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Abstract

Objective. Evidence suggests that caffeine use disproportionately impacts sleep functioning among youth with attention deficit/hyperactivity disorder (ADHD). The present study aimed to examine the association of caffeine use with disrupted sleep, and to test moderating effects of ADHD, by leveraging differences within twin pairs to explore potential quasi-causal (i.e., within-pair) effects. **Methods.** N=765 complete same-sex twin pairs (mean age at baseline=10.14 [SD=0.5]; 49% girls; 73% white) from the ABCD Study reported caffeine use and frequency of disrupted sleep; parents reported youth ADHD symptoms. Co-twin control analyses predicted disrupted sleep from caffeine use, ADHD, and their interaction at ages 10 and 12. **Results.** Neither quasi-causal within-pair effects of caffeine use on disrupted sleep, nor a moderating role of ADHD were identified. Post-hoc biometric models indicated that genetic and environmental influences on these phenotypes may change over time, such that genetic influences on disrupted sleep began to emerge more robustly around early adolescence. Additionally, caffeine use and disrupted sleep, but not ADHD, displayed overlapping genetic influences (12-13% of total phenotypic variance) at age 10. **Conclusions.** In a sample of pre-adolescent twin pairs from the ABCD Study, we did not observe evidence that caffeine use was quasi-causally associated with disrupted sleep at this early developmental stage. However, caffeine use and disrupted sleep emerged with shared etiologic influences. In sum, this study sets the stage for examining these dynamic patterns in future examinations of this critical and timely ABCD Study sample, as genetic and environmental influences on behavior are known to change throughout development.

Keywords: ABCD Study®, twin study, adolescents, caffeine, sleep, ADHD

Twin Study of Caffeine Use, ADHD, and Disrupted Sleep in ABCD Youth

Caffeine use is prevalent and widespread among youth within the United States (U.S.) (Temple, 2019), and the relationship between caffeine use and sleep disruption in this age group has been well-established (Clark & Landolt, 2017; Drake et al., 2013). Disrupted sleep in youth has been associated with deleterious outcomes (e.g., disruptions in mood and behavior, overeating/being overweight) (Palmer et al., 2018; Medic et al., 2017). Research suggests that youth with attention deficit/hyperactivity disorder (ADHD) may be disproportionately impacted by these effects, such that youth with ADHD tend to use caffeine at relatively higher rates (Cusick et al., 2020) and experience greater sleep disruptions than youth without ADHD (Becker et al., 2019); as such, it may be the case that caffeine-related sleep disruption is compounded among youth with ADHD, in turn compounding risk for mental, behavioral, and physical health sequalae. There is some evidence that afternoon and evening caffeine consumption may be associated with self-reported sleep disruption among youth with ADHD (Cusick et al., 2020). However, the direction of effects is unclear. Sleep problems can precede or follow from caffeine use, and, while stimulants can certainly disrupt sleep (Kidwell et al., 2015), stimulant treatments may actually improve sleep for at least some children with ADHD (Becker et al., 2016). Because the effects of caffeine and other stimulants can have both beneficial and adverse effects on youth with ADHD, it is important to understand the nature of the relationship between caffeine intake, ADHD, and sleep disruption in order to inform best routes to effectively mitigate risk for sequalae associated with disrupted sleep in this group.

Twin studies have helped elucidate genetic and environmental influences on these phenotypes and how the magnitude of such influences may change from early adolescence to middle adulthood (e.g., Kendler et al., 2008), though we could find no published studies

examining how ADHD symptoms may moderate the relationship between caffeine use and disrupted sleep in youth. The present study aimed to examine these relationships, and how they may differ at different developmental stages. Leveraging twin data from the ABCD Study (Jernigan et al., 2018), we implemented a co-twin control (i.e., discordant twin) design assessing youth in childhood (at age 10), and then around prepubescence (at age 12; i.e., the oldest age and latest follow-up for which for which ABCD Study data are available). Because twins are, by nature, matched for genes and familial environment, twins discordant for a particular characteristic provide a natural experiment in which each individual's co-twin serves as a case-control, such that co-twins approximate each other's outcomes (e.g., disrupted sleep) under a distinct set of unique environmental exposure conditions (e.g., frequency of caffeine consumption) (McGue et al., 2010). This design can thus provide insight into whether caffeine use might be quasi-causally associated with disrupted sleep in youth, and whether ADHD may moderate this relationship at different points in development. It was hypothesized that caffeine use would exert a quasi-causal effect on disrupted sleep, and that this effect would be moderated by ADHD symptoms at age 10 such that sleep problems would be exacerbated among youth with ADHD. In light of evidence that genetic influences on caffeine intake increases in early adolescence (e.g., Kendler et a., 2008), we expected that familial effects would emerge more robustly at age 12.

Methods

Participants & Procedure

Participants were N=765 complete twin pairs from the ABCD Study (N=159 monozygotic [MZ] female pairs, N=173 MZ male pairs, N=218 dizygotic [DZ] female pairs, and N=215 DZ male pairs). Zygosity was genetically determined via saliva and blood samples. The

sample was 49% girls; 73% white; 14% Hispanic/Latinx; and 10.14 years old at baseline (SD=0.54; range=9-11). Informed consent was obtained from parents of participants and assent was obtained directly from the youth themselves. Comprehensive interviews were independently conducted with youth and their parents at baseline and at 2-year follow-up (ABCD Study protocol is detailed at https://abcdstudy.org). Data collection was approved by the IRB at UCSD (i.e., the ABCD coordinating center). As the present study reflects only secondary analysis of deidentified data, it does not meet criteria for human subjects research; as such, IRB review was not required for these analyses.

Measures

Demographics

At baseline, youth reported their gender and age. Parents reported their household income, their own educational attainment, and their child's academic performance (letter grades). At baseline and 2 year follow-up, parents reported their child's current medications.

Caffeine Use

To assess caffeine use, youth were asked "typically, how many drinks of the following beverages did you have per week in the past (6 months/1 month)?" at baseline/2 year follow-up, respectively, with response options for coffee, espresso, tea with caffeine, soda with caffeine, and energy drinks. Responses were summed for an index of total weekly caffeine use.

Attention Deficit/Hyperactivity Disorder

At baseline and 2 year follow-up, parents reported their child's ADHD symptoms via the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) for DSM-5 (Kaufman et al., 2016). Items were summed to create a total symptom count score.

Disrupted Sleep

Within the K-SADS, youth were asked "in the past 2 weeks, how often did you have trouble falling asleep or staying asleep when you were tired and wanted to sleep?" Response options included not at all (0), rarely (1), several days (2), more than half the days (3), and nearly every day (4).

Statistical Analysis

Analyses were conducted using SAS version 9.4 (SAS Inc, 2014). To accommodate clustered data (i.e., twins nested within pairs), two-level random intercept generalized linear mixed models were run using PROC GLIMMIX. Caffeine use variables were coded to test within-pair effects (i.e., comparison of twin and co-twin's caffeine use score deviations from their pair average) and between-pair effects (i.e., comparison of twin pair caffeine use score averages across twin pairs). The former examines associations between the predictor and outcome free of familial confounding, including any quasi-causal effects, and the latter evaluates aggregate influence of familial factors (genes, familial environment). ADHD symptom count was included as a predictor alongside a within-pair caffeine use by ADHD symptoms interaction term. A multinomial distribution was used to model the disrupted sleep outcome variable; parameter estimates were exponentiated to produce odds ratios.

A series of three models was run for each time point (baseline, 2 year follow-up): a model comprised of both MZ and DZ twins ("MZ-DZ model"), an MZ-only model, and a DZ-only model. The MZ-DZ model takes advantage of the full sample size and therefore maximizes power. The MZ-only model provides the strongest causal inference, as genes and shared environment are completely controlled for. The DZ-only model can be used as a comparator against the MZ-only model to provide insight into familial confounding. Youth gender, age, and

academic performance at baseline, as well as parental education and household income, were included as covariates in all models; zygosity was included as a covariate in MZ-DZ models.

Results

Within this ABCD Study sample, average weekly caffeine use at baseline and 2-year follow-up were 2.11 caffeinated drinks/week (SD=5.61; range=0-76) and 1.98 caffeinated drinks/week (SD=4.31; range=0-48), respectively. Average number of ADHD symptoms at baseline and 2-year follow-up were 0.61 (SD=2.28; range=0-17) and 0.44 (SD=1.96; range=0-17), respectively; at baseline and 2 year follow-up, 8% and 7% of the sample was prescribed a stimulant medication, respectively. Average frequency of disrupted sleep at baseline and 2-year follow-up were 0.82 (SD=0.99; range=0-4) and 0.68 (SD=0.87; range=0-4), respectively.

Results are presented in Table 1. We did not observe support for a quasi-causal influence of caffeine use on disrupted sleep, for an association between ADHD and disrupted sleep, nor for an interaction between caffeine use and ADHD symptoms (the product term was nonsignificant and failed to improve model fit) (McCabe et al., 2020). There was modest evidence for familial (i.e., between-pair) effects of caffeine use on disrupted sleep in the baseline MZ-only model, though not in the expected direction (OR=0.95, 95% CI 0.92-0.99]).

Given the absence of evidence for relationships between caffeine use, ADHD, and disrupted sleep, we conducted post-hoc biometric structural equation modeling (SEM) to explore genetic and environmental etiologies of each phenotype. These analyses were conducted in Mplus version 8 (Muthén & Muthén, 2017) with the same set of covariates as the primary models. First, univariate biometric models decomposed the variance in each trait into additive genetic (A), common/shared environmental (C), and unique/nonshared environmental (E) influences. Next, we examined the etiologic relationships between caffeine use, ADHD

symptoms, and disrupted sleep in a multivariate framework by running a freely estimated independent pathway model (Rijsdijk & Sham, 2002), which informs the degree to which genes and environment contribute to the covariance between phenotypes. This model decomposed the covariance of caffeine use, ADHD, and disrupted sleep into common (i.e., shared across the three phenotypes) A, C, and E influences, and estimated specific/residual (i.e., unique to each phenotype) A, C, and E influences (note that estimates of total contribution of A, C, and E to a given phenotype typically vary, to a degree, across univariate and multivariate models). Based on the estimates derived from the freely estimated model, we constrained various paths (factor loadings) to zero to identify the best-fitting and most parsimonious model. Independent pathway models for the 2 year follow-up data did not converge and are thus not presented here.

Results of univariate models are presented in Figure 1. Between baseline and 2-year follow up, A influence on caffeine use increased (6% to 23%), E influence on ADHD increased (62% to 79%), and A influence on disrupted sleep emerged more substantially (0% to 31%). Under the independent pathway model (AIC=17983.31; BIC=18145.63; $\chi(114)=328.45$, $p<.001$), there was significant variance in caffeine use (12% [95% CI: 3%-27%], $p<.001$) and disrupted sleep (13% [95% CI: 4%-25%], $p<.001$), but not ADHD (1% [95% CI: 0%-8%], $p=.41$), attributable to the common A factor. Estimates for all loadings on the common C and E factors were nonsignificant ($ps=.08$-$.45$), though the common E loading for disrupted sleep was large and imprecise (74% [95% CI: 0%-100%], $p=.45$). Caffeine use was largely attributable to phenotype-specific E influences (84% [95% CI: 73%-96%], $p<.001$), ADHD was largely attributable to phenotype-specific A influences (61% [95% CI: 51%-71%], $p<.001$), and disrupted sleep emerged with no significant loadings. As ADHD displayed no significant loadings the common factors, we constrained those paths to zero. This did not deteriorate model

fit (Wald $\chi(3)=3.83$, $p=.28$), suggesting shared etiology of and caffeine use and disrupted sleep, but not ADHD.

Discussion

The present study examined the relationship between caffeine use, ADHD symptoms, and disrupted sleep in a sample of twins from within the ABCD Study. Within this first-phase examination of ABCD Study twins, results did not support a quasi-causal relationship between caffeine use and disrupted sleep in childhood (age 10) or pre-pubescence (age 12). Such findings suggest that a low to moderate level of caffeine use is not a causal driver of sleep problems in these age groups. Given the observed lack of association, we subsequently explored the genetic and environmental etiologies of these three phenotypes. Univariate models suggested that environmental influences drive sleep disruption at age 10, with genetic influences emerging more prominently at age 12. Additionally, we found that a freely estimated independent pathway model could be parameterized to allow loadings only on phenotype-specific factors for ADHD, but not caffeine use or disrupted sleep, without significant deterioration of model fit. That is, despite the frequent co-occurrence of sleep disruption and caffeine use with ADHD symptoms, they appear to have distinct genetic and environmental causes at age 10, at least in this first, early-stage evaluation of the ABCD Study twin sample. As genetic and environmental influences on behavioral phenotypes, including caffeine use, ADHD, and disrupted sleep, can vary over the course of development (e.g., Barclay et al., 2016; Kendler et al., 2008), these findings may reflect time-limited etiologic processes at this particular developmental stage. As such, the present study sets the stage for future examination of the stability of these relationships as the ABCD twin sample evolves throughout their development.

Limitations and Future Directions

While the ABCD sample is unprecedented in many respects, these findings should be interpreted in light of the following limitations. The ABCD twin sample is a large, current, geographically diverse sample recruited from 4 sites throughout the U.S. (Minnesota, Colorado, Virginia, Missouri), meaning that data are highly relevant to youth throughout many parts of the country. However, due to the inherent design and nature of the large-scale parent study, it was not designed to fully mirror the demographics of the U.S. in terms of race, ethnicity, or socioeconomic status. Thus, generalizability of current findings should be interpreted with these caveats in mind. Related, large samples almost invariably require a trade-off in terms of breadth and depth of measurement. Here, measures related to time of day at which caffeine was consumed, detailed assessment of sleep disruption (e.g., sleep latency, sleep duration, daily sleep reports), and objective measures of sleep quality (e.g., actigraphy) were not available. Finally, the evaluated sample reported relatively low levels off caffeine intake, ADHD symptoms, and disrupted sleep (Wheaton, 2018)- potentially due to the young age of the sample- which may have precluded sufficient variance to permit meaningful prediction. The low endorsement of these phenotypes across subjects may have impacted the results herein; future studies may benefit from re-examining these questions in other samples of youth with higher levels of caffeine intake, ADHD symptoms, and disrupted sleep, and/or with the ABCD sample at later follow-ups when they are older and more likely to show increases in these behaviors.

Conclusions

Overall, the present study provides a novel approach to exploring the associations between caffeine use, ADHD symptoms, and disrupted sleep in a sample of pre-adolescent twins, and suggests that further research in this area may be warranted. Our team looks forward to continuing to evaluating if the observed patterns hold, or if there are adolescent-emergent

associations between these behaviors, which we will evaluate during once ABCD data are available within the teen years when rates of caffeine use and sleep disruption tend to escalate (Branum et al., 2014; Paus et al., 2008; Wheaton et al., 2018).

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Tables

Table 1

Odds ratios from models predicting disrupted sleep from caffeine use and ADHD symptoms

Phenotype	Baseline	Year 2
	OR (95% CI)	OR (95% CI)
	MZ-DZ Model	
Within-Pair Caffeine Use	1.01 (0.98-1.04)	0.98 (0.93-1.03)
Between-Pair Caffeine Use	0.99 (0.96-1.01)	0.98 (0.94-1.02)
ADHD Symptoms	0.99 (0.94-1.04)	0.99 (0.93-1.06)
Caffeine WP * ADHD Symptoms	1.02 (0.99-1.05)	1.02 (0.99-1.05)
	MZ-Only Model	
Within-Pair Caffeine Use	1.05 (1.00-1.09)	0.93 (0.85-1.03)
Between-Pair Caffeine Use	**0.95 (0.92-0.99)**	1.00 (0.93-1.06)
ADHD Symptoms	1.00 (0.92-1.09)	0.99 (0.88-1.12)
Caffeine WP * ADHD Symptoms	1.02 (0.98-1.06)	1.02 (0.94-1.10)
	DZ-Only Model	
Within-Pair Caffeine Use	1.00 (0.96-1.04)	1.01 (0.94-1.07)
Between-Pair Caffeine Use	1.00 (0.96-1.04)	0.97 (0.91-1.06)
ADHD Symptoms	0.98 (0.92-1.05)	0.99 (0.91-1.06)
Caffeine WP * ADHD Symptoms	1.02 (0.97-1.07)	1.02 (0.99-1.05)

Note. WP=within=pair effect; bold type indicates significant effect at $p<05$.

Figures

Figure 1

Results of univariate models for focal variables at baseline (a) and 2-year follow-up (b)