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Short communication

Intrauterine cannabis exposure leads to more aggressive behavior and attention problems in 18-month-old girls☆

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ABSTRACT

Background: The development of the fetal endocannabinoid receptor system may be vulnerable to maternal cannabis use during pregnancy and may produce long-term consequences in children. In this study, we aimed to determine the relationship between gestational cannabis use and childhood attention problems and aggressive behavior.
Methods: Using a large general population birth cohort, we examined the associations between parental prenatal cannabis and tobacco use and childhood behavior problems at 18 months measured using the Child Behavior Checklist in $N = 4077$ children. Substance use was measured in early pregnancy.
Results: Linear regression analyses demonstrated that gestational exposure to cannabis is associated with behavioral problems in early childhood but only in girls and only in the area of increased aggressive behavior ($B = 2.02$; 95% CI: 0.30–3.73; $p = 0.02$) and attention problems ($B = 1.04$; 95% CI: 0.46–1.62; $p < 0.001$). Furthermore, this study showed that long-term (but not short term) tobacco exposure was associated with behavioral problems in girls ($B = 1.16$; 95% CI: 0.20–2.12; $p = 0.02$). There was no association between cannabis use of the father and child behavior problems.
Conclusions: Our results suggest that intrauterine exposure to cannabis is associated with an increased risk for aggressive behavior and attention problems as early as 18 months of age in girls, but not boys. Further research is needed to explore the association between prenatal cannabis exposure and child behavior at later ages. Our data support educating future mothers about the risk to their babies should they smoke cannabis during pregnancy.

1. Introduction

Early brain development involves a complex cascade of events that can be influenced by prenatal environmental factors. These events can have downstream effects, influencing postnatal development and behavior (Barker, 1998; Huizink et al., 2004). Cannabinoids readily cross the placental (Behnke and Eyler, 1993; Little and VanBeveren, 1996) and blood brain barriers (Schou et al., 1977). Despite the known importance of the endocannabinoid system in neurodevelopment (Harkany et al., 2007), there has been little research exploring the effects of prenatal cannabis use with later child behavior.

Pregnant women who use cannabis often smoke tobacco. Thus examining the effects of gestational cannabis exposure is often challenging, as smoking during pregnancy can also influence neurodevelopment. In this study, we compared several groups (i.e. pregnant women who smoked tobacco only versus women who

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combined cannabis with tobacco use) to examine if intrauterine exposure to cannabis has an independent effect from intrauterine exposure to tobacco. We also took paternal cannabis use into account as a contrast. By comparing the strength of association between maternal exposure during pregnancy and child behavior, with paternal exposure to the same substance in the same period and child behavior, one may be able to discard non-intrauterine environmental causes (Smith, 2008).

Based on prior literature reporting increased attention problems and delinquency in prenatal cannabis-exposed school-age children and adolescents (Fried et al., 1992; Goldschmidt et al., 2000; Leech et al., 1999), we aim to determine the relationship between prenatal cannabis use and early indications of childhood attention problems and aggressive behavior. It is important to investigate early childhood behavior, because it has been shown that childhood behavior disturbances may be predictive for psychopathology in adulthood (Caspi, 2000). We did this using a well-validated instrument in a general population birth cohort of children at 18 months of age.

2. Methods

2.1. Setting

This study was conducted within the Generation R Study, a population based birth cohort in Rotterdam, the Netherlands (Jaddoe et al., 2008, 2010). More information on the Generation R Study, including eligibility, recruitment, and enrollment can be found in the Supplemental material. The study was conducted in accordance with the guidelines proposed in the World Medical Association Declaration of Helsinki, and was approved by the Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam. Written informed consent was obtained from all participating parents and anonymity was guaranteed.

2.2. Study population

Information on prenatal substance use was available for 5512 children. Information on child behavioral problems at 18 months was available in 4077 children (74.0% of 5512). These children form the study population for the analyses.

2.3. Tobacco, alcohol and substance exposure

Tobacco, alcohol and substance use were measured using a self-report questionnaire given to both parents during the first trimester of pregnancy. More information on these questionnaires is provided in the Supplemental material. The agreement between maternal self-report and urinalyses was good (Yule's $Y = 0.77$) and has been described previously (El Marroun et al., 2011). The self-reported prevalence was in agreement with national numbers in the same period (Rodenburg et al., 2007).

The pregnant mothers were also asked about the father's cannabis use. We used maternal report of paternal cannabis use only when the fathers did not complete the questionnaire (26%). Maternal report of paternal cannabis use was highly correlated to paternal self-reported cannabis use ($r = 0.83$ $p < 0.001$). In order to assess the gestational influence of cannabis, we categorized intrauterine exposure into four non-overlapping groups, according to cannabis and/or tobacco use.

1. Cannabis exposure in pregnancy ($n = 88$), mostly with co-use of tobacco during pregnancy (84.5%),
2. Tobacco-only exposure in early pregnancy ($n = 435$),
3. Tobacco-only exposure throughout pregnancy ($n = 276$),
4. Non-use of cannabis or tobacco in pregnancy ($n = 3278$).

Paternal cannabis use during maternal pregnancy occurred in 9.3% of the cohort ($n = 384$).

2.4. Child behavioral and emotional problems

The Child Behavior Checklist for toddlers (CBCL 1½–5 years) was used to acquire a standardized maternal report of children's problem behaviors. We focused on three specific syndrome scales: Anxious/Depressed, Attention Problems and Aggressive Behavior. Each item is scored 0 = not true, 1 = somewhat or sometimes true and 2 = very true or often true, based on the preceding two months. Good reliability and validity have been reported for the CBCL (Achenbach and Rescorla, 2000). We used both continuous scores for the CBCL and dichotomous cut-off scores reflecting clinical cases. Children scoring in or above the 93rd percentile of the syndrome scale were classified as possible clinical cases (Tick et al., 2007).

2.5. Covariates

Demographic and obstetric information such as maternal age, ethnicity, and education, was assessed using self-report. Parental educational level and national origin were defined according to the classification of Statistics Netherlands (Statistics Netherlands, 2004a,b). Parental psychopathology was measured using the Brief Symptom Inventory (BSI), a validated 53-item (5-point scale) self-report symptom inventory that ascertains the psychological state (Derogatis and Melisaratos, 1983); the Global Severity Index subscale was used to determine general psychopathology symptoms.

2.6. Statistical analysis

Multiple linear regression models were conducted to examine the associations of maternal cannabis use, tobacco use and non-use of cannabis and tobacco with the continuous scores of child behavioral problems. All models controlled for age and gender of the child, parental education, national origin and psychopathology. Correction for alcohol use and other drug use did not significantly change the results; therefore we report results obtained by correcting only for covariates that significantly influenced the model. Identical analyses were carried out to examine the association between paternal cannabis use and child behavioral problems. The paternal models were additionally corrected for maternal cannabis and/or tobacco use. We performed stratified analyses for the effects of parental cannabis use and behavioral problems for boys and girls, because the multiplicative interaction terms between gender and maternal cannabis and tobacco use were significant.

Using a categorical distinction to classify children as having behavioral problems in the clinical range, we performed logistic regression analyses. The main reason for the use of this categorical variable was to determine the clinical relevance. The data were somewhat skewed (0.78 for attention and 0.76 aggression) and kurtotic (0.28 for attention and 0.63 for aggression); these numbers lie within the range for normal distribution. Measures of association (Beta's (B) and Odds Ratios, OR's) are presented with the 95% Confidence Intervals (CI's). Statistical analyses were performed using the Statistical Package of Social Sciences version 15.0 for Windows (SPSS Inc., Chicago, IL).

3. Results

3.1. Descriptive statistics

Table 1 depicts the sample characteristics used in the study. Women using cannabis predominantly used cannabis in early pregnancy, 19.3% of the mothers who used cannabis continued

Table 1
Parental and child characteristics in cannabis-using, tobacco-using and non-using subgroups.

	Cannabis use in pregnancy[a] ($n=88$)	Only tobacco use in early pregnancy ($n=435$)	Only tobacco use throughout pregnancy ($n=276$)	No intra-uterine exposure to tobacco or cannabis ($n=3278$)
Maternal characteristics				
Cannabis use in pregnancy (%)				
Early cannabis use	80.7	0.0	0.0	0.0
Continued cannabis use	19.3	0.0	0.0	0.0
Non-use/before pregnancy	0.0	100.0	100.00	100.00
Tobacco use in pregnancy (%)[b]				
Early tobacco use	28.4	100.0	0.0	0.0
Continued tobacco use	52.3	0.0	100.0	0.0
Non-use/before pregnancy	19.3	0.0	0.0	100.0
Alcohol use in pregnancy (%)				
Early alcohol use	18.4**	23.2	10.9	13.5
Continued alcohol use	56.3	55.8	43.8	45.0
Non-use/before pregnancy	25.3	21.0	44.2	41.5
Educational level (%)				
Primary	18.6**	7.3*	13.1**	5.2
Secondary	51.2	38.3	62.9	33.6
Higher	30.2	54.5	24.0	61.2
National origin (%)				
Dutch	62.5*	66.9**	60.9*	62.8
Psychopathology				
Global severity index	0.42 ± 0.43**	0.26 ± 0.31*	0.34 ± 0.35**	0.23 ± 0.28
Paternal characteristics				
Paternal cannabis use	84.5**	10.6**	16.9**	6.9
Educational level (%)				
Primary	11.3**	3.5**	9.6**	4.3
Secondary	60.4	42.1	58.8	32.2
Higher	28.3	54.4	31.6	63.5
National origin (%)				
Dutch	55.2**	67.2**	59.1**	65.4
Child characteristics				
Age at assessment (months)	18.6 ± 1.2	18.4 ± 1.0	18.4 ± 1.1	18.4 ± 1.1
Behavioral problems measured with CBCL				
Internalizing problem score	5.3 ± 4.1	4.6 ± 3.9	5.8 ± 5.0*	5.0 ± 4.6
Externalizing problem score	13.0 ± 6.5**	10.5 ± 6.4	12.7 ± 6.6**	10.7 ± 6.7

Note: Values are means ± SDs for continuous variables and percentages for categorical variables. P-values are derived from ANOVAs for parametric continuous variables, Kruskal–Wallis tests for non-parametric continuous variables and χ^2-tests for categorical variables.

[a] Cannabis use during pregnancy could also have concurrent tobacco use.

[b] Statistical analyses on cannabis and tobacco use were not performed, because the groups were selected on the basis of these variables.

* $p < 0.05$.

** $p < 0.01$.

their use after the first trimester. Compared to non-using mothers, mothers who used cannabis during pregnancy often drank alcohol during pregnancy, were less educated, and had lower psychopathology scores. Additionally, women using cannabis during pregnancy were more often of Surinamese (12.5% in the cannabis-users vs. 5.4% in the non-users) and Antillean national origin (14.5% in the cannabis-users vs. 1.8% in the non-users). Women using tobacco during pregnancy were less educated. Women that continued using tobacco throughout pregnancy were more likely to be Turkish (14.9% in the continued tobacco users vs. 5.8% in the non-users) and less likely to be Moroccan (1.1% in the continued tobacco users vs. 4.1% in the non-users). Paternal cannabis use occurred more often when mothers used cannabis or tobacco.

3.2. Aggressive behavior

Table 2 demonstrates that exposure to cannabis was associated with increased scores on the aggressive behavior scale of the CBCL in girls, but not in boys. Interestingly, early exposure to tobacco was not associated with increased aggression in either girls or boys. However, tobacco exposure throughout pregnancy was associated with an increased score for aggressive behavior in girls, but this association was less pronounced in boys. In contrast, paternal cannabis use was not associated with aggressive behavior in girls or in boys. Furthermore, logistic regression analyses, using the cut-off score of the CBCL, showed that girls exposed to cannabis had an increased risk for developing aggressive behavior, but this risk was not statistically significant (OR = 1.66; 95%CI: 0.38–7.26; $p = 0.50$).

3.3. Attention problems

Table 2 demonstrated that exposure to cannabis is associated with increased scores on the attention problems scale of the CBCL in girls but not in boys. Early gestational exposure to tobacco was not associated with increased scores in girls or boys. Continued tobacco exposure was associated with an increased score for attention problems in both girls, and boys. In contrast, paternal cannabis use was not associated with attention problems scores in girls or boys. Using a dichotomous analysis with a cut-off score for the CBCL demonstrated that girls exposed to cannabis had an increased risk for developing Attention Problems (OR = 2.75; 95% CI: 1.27–5.96; $p = 0.01$).

3.4. Anxious and/or depressive problem score

No association was found between exposure to cannabis in girls and anxious or depressive symptoms ($B = -0.02$; 95% CI: −0.40–0.45; $p = 0.91$), and no relation between gestational expo-

Table 2
Linear regression models of parental cannabis use and gender-specific child aggressive behavior scores and attention problem scores.

Aggressive behavior[a]						
	B (95% C.I.)					
	Total (N = 4077)		Boys (N = 2017)		Girls (N = 2060)	
No intrauterine exposure[b] (N = 3278)	Reference		Reference		Reference	
Cannabis exposure[c] (N = 88)	0.91 (−0.22 2.04)	p = 0.11	−0.15 (−1.65; 1.35)	p = 0.84	2.02 (0.30; 3.73)	p = 0.02
Contrasting exposures						
Only tobacco exposure early (N = 435)	−0.17 (−0.69; 0.36)	p = 0.54	−0.48 (−1.25; 0.29)	p = 0.23	0.13 (−0.59; 0.86)	p = 0.72
Only tobacco exposure continued (N = 276)	1.16 (0.50; 1.82)	p = 0.001	0.91 (0.00; 1.82)	p = 0.05	1.16 (0.20; 2.12)	p = 0.02
Explained variance (R^2)	0.059		0.072		0.052	
Paternal cannabis use[d] (N = 384)	0.54 (−0.06; 1.14)	p = 0.08	0.54 (−0.32; 1.39)	p = 0.22	0.59 (−0.26; 1.44)	p = 0.17
Explained variance (R^2)	0.059		0.072		0.053	
Attention problems[a]						
	B (95% C.I.)					
	Total (N = 4066)		Boys (N = 2010)		Girls (N = 2056)	
No intrauterine exposure[b] (N = 3270)	Reference		Reference		Reference	
Cannabis exposure[c] (N = 87)	0.36 (−0.02; 0.74)	p = 0.06	−0.20 (−0.69; 0.30)	p = 0.43	1.04 (0.46; 1.62)	p < 0.001
Contrasting exposures						
Only tobacco exposure early (N = 433)	−0.01 (−0.19; 0.16)	p = 0.89	−0.03 (−0.28; 0.22)	p = 0.81	0.01 (−0.23; 0.26)	p = 0.91
Only tobacco exposure continued (N = 276)	0.46 (0.24; 0.68)	p < 0.001	0.35 (0.05; 0.65)	p = 0.02	0.55 (0.22; 0.87)	p = 0.001
Explained variance (R^2)	0.051		0.058		0.050	
Cannabis use father[d] (N = 383)	0.09 (−0.11; 0.29)	p = 0.40	0.14 (−0.14; 0.43)	p = 0.31	0.02 (−0.27; 0.30)	p = 0.92
Explained variance (R^2)	0.049		0.056		0.049	

Note: the number of subjects in the analyses for attention problems (N = 4066) differed from the number of subjects with aggression problems (N = 4077) due to missing scores on items in the subscale. These linear regression models were corrected for the following confounders: age of the child at assessment, maternal education, ethnicity and psychopathology.

[a] Maternal report on the child behavioral checklist.
[b] No tobacco or cannabis use during pregnancy.
[c] Cannabis use during pregnancy could also have concurrent tobacco use.
[d] Corrected for maternal cannabis and tobacco use.

sure to cannabis and anxious or depressive symptoms in boys (B = −0.36; 95% CI: −0.73–0.01; p = 0.06) was observed.

4. Discussion

This study investigates the association between cannabis and tobacco exposure during pregnancy and child behavior in boys and girls at 18 months of age. Interestingly, we found that gestational exposure to cannabis is associated with behavioral problems in early childhood only in girls and only in the areas of aggression and attention problems. Furthermore, long-term tobacco exposure was associated with similar behavioral problems. We found no association with paternal use and aggression or attention problems in boys or girls, which supports our idea that maternal cannabis use is affecting girl's behavior through biological mechanisms.

The fact that there was no effect in 18-month-old boys was surprising in itself and could be due to chance, but could also be due to the remarkable differences between boys and girls early in neurodevelopment. It may well be that there will be gender-age differences, with the effects on boys becoming more prominent later in development.

The findings of this study are especially important as they focus concerns on outcomes of young girls. Many prior studies focus on the negative pathways of aggression and attention in males, however it is also true that girls are equally at risk for these negative outcomes once diagnosed. It has been demonstrated that childhood externalizing problems have been associated with later juvenile delinquency, adult crime and violence (Betz, 1995; Farrington, 1989; Liu, 2004; Moffitt, 1993). It is important to have a good indication of behavior at early ages, as a starting point for later developmental trajectories of behavior problems. Furthermore, aggression and attention problems in childhood have been associated with substance use disorder in adolescence and adulthood as well (Wilens, 2007). One can easily see the circularity of this problem. If a child's mother smokes cannabis or tobacco during pregnancy, her child may be at risk for later behavioral problems. That child herself may be at increased risk to smoke cannabis and tobacco during her pregnancies, and so forth. Interrupting this potentially damaging cycle should become the focus of health care prevention strategies and one easy marker of risk is to focus on female offspring of mothers who smoked cannabis and tobacco during pregnancy. Obviously, follow-up of our prenatally exposed infants is needed to model their developmental trajectories in time, and to determine whether behavioral problems we found in girls are transient or last and develop into childhood and adolescent problems.

The current study has both strengths and limitations. Strengths are the population-based cohort with information on numerous explaining variables, and paternal information on cannabis use. Limitations include the use of maternal reports about their child's behavior. Our response analyses revealed that mothers who did not participate in analyses were younger, less educated and had higher psychopathology symptom scores than the ones included in the analyses. Based on these characteristics, non-responders were at higher risk for cannabis use during pregnancy. Likewise, their children may have been at higher risk for behavior problems. So, our study may in fact be an underestimation of the risk between maternal cannabis use and negative offspring outcomes.

5. Conclusion

Our results suggest that intrauterine cannabis exposure is associated with an increased risk for aggression and attention problems

as early as 18 months of age in girls. Further research is needed to explore the association between prenatal cannabis exposure and child behavior at later ages. Our data support educating future mothers about the risk to their babies should they smoke in pregnancy.

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Contributors

Henning Tiemeier, Eric A.P. Steegers, Vincent W.V. Jaddoe, Albert Hofman, and Frank C. Verhulst designed the study. Hanan El Marroun, James J. Hudziak, Henning Tiemeier and Anja Huizink designed the analyses. Hanan El Marroun conducted the literature search and conducted the analyses. All authors contributed to the writing of the submitted manuscript.

Conflict of interest statement

The authors have no conflict of interest in relation to the content of this article. Disclosure: Dr. Verhulst is author and head of the Department of Child and Adolescent Psychiatry at Erasmus MC, which publishes the Achenbach System of Empirically Based Assessment (ASEBA) and from which he receives remuneration. The other authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.drugalcdep.2011.03.004.

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