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RESEARCH ARTICLE

Associations of maternal peripregnancy cannabis use with behavioral and developmental outcomes in children with and without symptoms of autism spectrum disorder: Study to Explore Early Development

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Abstract

Some studies report increased prevalence of autism spectrum disorder (ASD) and associated symptoms with prenatal cannabis exposure. We examined whether associations of maternal cannabis use from 3 months preconception through delivery ("peripregnancy") with behavior and development in the offspring varied with the presence of ASD symptoms. Children ages 30–68 months with ASD symptoms (i.e., met study criteria for ASD or had ASD symptoms on standardized assessments or community ASD diagnosis, $N = 2734$) and without ASD symptoms (other developmental delay/disorders or general population sample, $N = 3454$) were evaluated with the Child Behavior Checklist and Mullen Scales of Early Learning. We examined cannabis use during three time periods: peripregnancy, pregnancy, and only preconception. Peripregnancy cannabis exposure was reported for 6.0% of children with and 4.6% of children without ASD symptoms. Preconception-only cannabis use (versus no use) was associated with more aggressive behavior, emotional reactivity, and sleep problems in children with ASD symptoms, but not in children without ASD symptoms. Cannabis use during pregnancy was associated with increased attention and sleep problems in children with ASD symptoms; these associations did not differ significantly by ASD symptoms. Peripregnancy cannabis use was not associated with child developmental abilities regardless of ASD symptoms. In summary, associations of peripregnancy cannabis use with some behavioral outcomes differed in children with and without ASD symptoms. With rising cannabis use among pregnant women, future studies that examine a range of developmental risks associated with timing and patterns

At the time this work was conducted. Dr. Windham is now retired.

of cannabis use prior to conception as well as during pregnancy could inform clinical guidance.

Lay Summary

Children exposed to prenatal cannabis more often have behavior problems. Some behavior problems are also more common in children with autism spectrum disorder (ASD). We examined whether maternal cannabis use around the time of pregnancy was related to different behavior and learning problems in children with and without ASD symptoms. We found that among children with ASD symptoms, aggressive behavior, emotional reactivity, and sleep problems were more common if their mothers used cannabis before conception compared to mothers who did not. We did not find these relationships in children without ASD symptoms.

KEYWORDS

autism spectrum disorder, cannabis, child behavior, child preschool, developmental disabilities, pregnancy, prenatal risk factors, sleep wake disorders

INTRODUCTION

Among U.S. women, self-reported past-month cannabis use during the first trimester of pregnancy, when fetuses may be most susceptible to harm, increased from 5.6% in 2002–2005 to 8.1% in 2014–2017, with the highest use in the first month, before many women are aware of their pregnancy (Alshaarawy & Anthony, 2019). In 2017, 9.8% of recently delivered U.S. women reported using cannabis in the 3 months before pregnancy and 4.2% during pregnancy (Ko et al., 2020). Women may continue using cannabis during pregnancy to treat pregnancy-related symptoms (Bayrampour et al., 2019) or because they perceive little risk from use (Bayrampour et al., 2019; Jarlenski et al., 2017; Westfall et al., 2006).

The endocannabinoid system plays an important role in fetal brain development (Helliwell et al., 2004; Richardson et al., 2016). Cannabinoid receptors are widespread in the fetal cerebral cortex, hippocampus, and basal ganglia (Jutras-Aswad et al., 2009). Further, Δ9-tetrahydrocannabinol (THC) and its metabolites freely pass the placental and fetal blood–brain barriers (Little & VanBeveren, 1996). There is concern that perinatal exposure to exogenous cannabinoids could permanently alter neurodevelopmental processes in the offspring. In some animal models, prenatal cannabis exposure results in persistent adverse changes in cognitive performance, behavior, and stress response (Roncero et al., 2020). Comprehensive reviews of human studies have not identified consistent effects on global developmental level (Grant et al., 2018; Roncero et al., 2020; Warner et al., 2014). However, longitudinal human studies have reported associations between prenatal cannabis exposure and behavioral regulation deficits in the offspring, including increased externalizing behavior, impulsivity, hyperactivity, and delinquency, starting at ages 3–4 years and continuing into adolescence (Grant et al., 2018; Huizink, 2014; Metz & Borgelt, 2018; National Academies of Sciences, 2017; Richardson et al., 2016; Roncero et al., 2020). Some studies have documented increased anxiety and depressive symptoms in the offspring associated with first trimester cannabis use (Day et al., 2011; Gray et al., 2005; Leech et al., 2006). Disturbed sleep patterns during infancy and childhood have also been reported with prenatal cannabis exposure (Dahl et al., 1995; Day & Richardson, 1991).

One large retrospective birth registry study found that prenatal cannabis use recorded at the first prenatal visit (median 79th gestational day), versus no exposure, was associated with a significantly increased likelihood of being diagnosed subsequently (median follow-up 7.4 years) with autism spectrum disorder (ASD) (Corsi et al., 2020) although a smaller case–control study of children ages 3–5 found no association of ASD with cannabis use in the 3 months before pregnancy, during pregnancy, or in any trimester (DiGuiseppi et al., 2022). Persons with ASD commonly demonstrate deficits similar to those observed with prenatal cannabis use (as described above), such as attention deficits, anxiety, depression, and sleep disturbances, as well as intellectual disability (reviewed in Lyall et al., 2017). Associations of prenatal cannabis use with cognitive and behavioral outcomes might differ in children with symptoms of ASD compared to children without such symptoms, due to several possible mechanisms. Peripregnancy cannabis use could alter epigenetic processes relevant to neurodevelopment (Smith et al., 2020; Vassoler et al., 2014) that could influence the occurrence of both ASD symptoms (Smith et al., 2020) and behavior problems, or amplify the severity of behavior problems that often co-occur with ASD (Bacherini et al., 2021; Kanne & Mazurek, 2011; Mazurek et al., 2013; Richdale & Schreck, 2009; Wiggins, Levy, et al., 2015). Another potential mechanism is maternal psychopathology, which is associated with cannabis use (Defoe et al., 2019; Galéra et al., 2010; Galéra et al., 2013; Jacobus et al., 2016; Pedersen

et al., 2001; Pingault et al., 2013), and is also associated with having offspring with ASD (e.g., Chen et al., 2020; Chien et al., 2022; Jokiranta et al., 2013) *and* with more severe behavioral problems in their children with ASD (Baker et al., 2011; Ekas & Whitman, 2010; Firat et al., 2002; Machado Junior et al., 2016). Another possible mechanism is the resumption or persistence of maternal cannabis use in the post-partum period, which can adversely affect maternal caregiving (Dunn et al., 2002; Neger & Prinz, 2015) and, when combined with parental stress associated with parenting a child with symptoms of ASD (Crowell et al., 2019), might intensify problem behaviors in children with ASD symptoms but have less impact on those without such symptoms.

The aim of this cross-sectional analysis of data from the Study to Explore Early Development (SEED) was to examine and report effect modification by ASD symptoms of the associations of maternal cannabis use shortly prior to conception or during pregnancy with child behaviors and cognitive functioning.

METHODS

Study design

SEED is a multi-site case–control study of preschool children examining phenotypic characteristics and risk factors for ASD, for which the methods have been previously detailed (Schendel et al., 2012). SEED was approved by institutional review boards at the Centers for Disease Control and prevention and each study site.

Participants

Children aged 2–5 years were enrolled in three phases —2007-2011 (SEED1), 2012–2016 (SEED2), and 2017–2020 (SEED3) — at sites in Colorado, Georgia, Maryland, and North Carolina (SEED1-3), California and Pennsylvania (SEED1-2), and Missouri and Wisconsin (SEED3). Children with ASD and other developmental delays/disorders were recruited from educational and clinical settings. Children from the general population were recruited from randomly sampled birth certificates. Families were sent an introductory letter then telephoned to assess eligibility. Eligible children were born in a study catchment area and, at the time of recruitment, resided in the same catchment area with their caregiver aged ≥18 years, who spoke English or, at California and Colorado sites, English or Spanish, and who had taken care of the child continuously since they were 6 months old (or younger). Demographics and characteristics of the study catchment sites have been described (DiGuiseppi et al., 2016; Schendel et al., 2012). Enrolled children were ages 30.0 to 68.9 months at their clinical evaluation, to maintain diagnostic accuracy for ASD and the appropriate age range for validated study instruments, while limiting potential maternal recall bias for events in pregnancy and early life. Written informed consent was obtained from participating families.

Data collection and study group classification

Enrolled families completed telephone interviews and self-administered forms about the child, parents, and household, including the Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2000) and the Social Responsiveness Scale (SRS) (Constantino, 2002). The Social Communication Questionnaire (SCQ) (Rutter et al., 2003) was administered to identify possible undiagnosed ASD, defined as a score ≥ 11 (Allen et al., 2007; Lee et al., 2007). Enrolled children received developmental assessments including the Mullen Scales of Early Learning (MSEL) (Mullen, 1995). Children who attended a clinic visit for developmental assessment were included in this analysis.

The process for classifying children into SEED study groups has been detailed previously (Wiggins, Reynolds, et al., 2015). Briefly, children considered possibly to have ASD based on pre-existing ASD diagnosis, SCQ score ≥ 11, or observed ASD symptoms during MSEL administration, regardless of source population, were evaluated with the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1999) and Autism Diagnostic Interview-Revised (ADI-R) (Gotham et al., 2007). Children meeting cutoff scores on these instruments were classified as having ASD (Schendel et al., 2012; Wiggins, Reynolds, et al., 2015), while those evaluated for possible ASD who did not meet study cutoff scores were classified as having a developmental disorder (DD) with ASD symptoms. Children with a previously diagnosed DD who were not considered to possibly have ASD (as defined above) were classified as having DD without ASD symptoms. Children from the birth certificate sample were classified as the general population group. For this analysis, children classified as ASD or DD with ASD symptoms were combined into the study group, "children with ASD symptoms." Children classified as DD without ASD symptoms or general population were combined into the study group, "children without ASD symptoms." As reported elsewhere (Wiggins, Levy, et al., 2015), in the two SEED classifications comprising "children with ASD symptoms," average SRS and ADOS scores indicated mild to moderate symptoms, while in the two classifications comprising "children without ASD symptoms," average SRS scores were within the typical range.

Exposure

During the interview, the child's biological mother was asked, "Between three months before becoming pregnant and the date of the child's birth, did you use any of the

following recreational or street drugs …?" followed by a list that included marijuana. Mothers responding "yes" were asked about their use each month from 3 months before pregnancy through delivery. "Any peripregnancy use" was defined as any maternal cannabis use from 3 months before pregnancy through the third trimester. "Any use during pregnancy" was defined as use during any trimester, regardless of any preconception use. "Use only preconception" was defined as any use in the 3 months before pregnancy but not during pregnancy. The latter two exposure periods are mutually exclusive. We also explored exposure to "any use during the first trimester."

Outcomes

Primary outcomes included emotional and behavioral problems, assessed by the CBCL, and cognitive functioning, assessed by the MSEL. The CBCL is a standardized assessment that asks mothers to report emotional and behavioral problems exhibited within the previous 2 months. Items are scored on the following syndrome scales: aggressive behavior and attention problems (i.e., externalizing behaviors); emotionally reactive, anxious/depressed, somatic complaints, and withdrawn (i.e., internalizing behaviors); and sleep problems. Syndrome scales are derived using data-driven techniques and include constructs not measured with DSM-5 oriented scales (e.g., aggressive behavior). The MSEL measures development from 0 to 68 months, assessing four cognitive domains (visual reception, fine motor skills, receptive language, and expressive language). Among children with ASD symptoms, we also examined ASD symptom severity based on the ADOS calibrated severity score (Gotham et al., 2009), which ranges from 1 to 10.

Other variables

Mothers were asked about any use of alcohol, tobacco, and illicit drugs during pregnancy, and history of ever being diagnosed with depression by a doctor or other healthcare provider ("maternal depression"). Sociodemographic variables included child sex, maternal race/ethnicity, maternal educational attainment at child's birth, and annual household income in the past 12 months, categorized as shown in Table 1.

Statistical analysis

We examined associations of each outcome with maternal cannabis use during the peripregnancy period, only during preconception, and during pregnancy, and explored associations with first trimester use. For all associations, the comparison group was children whose mothers reported no peripregnancy cannabis use (non-users). Mixed effects models were used to test mean differences in standardized t-scores and generalized linear mixed effects models were used to test odds of having a t-score in the clinical/borderline (CBCL syndrome scales, t-score ≥ 65 vs. <65) or below average (MSEL cognitive domains, *t*-score < 40 vs. ≥40) range. We used CBCL t-scores instead of raw scores because we were most interested in the degree to which our sample deviated from normative samples. Although CBCL *t*-scores are truncated at 50, both study groups (i.e., with and without ASD symptoms) included children with developmental delays, so distributions were less skewed than samples of children without any developmental delays. Given the differing legal status and social norms around cannabis use among the various states, site was included as a random effect in all models. SEED Phase was included as a covariate in all models to account for rising cannabis use over the past two decades. Statistical significance of fixed effects was tested using a type III F-test for fixed effects using Satterthwaite's degrees of freedom. Maternal education and any tobacco use and alcohol use while pregnant were included in all adjusted models, based on known associations of these characteristics with prenatal cannabis use (El Marroun et al., 2008; van Gelder et al., 2010) and cognitive and behavioral outcomes (Carneiro et al., 2016; Duncan & Magnuson, 2012; Huizink & Mulder, 2006). Children with missing covariate information ($N = 20$ for CBCL models, $N = 22$ for MSEL models) were excluded. As a supplementary analysis, we examined models including maternal depression, given reported associations of cannabis use with depressive disorders (Lev-Ran et al., 2013), and of maternal depressive symptoms with both children's behavioral problems (Goodman et al., 2011) and negatively biased reporting of child behavior (De Los Reyes & Kazdin, 2005). We did not include maternal depression in primary analyses because depression may lie in the causal pathway between maternal cannabis use and behavior problems in the offspring (National Academies of Sciences, 2017). To test for differences in associations between cannabis exposure and primary outcomes according to the presence or absence of ASD symptoms, we included an interaction between the exposure and presence of ASD symptoms as an interaction term in the respective models. The significance of these interactions was tested using a $\chi 2$ distribution, with two-sided alpha = 0.05. R version 4.3.1 (2023-06-16) and the tidyverse package v(2.0.0) were used for data manipulation. SAS version 9.4 M7 (2020-08-18) and the procedures MIXED and GLIMMIX were used for analysis.

RESULTS

There were 6256 children who completed the clinic visit and were classifiable into one of two study groups

TABLE 1 Maternal and child characteristics according to presence or absence of autism spectrum disorder (ASD) symptoms in the offspring, Study to Explore Early Development.

		No ASD symptoms $N = 3454$	ASD symptoms $N = 2734$
		N (%)	N (%)
Any peripregnancy cannabis use	Yes	158 (4.6)	164 (6.0)
Any cannabis use during pregnancy[a]	Yes	81 (2.3)	93 (3.4)
Cannabis use during preconception period only[a]	Yes	72 (2.1)	70 (2.6)
Child sex	Female	1488 (43.1)	604 (22.1)
	Male	1966 (56.9)	2130 (77.9)
Maternal race/ethnicity[b]	Hispanic	372 (10.8)	381 (13.9)
	Non-hispanic black	490 (14.2)	712 (26.1)
	Non-hispanic white	2306 (66.8)	1362 (49.9)
	Other/multiracial	284 (8.2)	277 (10.1)
Maternal education (at child's birth)	Bachelor's Degree or Greater	2281 (66.0)	1249 (45.7)
	Less than Bachelor's Degree	1173 (34.0)	1485 (54.3)
Household income (at time of pregnancy)	Less than $50,000	969 (28.7)	1244 (47.2)
	$50,000 or More	2405 (71.3)	1391 (52.8)
Ever smoker	Yes	1144 (33.1)	1039 (38.0)
Smoked while pregnant	Yes	323 (9.4)	453 (16.6)
Used alcohol while pregnant	Yes	2002 (58.1)	1257 (46.0)
Used other illicit drugs while pregnant (including cocaine, ecstasy, or methamphetamines)	Yes	41 (1.2)	39 (1.4)
Study cohort	SEED 1	1556 (45.0)	989 (36.2)
	SEED 2	1270 (36.8)	1058 (38.7)
	SEED 3	628 (18.2)	687 (25.1)
		Mean (SD)	**Mean (SD)**
Child age		55.1 (9.6)	55.4 (9.0)
Child Behavior Checklist (CBCL) syndrome scale T-Scores (missing = 190)			
Externalizing problems			
	Aggressive behavior	52.4 (5.7)	60.4 (10.9)
	Attention problems	53.0 (5.4)	63.0 (8.9)
Internalizing problems			
	Emotionally reactive	52.9 (5.5)	61.3 (10.4)
	Anxious/depressed	52.0 (4.3)	56.9 (8.7)
	Somatic complaints	53.1 (5.3)	59.4 (8.3)
	Withdrawn	53.3 (5.6)	68.0 (10.7)
Sleep problems		53.3 (5.4)	59.0 (10.6)
Mullen Scales of Early Learning domain T-scores (missing = 98)			
Visual reception T-score		50.9 (11.9)	36.4 (15.2)
Fine motor T-Score		46.9 (12.2)	31.5 (12.4)
Receptive language T-Score		49.1 (12.6)	31.8 (13.1)
Expressive language T-Score		47.9 (12.0)	31.0 (11.9)
Autism Diagnostic Observation Schedule (ADOS) severity score		–	6.2 (2.7)

Abbreviation: SD = Standard deviation.
[a]Missing data on specific time periods of use for 5 mothers of offspring with no ASD symptoms and 1 mother of offspring with ASD symptoms.
[b]Missing = 4 (<0.1%) for race/ethnicity, 179 (2.9%) for household income, 3 (<0.1%) for smoking during pregnancy and 12 (0.2%) for alcohol use during pregnancy.

TABLE 2 Cannabis use by time period among mothers with any peripregnancy use according to presence or absence of autism spectrum disorder (ASD) symptoms in the offspring, Study to Explore Early Development.

	No ASD symptoms *N* (%)	ASD symptoms *N* (%)	All *N* (%)
Any peripregnancy use[a]	158 (100)	164 (100)	322 (100)
Any use in 3 months preconception[b]	141 (92)	156 (96)	296 (94)
Use only in 3 months preconception	72 (47)	70 (43)	142 (45)
Any use during pregnancy	81 (53)	93 (57)	174 (55)
Any use in first trimester	74 (48)	86 (53)	160 (51)
Any use in second trimester	27 (18)	34 (21)	61 (19)
Any use in third trimester	22 (14)	24 (15)	46 (15)

[a]Cannabis use at any time from 3 months preconception through delivery.
[b]Denominator for use in specified time periods excludes missing data on period of use for 5 mothers of offspring with no ASD symptoms and 1 mother of offspring with ASD symptoms.

(i.e., children with and without ASD symptoms). Mothers of 6188 (98.9%) children supplied information on peripregnancy cannabis use and 6182 (98.8%) provided data on use by time period (i.e., preconception and trimester). Among those with information on peripregnancy cannabis use, CBCL data were complete on 5998 (96.9%) children and MSEL data were complete on 6090 (98.4%) children.

Mothers of 322 (5.2%) children reported any peripregnancy cannabis use, while 174 (2.8%) reported use during pregnancy. Of mothers of children with ASD symptoms, 164 (6.0%) reported any peripregnancy cannabis use versus 158 (4.6%) mothers of children without ASD symptoms ($p = 0.012$) (Table 1). Among mothers reporting peripregnancy cannabis use, use declined markedly over the course of pregnancy, from 94% in the pre-conception period to 15% in the third trimester, with similar declines in use by trimester in both study groups (Table 2).

Table 1 shows sociodemographic characteristics and maternal smoking, alcohol and other illicit drug use during pregnancy for each study group. Children with and without ASD symptoms differed statistically significantly ($p < 0.001$) for all sociodemographics and maternal substance use during pregnancy except child age ($p = 0.181$) and other illicit drug use during pregnancy ($p = 0.408$).

Table 1 shows mean CBCL t-scores for each syndrome scale and mean MSEL domain scores by presence or absence of ASD symptoms. Relationships of maternal cannabis use with child emotional and behavioral problems and cognitive functioning among children with and without ASD symptoms are presented below and in Figures 1 and 2 and Table 3. Figures 1 and 2 show adjusted mean differences (AMD) in CBCL and MSEL *t*-scores, respectively, between children whose mothers reported use in the specified time period versus no use, by presence or absence of ASD symptoms. Table 3 shows adjusted odds of having clinical/borderline CBCL syndrome scale t-scores (i.e., ≥ 65) and below average MSEL domain t-scores (i.e., <40), between children whose mothers reported use in the specified time period versus no use, in children without and with ASD symptoms.

Child emotional and behavioral problems

Externalizing behaviors

Adjusted associations of any peripregnancy cannabis use (i.e., use preconception and/or during pregnancy) and preconception-only cannabis use with aggressive behavior t-scores differed by presence of ASD symptoms (Figure 1). Among children with ASD symptoms, mean aggressive behavior *t*-scores were nearly 3 points higher in offspring of peripregnancy cannabis users compared to non-users, and more than 5 points higher in offspring of mothers who used cannabis only preconception vs. non-users, whereas peripregnancy and preconception-only cannabis use were not associated with higher aggressive behavior t-scores among children without ASD symptoms. Cannabis use during pregnancy (irrespective of preconception use) was not significantly associated with aggressive behavior t-scores in either group. Associations of peripregnancy, during pregnancy, and preconception-only cannabis use with clinical/borderline aggressive behavior t-scores did not differ significantly between children with and without ASD symptoms (Table 3). Among children with ASD symptoms, offspring of mothers who used cannabis at any time in the peripregnancy period or only during preconception were significantly more likely to score in the clinical/borderline range compared to those whose mothers did not use cannabis (Table 3).

Mean attention problem *t*-scores were modestly higher with cannabis use in all three periods, among both children with and without ASD symptoms, in adjusted models (Figure 1). Among children with ASD symptoms, increases with peripregnancy use and use during pregnancy were statistically significant. The odds of having clinical/borderline attention problem *t*-scores with cannabis use peripregnancy and during pregnancy compared to

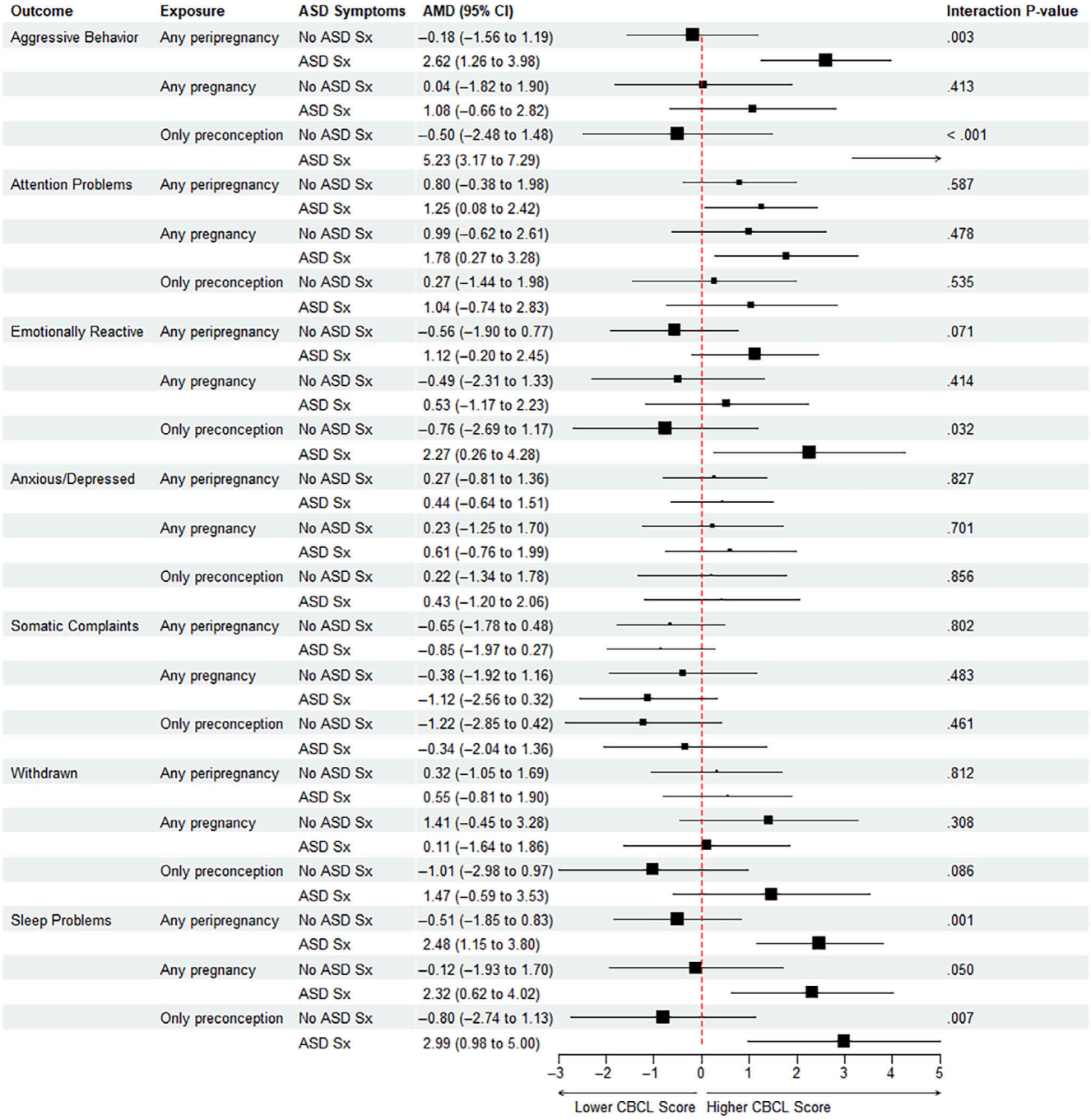

FIGURE 1 Adjusted mean differences in emotional and behavioral problems t-scores between children whose mothers did and did not report cannabis use during each specified period, according to the presence or absence of symptoms of autism spectrum disorder (ASD). Adjusted models include terms for maternal education, maternal alcohol and tobacco use during pregnancy, and SEED phase, with a random intercept for site. Sizes of the point estimates represent the inverse sizes of the interaction *p*-values. AMD, adjusted mean difference; ASD, autism spectrum disorder; CBCL, child behavior checklist; Sx, symptoms.

no use were modestly but not significantly increased in both children with and without ASD symptoms.

Internalizing behaviors

Findings were somewhat inconsistent for associations of maternal cannabis use with internalizing subscales. Adjusted associations of preconception-only cannabis use with mean emotionally reactive *t*-scores differed by presence of ASD symptoms (Figure 1). Among children with ASD symptoms, offspring whose mothers used cannabis only preconception had mean emotionally reactive t-scores more than 2 points higher than offspring of nonusers; among children without ASD symptoms, no difference was seen (Figure 1). A positive association of

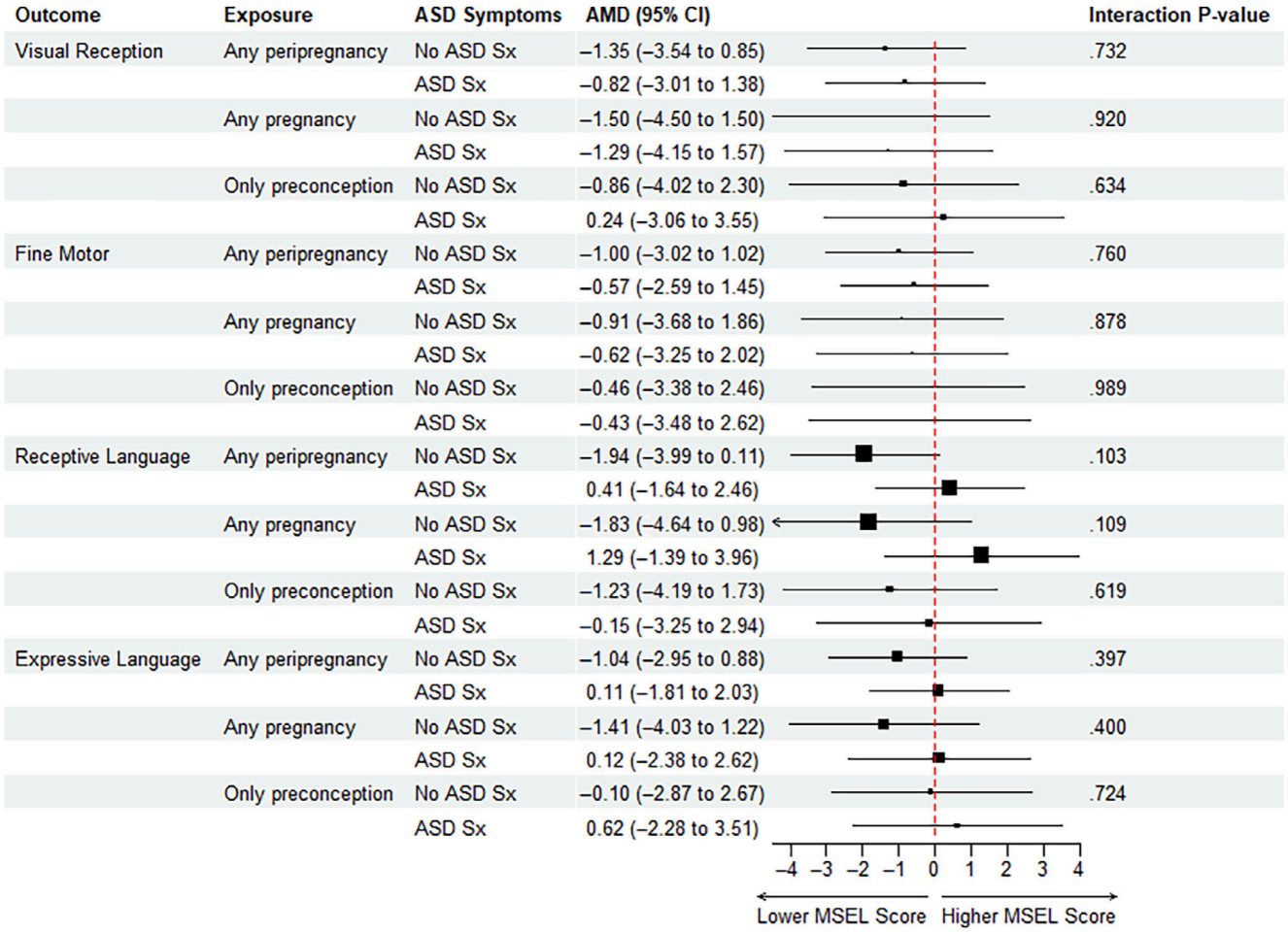

FIGURE 2 Adjusted mean differences in cognitive functioning t-scores between children whose mothers did and did not report cannabis use during each specified period, according to the presence or absence of symptoms of autism spectrum disorder (ASD). Adjusted models include terms for maternal education, maternal alcohol and tobacco use during pregnancy, and SEED phase, with a random intercept for site. Sizes of the point estimates represent the inverse sizes of the interaction *p*-values. AMD, adjusted mean difference; ASD, autism spectrum disorder; Sx, symptoms; MSEL, Mullen Scales of Early Learning.

preconception-only cannabis use with clinical/borderline emotionally reactive t-scores was not statistically significant. Adjusted associations of cannabis use in peripregnancy and pregnancy with odds of clinical/borderline anxious/depressed *t*-scores also differed by ASD symptoms (Table 3). Among children *without* ASD symptoms, the odds of having a clinical/borderline anxious/depressed *t*-score was more than twice as high among the offspring of mothers who used cannabis peripregnancy or during pregnancy compared to offspring of nonusers; these associations were not observed among children *with* ASD symptoms (Table 3). However, these results were inconsistent with AMDs in anxiety/depression scores with peripregnancy cannabis exposure, which did not differ significantly between groups. AMDs were uniformly small (0.2 to 0.6 points) and nonsignificant in both groups for all exposure periods. There were otherwise no associations between maternal cannabis use in any exposure period and any child internalizing subscales, regardless of ASD symptoms.

Sleep problems

Associations of cannabis use with sleep problem *t*-scores in the peripregnancy and preconception periods differed by presence of ASD symptoms (Figure 1). Mean *t*-scores were 2 to 3 points higher with use in each time period compared to no use among children with ASD symptoms, but not children without ASD symptoms. Adjusted odds of having clinical/borderline sleep problem *t*-scores did not differ between the two groups for any exposure periods; odds ratios were consistent with the null in both groups (Table 3).

Cognitive functioning

Associations of MSEL domain t-scores with maternal cannabis use, regardless of exposure period, did not differ between children with and without ASD symptoms and no AMDs were statistically significant in either group

TABLE 3 Odds of clinical/borderline behavior problems *t*-scores and below average cognitive functioning *t*-scores between children whose mothers did and did not report cannabis use in each specified time period, according to presence or absence of ASD symptoms, Study to Explore Early Development.

Outcome	Exposure	Adjusted odds ratio (95% CI)		Interaction test
		No ASD symptoms	ASD symptoms	*p*-value
CBCL scores				
Aggressive behavior clinical/borderline (≥ 65) versus normal (<65)	Any peripregnancy	1.55 (0.85, 2.80)	1.46 (1.03, 2.07)	0.868
	Any pregnancy	1.80 (0.86, 3.75)	1.11 (0.71, 1.74)	0.265
	Only preconception	1.10 (0.39, 3.11)	2.33 (1.38, 3.95)	0.204
Attention problems clinical/borderline (≥ 65) versus normal (<65)	Any peripregnancy	1.23 (0.70, 2.16)	1.33 (0.94, 1.88)	0.799
	Any pregnancy	1.22 (0.57, 2.60)	1.57 (0.99, 2.46)	0.569
	Only preconception	0.76 (0.27, 2.13)	1.18 (0.70, 1.99)	0.450
Emotionally reactive clinical/borderline (≥ 65) versus normal (<65)	Any peripregnancy	1.01 (0.56, 1.80)	1.12 (0.79, 1.57)	0.764
	Any pregnancy	1.07 (0.50, 2.29)	0.90 (0.58, 1.40)	0.689
	Only preconception	0.86 (0.34, 2.18)	1.56 (0.92, 2.62)	0.273
Anxious/depressed clinical/borderline (≥ 65) versus normal (<65)	Any peripregnancy	2.23 (1.17, 4.25)	1.01 (0.67, 1.53)	0.038
	Any pregnancy	2.73 (1.25, 5.95)	1.07 (0.64, 1.80)	0.046
	Only preconception	1.83 (0.64, 5.21)	0.97 (0.51, 1.84)	0.308
Somatic complaints clinical/borderline (≥ 65) versus normal (<65)	Any peripregnancy	0.85 (0.45, 1.60)	0.81 (0.56, 1.17)	0.906
	Any pregnancy	1.20 (0.56, 2.56)	0.72 (0.45, 1.17)	0.259
	Only preconception	0.54 (0.17, 1.73)	0.95 (0.55, 1.65)	0.380
Withdrawn clinical/borderline (≥ 65) versus normal (<65)	Any peripregnancy	1.47 (0.79, 2.73)	0.88 (0.63, 1.24)	0.152
	Any pregnancy	1.65 (0.74, 3.68)	0.89 (0.57, 1.38)	0.176
	Only preconception	1.13 (0.40, 3.15)	0.93 (0.56, 1.57)	0.747
Sleep problems clinical/borderline (≥ 65) versus normal (<65)	Any peripregnancy	1.10 (0.56, 2.18)	1.28 (0.88, 1.85)	0.700
	Any pregnancy	1.45 (0.64, 3.26)	1.30 (0.82, 2.08)	0.825
	Only preconception	0.80 (0.25, 2.61)	1.33 (0.76, 2.34)	0.441
Mullen Scores				
Visual reception below average (< 40) versus normal (≥ 40)	Any peripregnancy	1.08 (0.69, 1.69)	1.14 (0.81, 1.62)	0.852
	Any pregnancy	1.38 (0.79, 2.42)	1.09 (0.69, 1.71)	0.502
	Only preconception	0.62 (0.28, 1.38)	1.08 (0.65, 1.82)	0.249
Fine motor below average (< 40) versus normal (≥ 40)	Any peripregnancy	1.15 (0.79, 1.67)	1.10 (0.74, 1.63)	0.871
	Any pregnancy	1.13 (0.68, 1.88)	1.09 (0.64, 1.83)	0.906
	Only preconception	0.99 (0.57, 1.72)	1.00 (0.56, 1.78)	0.977
Receptive language below average (< 40) versus normal (≥ 40)	Any peripregnancy	0.95 (0.64, 1.41)	0.98 (0.66, 1.46)	0.909
	Any pregnancy	0.84 (0.49, 1.45)	0.76 (0.46, 1.26)	0.792
	Only preconception	0.96 (0.53, 1.72)	1.26 (0.67, 2.34)	0.534
Expressive language below average (< 40) versus normal (≥ 40)	Any peripregnancy	0.86 (0.57, 1.29)	1.13 (0.75, 1.71)	0.338
	Any pregnancy	0.73 (0.42, 1.29)	1.04 (0.61, 1.77)	0.373
	Only preconception	0.97 (0.54, 1.75)	1.15 (0.62, 2.14)	0.696

Note: Adjusted models include terms for maternal education, maternal alcohol and tobacco use during pregnancy, and SEED phase, with a random intercept for site.

(Figure 2). Odds of having below average MSEL domain scores with maternal cannabis use in any exposure period vs. no use did not differ in children with and without ASD symptoms, and no associations were statistically significant (Table 3).

ADOS severity score

Among children with ASD symptoms, the mean severity score was nearly one point higher in offspring of mothers who used cannabis only preconception versus mothers who did not use cannabis (AMD = 0.76 [95% CI: 0.14, 1.37]). Severity scores did not differ significantly between offspring of mothers with peripregnancy use (AMD = 0.34 [−0.08, 0.77]) or use during pregnancy (AMD = 0.05 [−0.50, 0.60]) compared to offspring of mothers without cannabis use.

Maternal depression

Additional adjustment for maternal depression did not substantively change the magnitude or direction of the observed associations (Tables S1 and S2).

Exploratory analysis

Associations of any first trimester cannabis use with emotional/behavioral and cognitive outcomes were consistent with findings for any use during pregnancy: neither mean differences in *t*-scores nor odds of clinical/borderline CBCL *t*-scores or below average MSEL domain *t*-scores differed between children with and without ASD symptoms ($p_{interaction}$ >0.05 for all outcomes). Among children with ASD symptoms, the association of first trimester cannabis use with mean sleep problems t-scores (AMD = 2.10 [0.33, 3.87]) was similar in magnitude, direction and significance to the association observed with any pregnancy use. Associations of first trimester use with mean attention problems *t*-scores in children with ASD symptoms, and with odds of clinical/borderline anxious/depressed *t*-scores in children *without* ASD symptoms, were similar in direction but attenuated compared to associations observed with any use during pregnancy, and no longer statistically significant. No other significant associations of cannabis use during the first trimester with behavioral or cognitive outcomes were observed.

DISCUSSION

Although a previous analysis of SEED data did not find an association between peripregnancy cannabis use and ASD (DiGuiseppi et al., 2022), in our current analysis we observed that associations of maternal cannabis use during peripregnancy with selected child emotional and behavioral problems varied in the presence of ASD symptoms. We did not observe associations of peripregnancy cannabis use with developmental indicators, regardless of ASD symptoms.

Among children with ASD symptoms, aggressive behavior problems t-scores were on average more than 5 points higher, and the odds of having clinical/borderline aggressive behavior problems *t*-scores was twice as likely, in offspring of mothers who used cannabis only during preconception compared to offspring of mothers who did not use cannabis. In a Dutch population-based birth cohort, cannabis use only before pregnancy was similarly associated with significantly increased externalizing (but not internalizing) problems at age 8 years (El Marroun et al., 2019). In contrast, we did not observe an association between preconception-only cannabis use and aggressive behavior problems in offspring without ASD symptoms. We also found that maternal preconception-only cannabis use was associated with sleep problem t-scores that were nearly 3 points higher, and emotionally reactive t-scores that were more than two points higher, compared to no maternal cannabis use, but only in children with ASD symptoms.

Several potential explanations for the associations of preconception-only cannabis use with more aggressive behavior, emotional reactivity, and sleep problems in children with ASD symptoms but not children without such symptoms may warrant further research. As described in Sajdeya et al. (2021), preconception cannabis use could potentially lead to maternal hormonal, immunological, neurological, or genetic changes that interfere with neurodevelopment of the fetus. Animal evidence suggests that preconception cannabis exposure alters epigenetic processes, potentially resulting in heritable changes in genes and molecular pathways relevant to neurodevelopment (Smith et al., 2020; Vassoler et al., 2014). Such changes may mediate a relationship between preconception exposure to cannabis and occurrence of ASD (Smith et al., 2020), and may similarly mediate a relationship between preconception cannabis exposure and behavior problems.

Preconception cannabis exposure might also act to amplify regulatory and behavior problems that often co-occur with ASD. Although not primary features of ASD, aggressive behavior, emotional reactivity, and sleep problems are common in children with ASD (Bacherini et al., 2021; Kanne & Mazurek, 2011; Mazurek et al., 2013; Richdale & Schreck, 2009; Wiggins, Levy, et al., 2015). Epigenetic modifications (Smith et al., 2020), or maternal distress in early pregnancy (Weinstock, 2008) associated with cannabis withdrawal syndrome (Bahji et al., 2020; Graves et al., 2022), might mediate a relationship between preconception exposure to cannabis and increased *severity* of symptoms that co-occur with ASD, resulting in children with ASD

symptoms having on average higher behavior problem scores than children with ASD symptoms who were not exposed to cannabis. In contrast, among children without ASD symptoms, such amplification may not have been observed because co-occurring behavior problems were less common or milder to start with.

Rather than direct or indirect effects of preconception cannabis exposure on neurodevelopment, our findings could be explained if a common underlying etiology results in mothers both using cannabis and having children with problem behaviors and ASD symptoms. Maternal psychopathology is potentially one such etiology. Having externalizing behavior and conduct problems increases the likelihood of early initiation and use of cannabis, which is in turn associated with impaired mental health and problematic cannabis use (Defoe et al., 2019; Galéra et al., 2010; Galéra et al., 2013; Jacobus et al., 2016; Pedersen et al., 2001; Pingault et al., 2013). Aggressive behavior and antisocial problems in the mother also predict externalizing behaviors in the offspring (Davies et al., 2012) and are associated with maternal substance use problems, affective disorders, and low socioeconomic status, which can further contribute to child behavior problems (Antunez et al., 2018; Davies et al., 2012; Emery et al., 1999). The association between depression and substance use is also well-established (Lev-Ran et al., 2013), which may reflect shared neurocognitive mechanisms, common underlying risk factors, or self-medication of depressive symptoms with cannabis (Kuhns et al., 2022). Persistent depressive symptoms in the mother have been associated with greater emotional and behavioral difficulties in the offspring at age 5 years (van der Waerden et al., 2015). Parents with psychiatric diagnoses are also more likely to have offspring with ASD (e.g., Chen et al., 2020; Chien et al., 2022; Jokiranta et al., 2013), and their offspring with ASD are more likely to have more severe behavioral problems (Baker et al., 2011; Ekas & Whitman, 2010; Firat et al., 2002; Machado Junior et al., 2016). Thus, maternal psychopathology may underlie greater likelihood of maternal cannabis use, ASD symptoms and behavioral problems in the offspring. Adjustment for mother having ever been diagnosed with depression did not materially change our results. However, we had no measures of current depression symptoms or symptom severity, nor of maternal aggressive behavior or antisocial problems.

Another possible mechanism is effects of maternal cannabis use in early childhood on caregiving. Many women who achieve abstinence during pregnancy will resume cannabis use post-partum. Preconception cannabis use may thus be a marker for maternal cannabis use in infancy and early childhood (De Genna et al., 2022; Fried et al., 1985; Thomson et al., 2023). Some studies have shown that parents with substance abuse spend less time interacting with their children, are less satisfied with their parental relationships, have problems with attachment to the child, and exhibit low bonding behaviors starting in infancy (reviewed in Dunn et al., 2002; Neger & Prinz, 2015). Negative effects of maternal cannabis use during infancy and early childhood on caregiving and attachment, when combined with strains on parent–child interactions and parental stress associated with parenting a child with ASD (Crowell et al., 2019), may exacerbate problem behaviors in the child, compared to effects of maternal cannabis use on caregiving of children without ASD symptoms.

It is possible that preconception-only cannabis use is not associated with child behavior differently in children with ASD symptoms, but rather that mothers who use cannabis preconception differentially report both ASD symptoms and problem behaviors in their offspring. Whether cannabis use specifically, or substance use in general, leads to inaccurate reporting of emotional or behavioral problems in children has not been established (Chilcoat & Breslau, 1997; Olino et al., 2020). However, studies have demonstrated over-reporting of externalizing, and in some studies, internalizing, problem behaviors by parents experiencing depression, anxiety, or stress, with the strongest, most consistent evidence for parents with depressive symptoms (reviewed in De Los Reyes and Kazdin (2005)). Mental health disorders are associated with substance use, as noted above, raising the possibility that over-reporting could account for the associations of maternal cannabis use with child emotional and behavioral symptoms observed in our study. Systematic reviews have demonstrated high proportions of depressive, anxiety and obsessive-compulsive disorders diagnosed in mothers who have a child with ASD (Schnabel et al., 2020) and higher levels of stress among parents of children with ASD (Hayes & Watson, 2013), which could have similarly led mothers of children with ASD symptoms to over-report their child's behavior problems compared to mothers of children without ASD symptoms. Thus, we might have found stronger associations of pre-conception cannabis use with behavior problems in children with ASD symptoms compared to those without ASD symptoms due to inaccurate (i.e., over) reporting.

Mothers of children with both ASD symptoms and problem behaviors may also differentially recall or report their peripregnancy cannabis use. Mothers of offspring with ASD symptoms may be more likely to accurately recall cannabis use around the time of pregnancy than mothers of typically developing children, for example, if mothers of children with ASD symptoms have already thought carefully about their past exposure history in an effort to understand why their child might have developed ASD symptoms (i.e., recall bias). Since children with ASD symptoms are also more likely to have behavioral problems, this could result in observing an association between cannabis use and behavior problems only in children with ASD symptoms.

This study has several potential limitations. As noted above, maternal cannabis use was self-reported.

While self-reported prenatal cannabis use collected 1 year after delivery correlates moderately well with data from antenatal interviews (Jacobson et al., 2002), recall may be less accurate 4–5 years later. Women may have underreported cannabis use during pregnancy due to social stigma associated with substance use while pregnant. In addition, some SEED sites were in states without legalized cannabis use during data collection periods; perceived legal ramifications may have contributed to under-reporting. Women who used cannabis during pregnancy and had offspring with ASD may be particularly reluctant to report its use due to feelings of guilt and blame regarding their child's diagnosis (Elder, 1994; Gray, 1995; Mercer et al., 2006). We lacked information on route of ingestion, dose, or frequency of cannabis use. We included broad measures of deficits via the CBCL and MSEL but were unable to examine more nuanced indicators of executive functioning deficits. Although our sample included more than 6000 participants, relatively few mothers reported peripregnancy cannabis use, limiting power for some analyses. Sample reductions after stratification by exposure period precluded adjusting for a wider array of confounding variables, although we were able to adjust for indicators of socioeconomic status, other substance use, time trends (i.e., SEED phase), and in supplementary analyses, depression. Lifestyle and health-related behaviors of participants who agreed to take part in SEED's intensive research protocol may differ from those not represented in this study, affecting generalizability of our findings.

Study strengths include research-reliable administration of standardized instruments to evaluate behavior and cognitive development and to classify children with and without ASD symptoms, identification and inclusion of children not previously diagnosed with autism (perhaps reflecting milder symptoms), and ability to adjust for multiple covariates associated with cannabis use and child behavior (Schendel et al., 2012).

CONCLUSIONS

With rising cannabis use among pregnant women, our findings support the need for further research about its potential effects on the offspring. Future studies can examine a range of developmental risks associated with the timing and patterns of cannabis use prior to conception as well as during pregnancy. Another promising direction is the exploration of potential explanations for emotional and behavioral problems associated with maternal preconception cannabis use among children with ASD symptoms but not without ASD symptoms, for example, examining interactions between underlying genetic or epigenetic risk and cannabis exposure.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS STATEMENT

This study was approved by institutional review boards at the Centers for Disease Control and Prevention and each study site.

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