Original Research

Prenatal Nicotine or Cannabis Exposure and Offspring Neurobehavioral Outcomes

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OBJECTIVE: To study the association between nicotine or cannabis metabolite presence in maternal urine and child neurodevelopmental outcomes.

METHODS: We conducted a secondary analysis of two parallel multicenter randomized controlled trials of treatment for hypothyroxinemia or subclinical hypothyroidism among pregnant individuals enrolled at 8–20 weeks of gestation. All maternal–child dyads with a maternal urine sample at enrollment and child neurodevelopmental testing were included (N=1,197). Exposure was urine samples positive for nicotine (cotinine) or cannabis 11-nor-9-carboxy-delta-9-tetrahydrocannabinol [THC-COOH]) or both metabolites. Primary outcome was child IQ at 60 months. Secondary outcomes included cognitive, motor and language, attention, behavioral and social competency, and differential skills assessments at 12, 24, 36, and 48 months. Quantile regression analysis was performed with confounder adjustment.

RESULTS: Of 1,197 pregnant individuals, 99 (8.3%) had positive cotinine samples and 47 (3.9%) had positive THC-COOH samples; 33 (2.8%) were positive for both. Groups differed in self-reported race and ethnicity, education, marital status, insurance, and thyroid status. Median IQ was similar between cotinine-exposed and -unexposed children (90 vs 95, adjusted difference in medians −2.47, 95% CI −6.22 to 1.29) and THC-COOH-exposed and -unexposed children (89 vs 95, adjusted difference in medians −1.35, 95% CI −7.76 to 5.05). In

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secondary outcome analysis, children with THC-COOH exposure compared with those unexposed had higher attention scores at 48 months of age (57 vs 49, adjusted difference in medians 6.0, 95% CI 1.11–10.89).

CONCLUSIONS: Neither prenatal nicotine nor cannabis exposure was associated with a difference in IQ. Cannabis exposure was associated with worse attention scores in early childhood. Longitudinal studies assessing associations between child neurodevelopmental outcomes and prenatal nicotine and cannabis exposure with a focus on timing and quantity of exposure are needed.

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Nicotine product use has steadily decreased among U.S. adults over the past two decades,[1–3] whereas tetrahydrocannabinol (THC)-containing cannabis use has increased,[4,5] including among pregnant individuals.[6–8] Despite a decrease in cigarette smoking prevalence from 14.9% in 2005 to 10.7% in 2014 among pregnant individuals,[6] 7–25% of pregnant individuals report use of nicotine products.[9–11] From 2001 to 2013, self-reported cannabis use increased among pregnant individuals from 2.4% in 2002 to 3.9% in 2014 nationwide.[12] Similarly from 2009 to 2016, prenatal cannabis use increased from 4.2% to 7.1% in a single health system that used universal urine biochemical testing during prenatal care.[7]

Although prenatal use of nicotine and cannabis products is strongly discouraged due to concerns for maternal and neonatal risks,[13–16] the effect of prenatal nicotine[17–19] or cannabis[20–24] exposure on child neurodevelopmental outcomes remains unclear. Four longitudinal human studies demonstrated an association between prenatal cannabis exposure and long-term adverse child neurodevelopment.[25] A major limitation in the methodology for many studies related to prenatal nicotine and cannabis exposure and child neurodevelopmental outcomes is reliance on self-reported use, which may underestimate the true association.[26,27] To address these knowledge gaps, we examined the association between the presence of nicotine or cannabis metabolites in maternal urine during early pregnancy and child neurodevelopmental outcomes at 1–5 years of age. We hypothesized that children with exposure to either nicotine or cannabis would have worse neurodevelopmental outcomes compared with unexposed children.

METHODS

This is a secondary analysis of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network two parallel randomized controlled trials (RCTs) of treatment for hypothyroxinemia or subclinical hypothyroidism among pregnant individuals enrolled at 8–20 weeks of gestation. Study enrollment occurred from 2006 to 2009, and maternal–child dyad follow-up continued until 2015. The institutional review boards at each of the 15 centers approved the parent trials.[28] The local institutional review board deemed this study exempt because it is a secondary analysis of deidentified data. This study follows STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for reporting of observational studies.

The details of the parent trials were described previously. Briefly, from 2006 to 2009, participants with singleton gestations at 8–20 weeks of gestation who were diagnosed with either subclinical hypothyroidism (thyroid-stimulating hormone level of 4.0 milliunits/L or higher and a normal free thyroxine level [0.86–1.90 ng/dL]) (n=677) or hypothyroxinemia (free thyroxine level less than 0.86 ng/dL and a normal thyroid-stimulating hormone level [0.08–3.99 milliunits/L]) (n=526) were randomized either to levothyroxine or placebo to examine the effect of treatment with levothyroxine on child neurodevelopmental outcomes. Children underwent annual developmental and behavioral testing for 5 years and follow-up concluded in 2014 with a 96% longitudinal follow-up rate. In both trials, there were no significant differences by treatment group for maternal or pregnancy outcomes, or child neurodevelopmental outcomes at 12, 24, 36, 48 or 60 months of age. For the parent trials, pregnant individuals with known "illicit drug or alcohol abuse during current pregnancy" were excluded. For this secondary analysis, we included all participants with maternal urine samples at study enrollment and available child neurodevelopmental testing results.

Urine samples were obtained at the time of randomization as part of the original trial protocol. None of the samples underwent freeze–thaw cycles before this analysis. The most stable and prominent metabolites for nicotine (cotinine) and cannabis (11-nor-9-carboxy-delta-9-tetrahydrocannabinol [THC-COOH]) were selected as the primary biomarkers of exposure. Urine was refrigerated, shipped to the central laboratory, and frozen at −80°C until processing.

Urine samples were assessed qualitatively using immunoassay and samples with positive results were reflexed to confirmation by liquid chromatography tandem mass spectrometry using clinically validated tests at ARUP Laboratories (Salt Lake City, Utah).

The limit of detection for qualitative urine cotinine screening was 100 ng/mL and confirmatory limit of detection was 5 ng/mL. The limit of detection for screening and confirmation tests differ, because immunoassays tests are generally sensitive but often not precise whereas confirmatory tests are highly specific, with low false-positive and false-negative rates. For participants with self-reported tobacco use, the screening test was presumed to be positive, and urine samples were assessed using confirmatory testing only. If participants reported tobacco use but confirmatory testing was negative, they were included in the nonexposed group. Cotinine detection time is approximately 7 days with active nicotine use. Qualitative urine THC-COOH screening limit of detection was 20 ng/mL, and a confirmatory limit of detection was 15 ng/mL. Detection time for THC-COOH is approximately 3 days for a single use, 5–7 days for moderate use (four times per week), 10 days for heavy use (daily use), and 30 days for chronic heavy use (daily use for multiple months).[29,30] Quantitative values were reported for liquid chromatography tandem mass spectrometry confirmatory testing for both nicotine and THC-COOH in ng/mL.

The primary outcome was full-scale IQ assessed with the WPPSI-III (Wechsler Preschool and Primary Scale of Intelligence III) at 5 years of age. Results are expressed as age standardized scores, with an expected population mean of 100 and an SD of 15. Secondary outcomes in infants and children included the same neurodevelopmental outcomes as the parent randomized trials: 1) cognitive, motor, and language scores on the Bayley-III (Bayley Scales of Infant Development, Third Edition) at 12 months and 24 months of corrected age; 2) DAS (Differential Ability Scales) overall scores at 36 months of age; 3) specific scores on the DAS (subtests regarding recall of digits forward and recognition of pictures); 4) Conners' Rating Scales–Revised at 48 months of age for assessment of attention; and 5) scores on the Child Behavior Checklist at 36 months and 60 months of age for assessment of behavioral and social competency. Notably, the Conners Rating Scales is validated for use at 48 months of age.[31,32]

We compared individual-level covariates associated with THC-containing cannabis and nicotine product use and child neurodevelopmental outcomes, including maternal age, body mass index, and gestational age at delivery, and social determinants of health, including maternal education, marital status, insurance type, and self-reported race and ethnicity.[27,33,34] We included race and ethnicity as a covariate as pediatric neurodevelopmental tests are subject to racial and cultural bias[35] and access to early childhood education is not universal,[36] and therefore may influence our outcomes of interest. We categorized race and ethnicity as White, Black, Hispanic, and Other, which included Asian, American Indian, and a participant-selected option of "Other." Because of small sample size, we combined these groups to protect participant confidentiality. We also assessed differences between groups for study-related baseline characteristics including gestational age at urine sample collection, thyroid status (subclinical hypothyroidism or subclinical hypothyroxinemia) and randomized trial treatment group. Maternal baseline, delivery and study characteristics were compared between exposed and unexposed groups (cotinine-positive vs -negative; THC-COOH–positive vs –negative) using the χ^2 test, Fisher exact test and Wilcoxon rank sum test as appropriate. Due to insufficient numbers of women with dual exposure (cotinine– and THC-COOH–positive), a separate comparison of dual exposed could not be performed, and this group was included as exposed in both cotinine and THC-COOH models.

We estimated that with our fixed sample size there would be 80% power to show a difference of at least 6 IQ points based on a two-sided Mann-Whitney-Wilcoxon test, assuming an alpha level of 0.05, and that 60 participants would be tobacco users (5% of available cohort) and 1,096 tobacco nonusers. For marijuana use, we estimated that there would be 60 marijuana users (5% of available cohort) and 1,096 nonmarijuana users.

Quantile regression models were used for both the primary and secondary outcomes defined on a continuous scale with adjustment for potential confounders. Results are reported as adjusted median scores. Initial regression models were adjusted for thyroid status (hypothyroxinemia or the subclinical hypothyroidism) and treatment group in the parent trial and demographic variables that included education, race and ethnicity, insurance type, marital status, and child age at examination. Final parsimonious models were adjusted for differences in child age at examination, insurance type, race and ethnicity and maternal education. We chose to include race and ethnicity and maternal education as important social determinants of health that are associated with child neurodevelopmental examination performance.[37,38] For outcomes that were associated with either nicotine or THC-COOH exposure, we performed exploratory analyses to evaluate the correlation between quantitative values of the substance of interest and continuous scores for the neurodevelopmental outcomes of

interest. Statistical significance was defined as $P<.05$. No corrections were made for multiple comparisons as this was an unplanned secondary (hypothesis-generating) analysis using all available neurodevelopmental outcomes in the parent trials. All statistical analysis was completed using SAS 9.4.

RESULTS

Of 1,203 maternal–child dyads included in the parent trials, 1,197 (99.5% of the overall cohort) met inclusion criteria for this study (Fig. 1). Of these, 99 (8.3%) were positive for cotinine and 47 (3.9%) were positive for THC-COOH; 33 (2.8%) were positive for both (Fig. 1). Of the 99 participants who were cotinine-positive, 82 self-reported tobacco use (median 626, range 5–3,248 ng/mL). In addition, 17 individuals who did not self-report tobacco use were positive for cotinine (median 283, range 37–1,949 ng/mL). There were 14 individuals who self-reported tobacco use in pregnancy but had negative confirmatory urine testing for cotinine; they were included in the cotinine-negative group. Overall positive THC-COOH results ranged from 16 to 501 ng/mL. One individual was THC-COOH screen-positive with insufficient urine for confirmatory testing and was included in the THC-COOH–negative group. Five-year follow-up outcome data was assessed for 92% of the offspring.

When comparing the cotinine-positive and -negative groups, there were significant differences in completed education level, marital status, insurance, race and ethnicity, and baseline thyroid status (Table 1). In the analysis comparing the THC-COOH–positive and –negative groups, the baseline characteristic variables that differed between groups included the ones in the cotinine analysis, with additional difference in maternal age. There were no differences in median gestational age at urine sample collection or gestational age at delivery for either analysis.

Tables 2 and 3 include the main findings. In unadjusted analyses for cotinine, there were differences in IQ at 60 months, the Bayley Cognitive and Motor scores at 12 months, Cognitive and Behavioral Checklist scores at 36 months and DAS Digits Forward and Picture Recognition at 48 months. However, after adjustment for confounders, there were no differences by cotinine exposure group in the adjusted medians for either primary or secondary outcomes (Table 2). In unadjusted analyses for THC-COOH, there were differences in IQ at 60 months, Cognitive and Behavioral Checklist scores at 36 months, Conners' Attention Scale scores, DAS Digits Forward and Picture Recognition at 48 months (Table 3). However, after adjustment for confounders, the only finding that remained significant was that children exposed to THC-COOH compared with unexposed children had higher adjusted medians for the Conners' Attention Scale score at 48 months of age. In an exploratory analysis, there was no significant correlation between quantitative urine THC-COOH levels and attention scores (Spearman's correlation coefficient −0.029, $P=.86$).

DISCUSSION

In this secondary analysis of two parallel RCTs, we examined the association between cotinine and THC exposure and early childhood neurodevelopmental outcomes. In this study with more than 99% child follow-up for the primary outcome, we found no difference between exposed and unexposed in child IQ at 60 months of age. Cannabis exposure between 8 and 20 weeks of gestation was associated with higher Conners attention scores at 48 months of age. These results should be interpreted with caution. Although the difference between exposed and unexposed children was statistically significant, both groups' median T score was within the average range (40–59, 16–83 percentile), which is associated with typical levels of attention concern for the child's age and sex.[39] In addition, we did not adjust for multiple comparisons as this analysis was intended to be hypothesis-generating to guide future work in this area.

Our results build on previous research demonstrating an association between prenatal THC exposure and adverse neurodevelopmental outcomes among young children, particularly attention.[40] The endocannabinoid system is active in fetal brain development. The endocannabinoid receptor, CB1, plays a major role in fetal brain development by regulating neural progenitor differentiation into neurons and glia and guiding axonal migration and synaptogenesis. Therefore, dysregulation of this process through exposure to exogenous cannabis resulting in abnormal neurodevelopment is biologically plausible.

Evidence related to neurodevelopmental outcomes with cannabis exposure in humans comes predominantly from four longitudinal studies: the ABCD (Adolescent Brain Cognitive Development) study (data release 2.0.1), OPPS (the Ottawa Prenatal Prospective Study), MHPCD (Maternal Health Practices and Child Development), and Generation R, a population-based prospective cohort in the Netherlands starting in 2002. Long-term follow-up is complete for the ABCD, OPPS, and MHPCD studies, and Generation R is ongoing. For all of these studies, cannabis use was ascertained by maternal self-report.

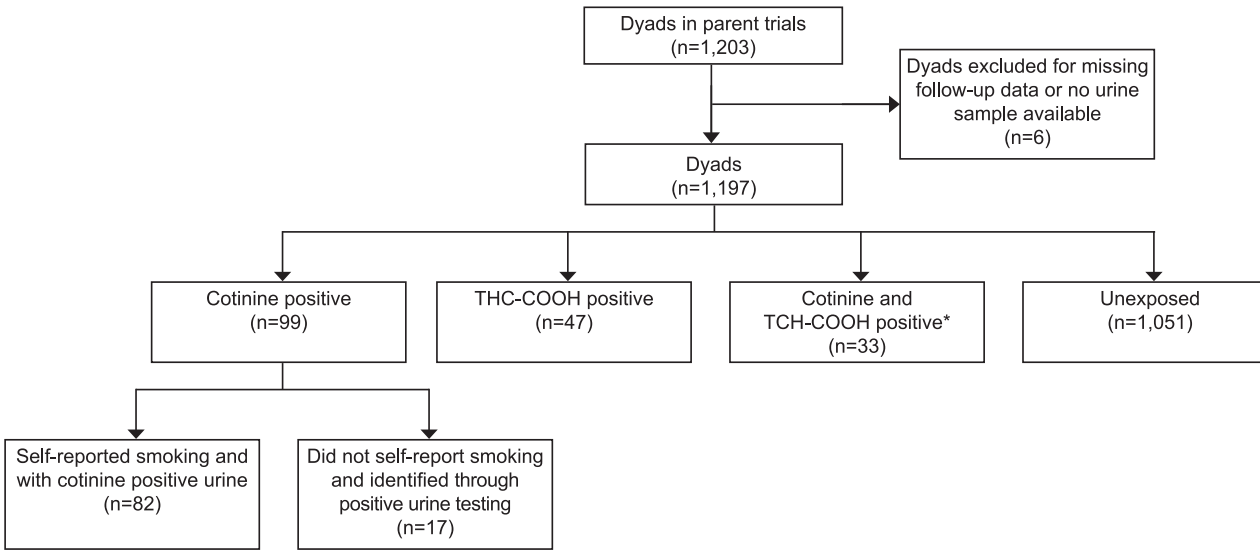

Fig. 1. Population cohort. *Not mutually exclusive with THC- and cotinine-positive groups. THC-COOH, 11-nor-9-carboxy-delta-9-tetrahydrocannabinol.

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Recent data from the ABCD study, a cross-sectional study of 11,489 children of whom 655 have prenatal cannabis exposure, demonstrated that exposure was associated with worse attention and hyperactivity on the Child Behavior Checklist (all $|\beta|>.047$; all false discovery rate–corrected $P<.001$). In the MHPCD study (N=564), at 6 years of age, prenatal cannabis exposure was associated with a significant

Table 1. Maternal and Study Characteristics by Exposure to Cotinine and THC-COOH

	Cotinine			THC-COOH		
Characteristic	Positive (n=99)	Negative (n=1,098)	*P*	Positive (n=47)	Negative (n=1,150)	*P*
Maternal age (y)	26.6±5.9	27.8±5.7	.05	26.1±6.1	27.8±5.7	.04
Maternal BMI (kg/m^2)	30.0±8.0	29.0±6.5	.47	29.3±8.1	29.0±6.6	.65
Education			<.001			.003
Less than high school	33 (33)	498 (45)		20 (43)	511 (44)	
High school	61 (62)	354 (32)		25 (53)	390 (34)	
College	5 (5)	246 (22)		2 (4)	249 (22)	
Married or partner	41 (41)	838 (76)	<.001	21 (45)	858 (75)	<.001
Private insurance	13 (13)	325 (30)	<.001	3 (6)	335 (29)	<.001
Race or ethnicity			<.001			<.001
Black	41 (41)	136 (12)		21 (45)	156 (14)	
Hispanic	11 (11)	621 (57)		5 (11)	627 (55)	
Other*	2 (2)	23 (2)		2 (4)	23 (2)	
White	45 (46)	318 (29)		19 (40)	344 (30)	
Gestational age at randomization and urine sample (wk)	17.4±3.0	17.1±3.0	.21	17.5±2.9	17.1±3.0	.34
Gestational age at delivery (wk)	38.1±4.7	39.0±2.6	.42	38.5±4.4	39.0±2.7	.30
Levothyroxine treatment group	47 (48)	554 (51)	.57	25 (53)	576 (50)	.68
Thyroid status			<.001			<.001
Subclinical hypothyroxinemia	27 (27)	647 (59)		9 (19)	665 (58)	
Subclinical hypothyroidism	72 (73)	451 (41)		38 (81)	485 (42)	

THC-COOH, 11-nor-9-carboxy-delta-9-tetrahydrocannabinol; BMI, body mass index.
Data are mean±SD or n (%) unless otherwise specified.
* Includes Asian, American Indian and participant-selected "other" category for race.

Table 2. Cotinine Exposure and Primary and Secondary Child Neurodevelopmental Outcomes at 12–60 Months of Age

Outcome*	Cotinine		Unadjusted Difference in Medians (95% CI)	Adjusted Difference in Medians (95% CI)†
	Positive (n=85)	Negative (n=1,022)		
Primary outcome				
WPPSI III IQ score at age 60 mo‡	90 [81–100]	95 [85–104]	−5.0 (−8.82 to −1.18)	−2.47 (−6.22 to 1.29)
Secondary outcomes				
12 mo				
Bayley—Cognitive‡	105 [95–110]	100 [90–110]	5 (2.15–7.85)	0 (−4.95 to 4.95)
Bayley—Motor‡	97 [94–110]	97 [91–103]	0 (−3.75 to 3.75)	0 (−4.17 to 4.17)
Bayley—Language	97 [86–109]	94 [86–103]	3 (−1.33 to 7.33)	0.75 (−4.46 to 5.96)
24 mo				
Bayley—Cognitive	90 [85–100]	90 [85–95]	0 (0–0)	0 (−2.82 to 2.82)
Bayley—Motor	97 [91–103]	97 [91–103]	0 (−2.55 to 2.55)	0 (−3.94 to 3.94)
Bayley—Language	94 [84.5–100]	89 [79–97]	5 (1.71–8.29)	0 (−3.31 to 3.31)
36 mo				
DAS II General Conceptual Ability score	91.5 [81–100]	90 [81–100]	1.0 (−3.49 to 5.49)	−0.20 (−4.19 to 3.79)
CBCL T score‡	52 [43–58]	46 [40–54]	6.0 (3.54–8.45)	2.42 (−1.78 to 6.62)
48 mo				
Conners	52 [44–58]	49 [44–56.5]	3.0 (0.38–5.62)	0 (−2.54 to 2.54)
DAS II Subtest Digits Forward‡	91 [76–113]	84 [53–106]	7.0 (−0.63 to 14.63)	−0.22 (−10.81 to 10.36)
DAS II Subtest Picture Recognition‡	74 (46–94]	74 [65–94]	0 (−5.83 to 5.83)	−3.45 (−10.97 to 4.06)
60 mo				
CBCL T score	46 [40–55]	44 [37–53]	2.00 (−0.25 to 4.25)	1.67 (−2.54 to 5.88)

WPPS III, Wechsler Preschool and Primary Scale of Intelligence-III; Bayley, Bayley Scales of Infant Development-III; DAS II, Differential Ability Scales-II; CBCL, Child Behavior Checklist for behavioral and social competency; Conners, Conners' Rating Scales-Revised for assessment of attention.

Data are median [interquartile range] unless otherwise specified.

* Number of participants in each outcome: WPPS III: 1,107; 12 month Bayley cognitive: 1,106; 12 month Bayley motor: 1,103; 12 month Bayley language: 1,099; 24 month Bayley cognitive: 1,076; 24 month Bayley motor: 1,065; 24 month Bayley language: 1,053; DAS II: 1,088; 36 month CBCL: 1,092; 48 month Conners: 1,068; 48 month DAS II Digits Forward: 1,054; 48 month DAS II Picture Recognition: 1,057; 60 month CBCL: 1,110.

† Quantile regression model adjusters included insurance type, education, race and ethnicity, and child age at examination.

‡ $P<.05$ in univariate analysis based on the Wilcoxon rank sum test.

increase in impulsivity (more errors of commission) but a positive effect on attention (fewer errors of omission).[41] Similar findings in impairment of short-term memory and in verbal and abstract or visual reasoning were found in the MHPCD cohort at 3 years of age.[42,43] At 6 years of age, the OPPS study (N=698) found that prenatal cannabis exposure was associated with decreased attention and increased impulsivity and hyperactivity.[44] As the cohorts were followed over the subsequent 9–12 years, executive function and difficulty organizing and integrating specific cognitive and output processes were observed.[45–47] Data from the Generation R cohort demonstrate that prenatal self-reported cannabis use in early pregnancy correlated with worse attention using the Child Behavior Checklist among girls, but not boys, at age 18 months.[48] Thus, our findings are consistent with those of prior studies demonstrating an association between prenatal cannabis exposure and worse attention in childhood.

Limitations of these prior studies include the small sample of prenatal cannabis–exposed offspring; potential maternal underreporting of use during pregnancy; imprecise data on timing and amount, frequency, and potency of cannabis exposure; and lack of data on some potential confounders. Nevertheless, based on findings of these studies, the U.S. Surgeon General,[14] the American Academy of Pediatrics, and the American College of Obstetricians and Gynecologists[4] note concerns regarding the potential for maternal cannabis use to adversely affect fetal neurodevelopment.

Our study addresses two of the major limitations of these other studies. First, we ascertained exposure

Table 3. Tetrahydrocannabinol Exposure and Primary and Secondary Child Neurodevelopmental Outcomes at 12–60 Months of Age

Outcome*	THC-COOH		Unadjusted Difference in Medians (95% CI)	Adjusted Difference in Medians (95% CI)†
	Positive (n=41)	Negative (n=1,066)		
Primary outcome				
WPPSI III IQ score age 60 mo‡	89 [81–99]	95 [85–104]	−6.0 (−14.33 to 2.33)	−1.35 (−7.76 to 5.05)
Secondary outcomes				
12 mo				
Bayley—Cognitive	100 [95–112.5]	100 [90–110]	0 (−5.47 to 5.47)	0 (−6.54 to 6.54)
Bayley—Motor	97 [92.5–110]	97 [92.5–110]	0 (−4.02 to 4.02)	0 (−4.69 to 4.69)
Bayley—Language	95.5 [87.5–109]	94 [86–103]	3.0 (−2.37 to 8.37)	3.0 (−3.23 to 9.23)
24 mo				
Bayley—Cognitive	90 [85–95]	90 [85–100]	0 (−2.36 to 2.36)	0 (−3.88 to 3.88)
Bayley—Motor	97 [94–100]	97 [91–103]	0 (−3.17 to 3.17)	0 (−4.36 to 4.36)
Bayley—Language	94 [84.5–97]	89 [79–97]	5.0 (1.74–8.26)	−0.67 (−4.37 to 3.03)
36 mo				
DAS II General Conceptual Ability score	89 [81–99]	90 [81–100]	0 (−6.60 to 6.60)	−2.40 (−8.61 to 3.81)
CBCL T score‡	54 [43–62]	46 [40–54]	8.0 (4.12–11.88)	4.42 (−1.20 to 10.05)
48 mo				
Conners‡	57 [48–62]	49 [44–56]	8.0 (4.12–11.88)	**6.0 (1.11–10.89)**
DAS II Subtest Digits Forward‡	91 [76–113]	84 [53–106]	7.0 (−4.03 to 18.03)	4.89 (−10.31 to 20.09)
DAS II Subtests Picture Recognition‡	74 [46–7]	74 [65–94]	0 (−7.77 to 7.77)	−4.73 (−13.33 to 3.87)
60 mo				
CBCL T score	45 [39–55]	44 [37–53]	1.0 (−3.64 to 5.64)	−2.0 (−6.91 to 2.91)

Data are median [interquartile range] unless otherwise specified.

THC-COOH, 11-nor-9-carboxy-delta-9-tetrahydrocannabinol; WPPS III, Wechsler Preschool and Primary Scale of Intelligence-III; Bayley, Bayley Scales of Infant Development-III; DAS II, Differential Ability Scales-II; CBCL, Child Behavior Checklist for behavioral and social competency; Conners, Conners' Rating Scales-Revised for assessment of attention.

Bold indicates $P<.05$ in the adjusted analysis.

* Number of participants in each outcome: WPPS III: 1,107; 12 month Bayley cognitive: 1,106; 12 month Bayley motor: 1,103; 12 month Bayley language: 1,099; 24 month Bayley cognitive: 1,076; 24 month Bayley motor: 1,065; 24 month Bayley language: 1,053; 36 month DAS II: 1,088; 36 month CBCL: 1,092; 48 month Conners: 1,068; 48 month DAS II Digits Forward: 1,054; 48 month DAS II Picture Recognition: 1,057; 60 month CBCL: 1,110.

† Quantile regression model adjusters included insurance type, education, race and ethnicity, and child age at examination.

‡ $P<.05$ in the univariate analysis based on the Wilcoxon rank sum test.

through urine assays for nicotine and cannabis metabolites as opposed to self-report, which is important as self-report underestimates use by as much as tenfold.[26] Second, we had an extraordinarily high child follow-up rate in this cohort resulting in an available sample size exceeding that of most existing studies of neurodevelopment and maternal cannabis and nicotine product use.

Additional strengths include the generalizability of the cohort, which was assembled through recruitment of pregnant participants from 15 centers across the United States, resulting in a racially and socioeconomically diverse cohort. Prior studies are focused on subsets of the population in a single location. In addition, all study data were collected prospectively by experienced perinatal research staff. All neurodevelopmental testing was performed using standardized instruments after centralized training and certification. Finally, all laboratory analyses were performed by a CLIA-certified national reference laboratory for drug testing.

Limitations of this study are primarily related to the design as an unplanned secondary analysis and the number of children exposed to THC-COOH is low. Because this secondary analysis is exploratory, we did not adjust for multiple comparisons, which may have resulted in alpha error. We are not powered to detect modest differences in the primary and secondary outcomes based on our exposures of interest. However, the finding of worse attention scores with cannabis exposure is consistent with existing literature.[40–48] We only had a study enrollment urine specimen, which did not allow for investigation of quantity

and duration of perinatal substance use. The parent RCT excluded individuals with "known illicit drug or alcohol abuse during current pregnancy." Therefore, pregnant individuals with cannabis use disorder who may have the highest levels of exposure were excluded, potentially biasing the results toward the null. Nonetheless, nearly 4% of the study population were THC-COOH–positive, which is consistent with the estimated prevalence of prenatal marijuana use in the literature at the time of study enrollment. Additionally, other substance use including opioid, methamphetamine, cocaine and polysubstance use, which may significantly influence child neurodevelopmental outcomes was not evaluated with urine drug testing for this analysis due to small volumes of available urine.[49–57] In addition, small numbers of nicotine and cannabis dual exposure precluded meaningful analysis related to potential additive effects of dual exposure. Finally, although more than 99% of all children had data on the primary outcome available, 8–10% of children had missing data on the secondary outcomes, including attention at 48 months (n=1,068, 89.2%).

In terms of the urine testing, we assessed only the most stable metabolite of cannabis and nicotine. There are hundreds of active substances in cannabis and nicotine-containing products and these metabolites may not be the most predictive of adverse child neurodevelopmental outcomes. Additionally, urine toxicology has variable detection windows depending on quantity and timing of use. The presence or absence of metabolites in one sample indicates substance exposure in a limited window of detection, which likely biases these results toward the null. We are also unable to distinguish between the timing or type of maternal exposure (eg, smoking, vaping) based on urine metabolite testing. Additionally, we are unable to distinguish between active compared with passive use of cannabis- and nicotine-containing products.

Results on neurodevelopmental outcomes after prenatal cannabis exposure are inconsistent across studies and may be due to unmeasured confounding, including difference in postnatal environment and caregiver characteristics, including maternal mental health disorders.[58] Although maternal depression treated with tricyclic antidepressants and selective serotonin reuptake inhibitors was an exclusion criteria for this trial, pregnant individuals undergoing nonpharmacologic treatment, untreated mental health disorder or other mental health conditions were not excluded. Only 242 participants (20.2% of cohort) completed depression assessments (Center for Epidemiological Studies - Depression); therefore, adjustment for baseline maternal mental health was not possible. Other unmeasured confounders may include paternal or other household member cannabis or nicotine product use, children's social and school environment,[59] maternal stress levels,[60] exposure to systemic violence[61] and discrimination,[62] which all influence child neurodevelopmental outcomes. Other significant risk factors for attention disorders include environmental exposures such as high levels of lead,[63] mercury[64] and polychlorinated biphenyls,[65] fetal alcohol exposure,[66] adverse childhood events,[67–69] and gene susceptibility,[70] which were not systematically collected as part of the parent study.

Neither prenatal cannabis nor cotinine exposure was associated with differences in child IQ at age 60 months. However, prenatal THC exposure was associated with higher (worse) attention scores at 48 months. Results of this study suggest the need for high quality studies that aim to examine the child neurodevelopmental effects of prenatal exposure to cannabis and nicotine. Future studies should include those with prospective longitudinal design assessing timing, quantity and co-exposure to nicotine, cannabis and other substances over the course of pregnancy, as well as assessment of critical confounding factors to better elucidate the relationship between maternal nicotine and cannabis use and child neurodevelopmental outcomes.

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