whether it reflects a learned behavior. Also, the associations between BMI and prenatal caffeine exposure could be confounded by soda use, which is correlated with BMI. Though we cannot establish causality it is possible that the thinning of the medial and superior frontal CT compromised self-regulation leading to more compulsive consumption of soda and other high calorie foods and a higher BMI. As we are not able to establish causation with a cross-sectional dataset, we analyzed BMI and soda separately as opposed to putting them in a certain order in a path analysis.

Caffeine intake in children particularly for higher doses has raised concerns because it can affect decision-making and risk-taking behaviors (Temple, Ziegler, Graczyk, & Crandall, 2017) and has also been associated with sleep and internalizing problems in children (Warzak, Evans, Floress, Gross, & Stoolman, 2011; Watson, Banks, Coates, & Kohler, 2017). In the follow-up ABCD assessments over the ensuing decade, it will be important to investigate whether prenatal caffeine exposure influences the use of alcohol, nicotine, or other drugs of abuse as these children transition into adolescence. Similarly, the longitudinal design will allow researchers to assess whether caffeine intake/soda consumption increases the risk of future drug use and obesity.

The associations between prenatal caffeine exposure and brain structural changes advances our knowledge on the neural mechanisms associated with behavioral differences in caffeine-exposed children. In this study, prenatal caffeine exposure was associated with CT and sulcal depth but not with surface area. One possible explanation is that CT and sulcal depth are more sensitive to environmental influences including the intrauterine environment, whereas surface area has a stronger influence from genetic factors (Garcia, Kroenke, & Bayly, 2018; Grasby et al., 2020; Quezada, Castillo-Melendez, Walker, & Tolcos, 2018; Wright et al., 2014). Notably, the brain correlates of prenatal caffeine exposure were most prominent in posterior cortical regions and no association was observed for striatum, which might reflect the type of adenosine receptor affected by prenatal caffeine exposure. Although caffeine nonselectively targets adenosine A_1 and A_{2A} receptors (Ferré, 2008; Karcz-Kubicha et al., 2003), most preclinical studies provide evidence for the effect of prenatal caffeine exposure on A_1 receptors in the brain rather than A_{2A} receptors (Porciúncula, Sallaberry, Mioranzza, Botton, & Rosemberg, 2013), which have low or even undetectable levels until birth (Ådén, Herlenius, Tang, & Fredholm, 2000). A_1 receptors are widely expressed in the brain, whereas A_{2A} receptors are highly concentrated in the striatum (Ferré, 2008; Karcz-Kubicha et al., 2003). The striatum is therefore less likely to be affected by prenatal caffeine exposure, in line with results observed here. The higher vulnerability of posterior regions to early-life caffeine exposure was previously reported in preclinical studies showing reduced number of interneurons in the occipital cortex (Fazeli et al., 2017). Brain imaging studies in human adults, have documented close to 50% blockade of A_1 receptors by caffeine in cortical regions including occipital cortex (Elmenhorst, Meyer, Matusch, Winz, & Bauer, 2012) and have reported that whereas caffeine increased relative cerebral blood flow in posterior cortical regions, it decreased it in anterior regions (Xu, Liu, Pekar, & Lu, 2015) consistent with reports of increases oxygen metabolism in the occipital cortex following caffeine administration (Griffeth, Perthen, & Buxton, 2011). Stimulatory effects of caffeine in occipital and other posterior cortical regions could underline the increases in CT with prenatal caffeine exposures though the association could also reflect neurodevelopmental delay as described below. Additionally, exposure-related lower medial and superior frontal CT was found. The underlying mechanism is not clear. In animals, long-term consumption of caffeine causes changes to behavior and protein expression in the orbitofrontal cortex (Franklin et al., 2016). In humans, the evidence is scant.

The association between BMI and gray matter reduction especially in prefrontal regions is well-documented (Alosco et al., 2014; Laurent et al., 2020; Maayan, Hoogendoorn, Sweat, & Convit, 2011; Raji et al., 2010) and gray matter reduction predicted future weight gain (Yokum, Ng, & Stice, 2012). Prior reports on the relationship between externalizing problems and CT have been inconsistent (Dabbs, Jones, Jackson, Seidenberg, & Hermann, 2013; Hyatt, Haney-Caron, & Stevens, 2012; Oostermeijer et al., 2016; Whittle, Vijayakumar, Simmons, & Allen, 2020), which might reflect rapid developmental and nonlinear changes in brain structure during late-childhood through early adulthood (Gogtay et al., 2004). Cortical thinning is part of the brain's maturation process and the left hemisphere matures earlier than the right (Giedd et al., 1996; Gogtay et al., 2004). Greater posterior CT in

the left hemisphere (Table 3) associated with prenatal caffeine exposure might reflect developmental delay of cortical thinning and cortical pruning, which could lead to the greater externalizing problems (Oostermeijer et al., 2016; Whittle et al., 2020). Similar patterns were observed in children with prenatal alcohol exposure (Lees et al., 2020). In contrast, a recent study on the effect of prenatal illicit drug exposures on brain structure in newborns reported that prenatal exposure to illicit drugs might accelerate fetal brain maturation (Peterson et al., 2020). This highlights the importance of investigating developmental stage-specific brain correlates of specific prenatal drug exposures including polysubstance.

Finally, this study identified parents' characteristics associated with high caffeine consumption during pregnancy. Consistent with previous large cohort studies, older, white parents appear to have more caffeine intake during pregnancy than the other groups studied (Chen et al., 2019; Li et al., 2015; Voerman et al., 2016). Previous studies had shown that pregnant women who consume tobacco and alcohol had greater caffeine intake than their counterparts who did not consume other substances (Loomans et al., 2012). In this study, although mothers with co-use of drugs of abuse after knowing of pregnancy were excluded, we found that mothers who consumed more tobacco and alcohol before knowing of pregnancy had greater caffeine consumption after knowing of pregnancy. Unlike previous studies that showed a positive association between socioeconomic status and caffeine intake (Modzelewska et al., 2019; Voerman et al., 2016), we found that mothers with higher education and income had moderate caffeine intake during pregnancy (weekly or less than weekly). It is possible that their caffeine consumption was influenced by negative social attitudes toward caffeine use during pregnancy, which could also explain the observed association between early awareness of pregnancy and less caffeine intake. Finally, we found that mothers who had greater behavioral, emotional, and social problems had higher caffeine intake during pregnancy, which is a strong confounder as it can mediate the severity of any exposure-related outcomes in various ways, whether by genes, modeled behavior, parenting behavior and/or maternal reporting ability. As shown in this study, after controlling for parental psychopathology, exposure-related child sleep disturbance and internalizing problems were no longer significant, while exposure-related externalizing problem, BMI and soda use remained robust.

Strengths of this study include a large sample size and a wide range of measures, whereby we were able to explore various developmental outcomes correlated with prenatal caffeine exposure. Although the magnitude of the effect size for our main finding, i.e. association of externalizing problems with prenatal caffeine exposure, is relatively small ($b = 1$ in the whole sample and $b = 1.3$ in boys [daily vs. No exposure]), it is comparable with that reported with prenatal alcohol exposure ($b = 1.23$; Lees et al., 2020) and prenatal cannabis exposure ($b = 0.1$–2.0; Paul et al., 2020) for their association with externalizing problems from previous ABCD publications. The small effect sizes observed in studies based on ABCD data might be due in part to the overrepresentation of high functioning children and families in the sample (Thompson et al., 2019). At the individual level, the effect size of prenatal drug exposures can be strongly affected by environmental factors during different developmental stages. A high functioning family and social environment might buffer the negative consequences of prenatal drug exposure. As discussed earlier, some correlates of prenatal caffeine exposure such as BMI attenuated with age such that they could only be observed with high exposure (or not at all) at age 9–11 years, which could reflect emerging environmental factors. Future prospective studies in infants and children starting at a younger ager such as the HEALthy Brain and Child Development (HBCD) study that evaluate prenatal caffeine exposures throughout pregnancy are needed to fill this knowledge gap. Further, with current advances of acquisition and analysis methods developed for fetal MRI (Wilson et al., 2021), future studies directly examining the effect of prenatal drug exposure on brain development in utero will provide more direct evidence of caffeine's effects during these early stages of development. Also, in discussing the clinical significance of small effects sizes, it is important to consider them in the context of the prevalence of the variable/factor exposure in the population, such that for infrequent events, small effects might be inconsequential, whereas for frequent events such as is the case of caffeine exposure during pregnancy (58% of participant's mothers drank coffee during pregnancy), even small effect sizes will have an impact at the population level. Although we excluded children whose mothers used drugs of abuse after learning of their pregnancy, it is likely that some mothers did not learn about their pregnancy at the early stage, which could be a relevant confounding factor. However, our follow-up analyses showed that the findings are robust after adjusting for mothers' use of drugs of abuse before knowing of pregnancy. To our knowledge, this is the first study examining brain correlates of in utero caffeine exposure. Nonetheless, our data obtained from ABCD is cross-sectional and no causality can be established. Even though we controlled for a broad range of covariates, the observed associations may still be caused by residual confounds. Further, the measure of prenatal caffeine exposure in the ABCD study was based on retrospective recall, which might be affected by memory bias. Precise data on dose, source and timing of prenatal caffeine exposures were absent. We expect that the exposures might have been larger than that

reported by the mothers because caffeine from sources such as soft drinks, chocolate, and medication has not been assessed in the ABCD study. This could also account for why a prospective study conducted in San Francisco that assessed caffeine intake in pregnant women in much greater detail through concurrent interviewing reported rates of caffeine consumption (78%) higher than 59% in the ABCD sample (Li et al., 2015). Finally, as large storage, computational and personal capacities are required for analyzing the extremely large brain imaging data set from ABCD, our current analyses have been limited to extracted regions of interest, which has been released by the ABCD data processing group; in the future voxel-wise/vertex-wise analyses might help to delineate more precisely the brain regions that are most sensitive to prenatal caffeine exposure.

Conclusion

Prenatal caffeine exposure was associated with externalizing problems and altered brain structure in children even at the currently recommended 'safe' dose and were associated with higher BMI and soda consumption with the higher dose exposures. These findings have implication for guidelines of caffeine consumption during pregnancy and indicate that the currently recommended 'safe' caffeine dose must be carefully reassessed to ensure that it does not have any negative effects in children's brain development and behavior. Our findings also highlight the importance of including the effects of prenatal caffeine exposure when examining the prenatal effects of drugs of abuse, which so far has been neglected (Lees et al., 2020; Paul et al., 2020).

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Supplemental methods.
Appendix S2. Supplemental results.
Appendix S3. Data files from ABCD study.

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Key points

- Caffeine is the most commonly used psychostimulant in the United States and worldwide. During pregnancy, maternal caffeine metabolism is markedly reduced. Fetuses and newborns have very limited capacity to metabolize caffeine.
- This study identifies various behavioral and brain correlates of prenatal caffeine exposure in children and evaluates dose effects.
- These findings have implication for guidelines of caffeine consumption during pregnancy and indicate that the currently recommended 'safe' caffeine dose must be studied more closely, for it may have negative effects in children's brain development and behavior. Our findings also highlight the importance of including the effects of prenatal caffeine exposure when examining the prenatal effects of alcohol, tobacco and illicit drugs, which so far has been neglected.

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