Drug and Alcohol Dependence 225 (2021) 108751

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Parental cannabis and tobacco use during pregnancy and childhood hair cortisol concentrations

Kim N. Cajachagua-Torres [a,b], Vincent W.V. Jaddoe [a,b,*], Yolanda B. de Rijke [c,d], Erica L. T. van den Akker [b,d], Irwin K.M. Reiss [b], Elisabeth F.C. van Rossum [d,e], Hanan El Marroun [b,f,g]

[a] The Generation R Study Group, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands
[b] Department of Pediatrics, Erasmus MC, University Medical Center Rotterdam, P.O. Box 2040, 3000CA, Rotterdam, the Netherlands
[c] Department of Clinical Chemistry, Erasmus MC, University Medical Center Rotterdam, 3015GD, Rotterdam, the Netherlands
[d] Obesity Center CGG, Erasmus MC, University Medical Center Rotterdam, 3000CA, Rotterdam, the Netherlands
[e] Department of Internal Medicine, Division of Endocrinology, Erasmus MC, University Medical Center Rotterdam, 3000CA, Rotterdam, the Netherlands
[f] Department of Child and Adolescent Psychiatry, Erasmus MC, University Medical Center Rotterdam, 3000CB, Rotterdam, the Netherlands
[g] Department of Psychology, Education and Child Studies, Erasmus School of Social and Behavioral Sciences, Erasmus University Rotterdam, 3062PA, Rotterdam, the Netherlands

ARTICLE INFO

Keywords:
Pregnancy
Smoking
Cannabis
Hypothalamic-pituitary-adrenal axis
Child
Cortisol

ABSTRACT

Background: Fetal exposure to cannabis and tobacco during pregnancy leads to adverse fetal and childhood outcomes. We hypothesized that fetal exposure to cannabis and tobacco have persistent programming effects on hypothalamic pituitary adrenal (HPA) axis functioning in childhood. Therefore, we examined the associations of parental cannabis and tobacco use during pregnancy with childhood hair cortisol and cortisone concentrations at 6 years, as biomarkers of long-term HPA-axis functioning.

Method: In a population-based prospective birth cohort among 2577 mothers and their children, information of parental cannabis and tobacco use was collected by questionnaires, and maternal urine samples were additionally analyzed to detect cannabis metabolite concentrations. Cortisol and cortisone were measured in hair samples at 6 years. Linear regression analysis with adjustment for several confounders was used to test our hypothesis.

Results: As compared to non-exposed children, offspring exposed to cannabis during pregnancy (in combination with tobacco) had higher childhood cortisol concentrations (log-10 transformed difference 0.16, 95 % Confidence Interval 0.04 to 0.28). This association was not mediated by birth weight. No differences in cortisone concentrations among cannabis-exposed children were observed. Maternal tobacco use during pregnancy was not associated with childhood cortisol or cortisone concentrations. Further, paternal cannabis or tobacco use was not associated with childhood cortisol or cortisone concentrations.

Conclusions: Our findings suggest that maternal cannabis use, combined with tobacco, during pregnancy is associated with alterations in offspring HPA-axis functioning. Further studies need to replicate these findings, and assess the causality and long-term consequences of these associations.

1. Introduction

Fetal exposure to cannabis and tobacco during pregnancy seems to adversely affect fetal and childhood health outcomes. Cannabis is one of the substances most used worldwide (United Nations Office on Drugs and Crime, 2019). Cannabis use in the general population is relatively frequent with percentages of 13.8 % in North America, 10.9 % in Oceania, 10 % in West and Central Africa, and 7.4 % Western and Central Europe (United Nations Office on Drugs and Crime, 2019). Among pregnant women, the prevalence of cannabis use increased from 3.4%–

Abbreviations: HPA-axis, Hypothalamic-pituitary-adrenocortical axis; LC, Liquid chromatography; LC–MS/MS, Liquid chromatography tandem mass spectrometry; BSI, Brief Symptom Inventory; fMRI, functional magnetic resonance imaging; ECS, Endocannabinoid system; CBR1, Cannabinoid type 1 receptor; 11β-HSD, 11β-hydroxysteriod dehydrogenase; 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2.

* Corresponding author at: The Generation R Study Group, Erasmus MC, P.O. Box 2040, 3000CA, Rotterdam, the Netherlands.
E-mail address: v.jaddoe@erasmusmc.nl (V.W.V. Jaddoe).

https://doi.org/10.1016/j.drugalcdep.2021.108751
Received 18 December 2020; Received in revised form 19 March 2021; Accepted 3 April 2021
Available online 21 May 2021

7% between 2002–2017 in the United States (Volkow et al., 2019). Prenatal cannabis use has been associated with reduced fetal growth, cortical thickness, and behavioral and emotional problems in children (Calvigioni et al., 2014; El Marroun et al., 2019, 2016; Goldschmidt et al., 2000; Gunn et al., 2016; O'Donnell and Meaney, 2017). It is possible that prenatal exposure to cannabis may affect hypothalamic-pituitary-adrenocortical (HPA) axis regulation, as the fetal period may be a critical period, leading to long-term neuroendocrine, metabolic and neurobehavioral alterations (Franks et al., 2019; Hurd et al., 2019; Lovallo, 2006). Previous studies of adolescents and adults showed that cannabis use was related to higher salivary cortisol concentrations and lower stress-reactivity, potentially reflecting a disruption of the HPA-axis (Cservenka et al., 2018; Dow-Edwards and Silva, 2017; King et al., 2011; van Leeuwen et al., 2011). A previous study from Hawaii suggested that chronic cannabis users have higher basal morning salivary cortisol concentrations than non-users, particularly among males (King et al., 2011). Further, a prospective study in Dutch adolescents showed that life-time cannabis users have significantly lower stress-reactivity cortisol levels compared to abstainers or life-time tobacco users (van Leeuwen et al., 2011). Whether cannabis use during pregnancy is also related with HPA-axis functioning in offspring is not known yet. Since cannabis and tobacco use are often used together, the relation of fetal cannabis exposure and childhood HPA-axis function should be studied in combination with tobacco use. Worldwide, up to 25 % of women seem to smoke tobacco during pregnancy (Philips et al., 2020). Likewise, fetal tobacco exposure has been associated with adverse fetal and childhood health outcomes, but the effects on childhood HPA-axis function are not fully understood (Duijts et al., 2012; Durmus et al., 2011; El Marroun et al., 2014; Jaddoe et al., 2007; McDonald et al., 2006).

While the above-mentioned studies show associations of cannabis and tobacco use with (salivary) cortisol concentrations, it is also possible to assess cortisone, an inactive form of cortisol as a biomarker for HPA-axis functioning (Seckl and Meaney, 2004). The assessment of both cortisol and cortisone may provide more insight into the amount of active and inactive corticosteroids. Based on prior literature, we hypothesized that fetal cannabis and tobacco exposure are associated with alterations of HPA-axis, reflected by higher hair cortisol and cortisone concentrations (Chapman et al., 2013; Franks et al., 2019; Gunn et al., 2016; Hill and Tasker, 2012; Hurd et al., 2019; Karlén et al., 2013; McDonald et al., 2006; Seckl and Meaney, 2004). Also, birth weight may be a potential mediator, as fetal exposure to tobacco and cannabis previously has been associated with reduced fetal growth and low birth weight, and low birth weight has been associated with the disruption of HPA-axis a long-term (El Marroun et al., 2009; Jaddoe et al., 2007; Seckl and Meaney, 2004). We examined the associations of maternal cannabis and tobacco use during pregnancy with childhood hair cortisol and cortisone concentrations at age of 6 years. To assess whether any association was the result of direct fetal programming or explained by familial confounding (e.g. sociodemographic factors and others potential confounders), we compared maternal and paternal associations (Davey Smith et al., 2009). Stronger associations for maternal exposure would suggest direct fetal programming effects, whereas similar or stronger effects for paternal exposure would suggest confounding (Santos et al., 2019). Second, we examined whether these associations were mediated by birth weight.

2. Material and methods

2.1. Setting and population

This study was embedded in the Generation R Study, a population-based on prospective cohort study from fetal life (Kooijman et al., 2016). All women living in Rotterdam, who were expected to deliver between April 2002 and January 2006 were eligible to participate, of whom n = 8879 mothers (response rate 61 %) were included during pregnancy. The study was approved by the Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam. Written informed consent was obtained from all participants. In total, 8116 mothers had information about cannabis or tobacco use and had singleton live-born children. Of these, 5627 participated with their children in the childhood follow-up assessment at the age of 6 years. Hair samples collection for cortisol and cortisone assessment was included later in the protocol and successfully performed in a subgroup of 2577 children (**Supplementary Figure S1**).

2.2. Fetal cannabis and tobacco exposure

Assessments were performed in early pregnancy (median 12.9 weeks of gestation, 25^{th}-75^{th} percentiles 12.1–14.5), mid pregnancy (median 20.4 weeks of gestation, 25^{th}-75^{th} percentiles 20.4–20.9) and late pregnancy (median 30.21 weeks of gestation, 25^{th}-75^{th} percentiles 29.9–30.8). Information about cannabis and tobacco exposure was collected by maternal self-reports and cannabis metabolite concentrations were additionally measured in urine samples. In early pregnancy, mothers indicated whether they used cannabis before and during pregnancy, and whether they were still using cannabis (no, yes; daily, weekly or monthly) (El Marroun et al., 2011). Urine samples were collected in early, mid, and late pregnancy, and the first available sample were used for urinalysis of cannabis metabolite. Urine samples were available in a subset of the cohort, and were analyzed on the presence of 11-nor-Δ9-THC-9−COOH using DRI® Cannabinoid Assay (Microgenics) with a cutoff value of 50 μg/l as recommended by the manufacturer and the Substance Abuse and Mental Health Security Agency. The agreement between self-reported of cannabis use and the cannabis metabolite in urine sample using Yule's Y was 0.77, indicating a substantial agreement (El Marroun et al., 2011). Information about maternal smoking was prospectively collected by postal questionnaires in each trimester (Jaddoe et al., 2007). In early pregnancy, mothers were asked whether they smoked during their pregnancy, and whether they continued or stopped smoking. In mid and late-pregnancy, mothers were asked whether they had smoked in the last 2 months. Maternal smoking was categorized into: no smoking during the pregnancy, until pregnancy was known (first trimester only), and continued during pregnancy. In addition, the number of cigarettes were assembled in two categories (less than 5 per day, and more and equal than 5 per day). Given that cannabis is often used in combination with tobacco (Chabarria et al., 2016). We categorized mothers in four non-overlapping groups: cannabis before pregnancy, cannabis during pregnancy, continued tobacco use during pregnancy (without cannabis), and non-users (the non-users included women that quit smoking tobacco until pregnancy was known). Additionally, a second categorization was performed using three groups for maternal tobacco use only (without cannabis users): first trimester only, continued tobacco during pregnancy, and non-users (i.e. reference group).

Information of paternal cannabis and tobacco use was assessed by maternal report and paternal self-report during the first trimester of pregnancy, without a specific time frame. In this study, we used maternal reports of paternal cannabis and tobacco use, given that less fathers (63 %) completed questionnaires. The inter-rater reliability between maternal report of cannabis or tobacco use was highly consistent with paternal self-reported (Cohen's kappa $_{\text{cannabis use}} = 0.80$, $p < .001$ and Cohen's kappa $_{\text{tobacco use}} = 0.86$, $p < .001$).

2.3. Hair cortisol and cortisone concentrations

As described previously, cortisol and cortisone concentrations were determined using hair samples of children with median age 5.92 (95 % range 5.67–8.15) (Rippe et al., 2016). Briefly, hair samples were cut from vertex using a small surgical scissors, as proximate to the scalp as possible (Noppe et al., 2015). Parents completed a questionnaire about the frequency of hair washing, time elapsed since the last wash, use of hair products and glucocorticoid medication of their children (Rippe

et al., 2016). For the sample preparation, the proximal 3 cm of hair samples were weighed and cut into small pieces. Then, they were washed in Liquid chromatography (LC) grade isopropanol at room temperature, and left to dry for at least 2 days. Deuterium-labeled cortisol and cortisone were gathered before extraction. Extraction was performed using LC-grade methanol for 18 h at 25 degrees Celsius (°C), in a slightly shaking water basin. The extract was transferred to a glass tube, centrifuged at 4300 x g (gravidity), and evaporated to dryness at 37 °C under a constant flow of N_2 (Noppe et al., 2015). Subsequently, the extract was loaded on an offline solid phase extraction plate (HLB Oasis 96-well SPE plate, Waters Chromatography), washed with 1 mL 30 % LC-grade methanol, and eluted twice in 300 µL 100 % LC-grade methanol. The extract was evaporated to dryness at 50 °C under a constant flow of N_2 and stored at 4 °C until further analysis. Before analysis, samples were reconstituted in 100 µL eluent (circulating fluid), vortexed, and quantified using liquid chromatography tandem mass spectrometry (LC–MS/MS) (Xevo TQS, Waters Chromatography). Cortisol and cortisone concentrations were divided by hair sample weight, and expressed as picogram per milligram (pg/mg) (Noppe et al., 2015). The Spearman correlation between hair cortisol and cortisone concentrations was 0.66 (p-value < .001).

2.4. Covariates

Potential covariates were selected based on prior research (El Marroun et al., 2008; Goldschmidt et al., 2000; Gunn et al., 2016; Ko et al., 2015; Rippe et al., 2016), and presented as a directed acyclic graphic (DAG) **(Supplementary Figure S2).** Maternal age, paternal age, maternal ethnicity, paternal ethnicity, maternal education were based on self-report. Information on maternal alcohol use was collected using questionnaires in each trimester, as described above for smoking, and was categorized as 'never drank in pregnancy', 'drank until pregnancy was known' and 'continued drinking'. Paternal alcohol use was based on maternal report with a high inter-rater reliability of maternal and paternal-report (Cohen's kappa $_{\text{alcohol use}} = 0.81$, $p < .001$). Parental ethnicity was categorized according to classification of Netherlands Statistics (Statistics Netherlands, 2004a). Maternal education was categorized in three levels as primary, secondary, and higher education (Statistics Netherlands, 2004b). Maternal psychopathology score was assessed at 20 weeks of pregnancy with the Brief Symptom Inventory (BSI), a validated continuous self-reported measure of 53-items covering a spectrum of psychological state (Derogatis and Melisaratos, 1983). Birth weight, child age and birth date were extracted from medical records. Hair color of children was partially coded through parent report and was completed by two raters using desk photographs in four categories (red, blond, brown, black) (Rippe et al., 2016).

2.5. Statistical analyses

First, we explored descriptive statistics to gain better understanding of study population characteristics. We also performed a non-response analyses to compare children with and without information on hair cortisol and cortisone concentrations using chi-squared for categorical variables, and Student's *t*-test or Mann-Whitney U tests for continuous variables. Second, we used multiple linear regression analyses to assess the associations of maternal and paternal cannabis and tobacco use with childhood hair cortisol and cortisone concentrations. Both cortisol and cortisone variables were log10–transformed to meet homoscedasticity assumptions of the residuals (Noppe et al., 2015; Rippe et al., 2016). Potential confounders were a priori selected based on literature and the 5% change in estimate criterion (**Supplementary Figure S2**). We used two different models for the analysis. The basic model was adjusted for child sex and age, and the adjusted model was additionally corrected for maternal age, education, ethnicity, prenatal alcohol, and psychopathology score. For associations that remained present after adjustment of these sociodemographic and lifestyle factors, we assessed whether these associations were mediated by birth weight. A simple mediation model to assess a direct effect, an indirect effect, and the proportion of mediation using the mediation R package with 1000 simulations (Tingley et al., 2014). The indirect effect quantified the mediation effect of birth weight, and total effect quantified the sum of indirect effect with direct effect (Lee et al., 2019). To examine potential sex differences, we tested the statistical interaction terms of maternal cannabis and tobacco use during pregnancy with child sex in relation to cortisol and cortisone. No significant interactions were observed.

We performed three sensitivity analyses to test the robustness of the results. First, in the model examining maternal cannabis, we excluded mothers who used tobacco only. Second, in paternal exposure models, we corrected for paternal instead of maternal variables (age, ethnicity and alcohol use) and excluded maternal cannabis or tobacco users to examine exclusive paternal effects. Third, we additionally corrected for child glucocorticoid medication use and hair color in the adjusted model, separately.

The percentage of missingness in the covariates ranged from 0 % to 11.2 %, with the exception of parental psychopathology score (19 %). We used multiple imputation to impute missing information of the covariates in 25 datasets, using the mice package (van Buuren and Groothuis-Oudshoorn, 2011). For data analysis, the R statistical software version 3.6.3 was used.

3. Results

3.1. Descriptive statistics

Table 1 shows the characteristics of the study population. Of all mothers, 2.5 %, 25.0 % and 53.4 % respectively used cannabis, tobacco and alcohol during pregnancy. Of the women who used cannabis during pregnancy, 88.7 % reported co-use of tobacco (14.5 % until pregnancy was known and 74.2 % continued in pregnancy), and 73 % co-use of alcohol (27 % until pregnancy was known and 46 % continued in pregnancy) (**Supplementary Table S1**). Of all fathers, 9.8 % and 43.6 % used cannabis and tobacco, respectively. Median hair cortisol concentration in children was 1.7 pg/mg (95 % range 0.5–16.5) (Table 1). Characteristics according to the cannabis and tobacco exposure categories is presented in **Supplementary Tables S1 and S2.**

Results from the non-response analysis showed that as compared to mothers from children who had cortisol data available, mothers of children without cortisol data were younger, lower educated, more often used alcohol and continued tobacco in pregnancy (**Supplementary Table S3**).

3.2. Maternal cannabis and tobacco use and childhood hair cortisol or cortisone concentrations

Table 2 shows that compared to children whose mothers did not use cannabis during pregnancy, children exposed to cannabis in pregnancy had higher childhood cortisol concentrations (log10-transformed difference 0.16, 95 % Confidence Interval 0.04 to 0.28). No differences in hair cortisone concentrations were observed. Results were similar in the basic and adjusted models. Maternal cannabis use before pregnancy was not associated with child hair cortisol or cortisone concentrations. Table 3 shows that maternal tobacco use during pregnancy was not associated with childhood cortisol nor cortisone concentrations. Further, paternal cannabis or tobacco use was not associated with childhood cortisol or cortisone concentrations. In the mediation model, birth weight did not mediate the association between maternal cannabis use during and child hair cortisol concentration; the direct effect (log10-transfromed difference 0.15, 95 % Confidence Interval 0.04 to 0.28) and total effect (log10-transfromed difference 0.15, 95 % Confidence Interval 0.04 to 0.28) were similar and statistically significant.

Table 1
Subject characteristics.

	Total group (n = 2577)
Maternal characteristics	
Age, years, mean (SD)	30.4 (5.0)
Ethnicity	
Dutch (%)	52.3
Non-Dutch Non-Western (%)	35.5
Non-Dutch Western (%)	12.1
Educational level	
None/Primary (%)	10.6
Secondary (%)	42.8
Higher (%)	46.7
Psychopathology score, median (95 % range)	0.17 (0–1.48)
Maternal alcohol use	
Never drank in pregnancy (%)	46.6
Drank until pregnancy was known (%)	15.4
Continued drinking (%)	38.0
Maternal cannabis use	
No use (%)	94.9
Cannabis before pregnancy (%)	2.7
Cannabis during pregnancy (%)	2.5
Maternal tobacco use	
Never smoked in pregnancy (%)	75.0
Smoked until pregnancy was known (%)	9.1
Continued smoking in pregnancy (%)	15.9
Paternal characteristics	
Age, years, mean (SD)	33.7 (5.9)
Cannabis use, yes (%)	9.8
Tobacco use, yes (%)	43.6
Alcohol use, yes (%)	74.6
Ethnicity	
Dutch (%)	52.9
Non-Dutch Non-Western (%)	36.6
Non-Dutch Western (%)	10.6
Child characteristics	
Birth weight, grams, mean (SD)	3435.6 (531.5)
Gestational age, weeks, median (95 % range)	40.1 (36.3−42.3)
Female sex, yes (%)	52.3
Age, years, median (95 % range)	5.9 (5.7−8.2)
Child hair concentrations	
Cortisol, pg/mg, median (95 % range)	1.7 (0.4–37.1)
Cortisone, pg/mg, median (95 % range)	7.7 (2.7−33.4)
Hair color	
Red (%)	3.0
Blond (%)	51.7
Brown (%)	33.8
Black (%)	11.4
Glucocorticoid medication use, yes (%)	8.3

Note: Values are presented as means (SD), medians (95 % range), or percentages. There were no missing data on these variables as they were imputed using multiple imputation methods, to except parental cannabis and tobacco use, hair cortisol and cortisone concentrations. The subject characteristics according to the cannabis and tobacco exposure categories is given in Supplemental Tables S1 and S2. Abbreviations: SD: standard deviation.

3.3. Sensitivity analyses

First, the association of maternal cannabis use with child hair cortisol did not change when mothers who used tobacco were excluded (**Supplementary Table S4).** Second, the associations of paternal cannabis and tobacco use with child hair cortisol and cortisone concentrations did not change when the models were adjusted for paternal variables (age, ethnicity and alcohol use) instead of maternal confounders, or when excluding cannabis and tobacco using mothers (**Supplementary Table S5**). Finally, we additionally adjusted for child glucocorticoid medication use and hair color, and the results remained similar (**Supplementary Table S6 and S7**).

4. Discussion

In this population-based prospective birth cohort study, we observed that maternal cannabis use during pregnancy, in combination with tobacco, was associated with a higher hair cortisol, but not cortisone concentration, in children at age 6 years. This association was not explained by family-based sociodemographic and lifestyle factors. The association between maternal cannabis use during pregnancy and hair cortisol concentration on offspring was not mediated by birth weight. Maternal and paternal tobacco use only during pregnancy were not associated with childhood hair cortisol and cortisone concentrations.

4.1. Interpretation of main findings

The prevalence of cannabis use in pregnant women has increased (Volkow et al., 2019). Also, almost 45 % of cannabis users co-use tobacco (Chabarria et al., 2016). In our study, 88.7 % of maternal cannabis users co-use tobacco during pregnancy. Fetal exposure to maternal cannabis and tobacco exposure has been associated with various biological adaptations and subsequent childhood health outcomes. Both may have the potential to alter the course of fetal developmental and HPA-axis functioning in offspring (Franks et al., 2019; Hurd et al., 2019; McDonald et al., 2006; Seckl and Meaney, 2004). We hypothesized that fetal cannabis and tobacco exposure are associated with alterations of HPA-axis.

Our finding that maternal cannabis use during pregnancy was associated with cortisol, but not with cortisone, was not in line with our hypothesis. Cortisol, the end product of HPA-axis, can be interconverted to inactive cortisone by 11β-hydroxysteriod dehydrogenase (11β-HSD), and some studies suggest that 11β-HSD could be a potential additional marker of HPA-axis programming (Chapman et al., 2013; Seckl and Meaney, 2004). To our knowledge there are no prior studies examining prenatal cannabis exposure to both hair cortisol and cortisone in offspring, so further research is needed to elucidate the underlying mechanisms and increase our understanding on how prenatal cannabis exposure influences HPA-axis functioning in offspring.

A previous study among 111 neonates reported that maternal cannabis and tobacco use during pregnancy were associated with the disruption of HPA-axis function (Stroud et al., 2020). In this study, neonates exposed to maternal cannabis and tobacco during pregnancy had lower stress-reactivity compared to non-exposed neonates (Stroud et al., 2020). Also, only male neonates exposed to maternal cannabis and tobacco during pregnancy had lower baseline salivary cortisol (Stroud et al., 2020). These differences in results between our and the previous studies may be explained by method of cortisol measurement. It has been shown that stress-reactivity may be well measured by time point measures as saliva or serum cortisol, but making it difficult to assess stress over longer period of time (Short et al., 2016). In contrast to common used approaches such as salivary cortisol concentrations and stress-reactivity, we used hair cortisol measurements, which provide a long-term and cumulative measure of cortisol concentrations (Karlén et al., 2013; Short et al., 2016). Other potential explanations may be the timing of information on tobacco and cannabis use, and age of participating children (neonates versus children aged 6 years). Further, findings from another study suggest that fetal tobacco exposure was not related to cortisol, but was adrenocorticotropic in cord blood at birth (McDonald et al., 2006). Similarly, in the current study after adjustment for sociodemographic and lifestyle characteristics, including prenatal alcohol exposure, we did not observe associations of maternal tobacco use and childhood hair cortisol concentrations. As previously reported, prenatal alcohol exposure may be an important confounder in the association between prenatal cannabis exposure with HPA-axis functioning in offspring, because it has been shown that prenatal alcohol exposure is associated with prenatal tobacco and /or cannabis use (El Marroun et al., 2008), and with lower cortisol concentrations aged 6–9 years (Grimm et al., 2020; Weinberg et al., 2008).

To assess whether the observed associations were the result of direct fetal programming or explained by family-based confounding, we compared maternal and paternal associations (Davey Smith et al., 2009). In theory, stronger associations for maternal exposure would

Table 2
Associations of maternal and paternal cannabis and tobacco use with childhood hair cortisol and cortisone concentrations at 6 years.

	Childhood hair cortisol concentrations (log10-transformed)						Childhood hair cortisone concentrations (log10-transformed)					
		Basic model[a]			Adjusted model[b]			Basic model[a]			Adjusted model[b]	
	N	Difference	(95 % CI)	p	Difference	(95 % CI)	p	N	Difference	(95 % CI)	p	Difference	(95 % CI)	p
Maternal cannabis use during pregnancy														
No	2112	Reference		–	Reference		–	2076	Reference		–	Reference		–
Before pregnancy	66	−0.01	(-0.13; 0.11)	0.89	0.02	(-0.09; 0.14)	0.72	67	−0.02	(-0.08; 0.05)	0.65	−0.01	(-0.08; 0.06)	0.84
During pregnancy	59	0.17	(0.05; 0.29)	<0.01	0.16	(0.04; 0.28)	<0.01	62	−0.02	(-0.09; 0.05)	0.62	−0.02	(-0.09; 0.05)	0.57
Continued tobacco smoking only	306	0.02	(-0.04; 0.08)	0.45	0.00	(-0.05; 0.06)	0.89	297	0.01	(-0.03; 0.04)	0.65	−0.00	(-0.04; 0.03)	0.92
Paternal cannabis use during pregnancy														
No	2022	Reference		–	Reference		–	1992	Reference		–	Reference		–
Yes	215	0.03	(-0.04; 0.10)	0.40	0.04	(-0.02; 0.11)	0.20	214	−0.03	(-0.07; 0.01)	0.14	−0.03	(-0.07; 0.02)	0.22

Note. Values are regression coefficients and 95 % confidence interval (95 % CI). In models of regression analysis were used log10-transformed of hair cortisol and cortisone concentrations (pg/mg).
[a] Basic model was corrected for child sex and child age.
[b] Adjusted model was corrected for maternal age, maternal alcohol use, maternal education, maternal ethnicity, maternal psychopathology score, child sex, and child age.

suggest direct fetal programming effects, whereas similar or stronger effects for paternal exposure would suggests confounding (Santos et al., 2019). We did not observe associations of paternal use of cannabis or tobacco during pregnancy. These observations cautiously suggest that the associations of maternal cannabis during pregnancy with childhood hair cortisol concentrations could be due to direct intra-uterine mechanisms, as suggested in previous literature (Calvigioni et al., 2014; O'Donnell and Meaney, 2017). Further, our results cautiously suggest that maternal cannabis use during pregnancy is directly associated with higher hair concentrations in children aged 6 years, since no indirect effect through birth weight was detected. However, before such conclusions can be drawn further studies are needed to assess the causality and potential other mechanisms underlying the associations.

Taken together, these findings suggest that fetal life is a critical period for the maturation of the HPA-axis, and that potentially the endocannabinoid system may play a role. Several brain regions are involved in the regulation of the HPA-axis and are part of the endocannabinoid system, e.g. the amygdala, hippocampus and prefrontal cortex (Franks et al., 2019; Hurd et al., 2019). The prefrontal cortex has been shown to be sensitive for prenatal cannabis exposure: prenatal cannabis exposure has been related to changes in neural activity in the prefrontal cortex (and premotor cortex) during a response inhibition task measured by functional magnetic resonance imaging in adolescents (fMRI), and in our own study group prenatal cannabis exposure has been related to a thicker frontal cortex in childhood (El Marroun et al., 2016; Smith et al., 2004). Finally, other study reported that prenatal cannabis exposure impairs dopamine receptor expression in the amygdala in human fetal specimens (Wang et al., 2004). Further research is needed to elucidate the exact neurobiological mechanisms.

4.2. *Potential underlying mechanisms*

Several mechanisms may explain our findings. First, cannabis crosses the placenta and blood brain barrier and may impact endogenous HPA-axis activity through cannabinoid receptors of endocannabinoid system (ECS) (Calvigioni et al., 2014). ECS regulates the HPA-axis modulating excitatory and inhibitory synaptic neurotransmission via distinct actions within prefrontal cortex, amygdala and hypothalamus mainly through of cannabinoid type 1 receptor (CBR1) (Calvigioni et al., 2014; Franks et al., 2019; Hill and Tasker, 2012; Hurd et al., 2019). Exogenous endocannabinoids bind to CBR1 and are insensitive to hydrolysis of endocannabinoids enzymes, so, which may disrupt the balance and spatial organization of endocannabinoid signaling altering the HPA-axis functioning, and conducting an overexposure of cortisol in early life, given that the disruption of CBR1 function increases basal drive on the HPA-axis (Hill and Tasker, 2012; Keimpema et al., 2011). Second, cortisol concentrations in pregnant mothers may increase due to cannabis use, e.g. by hepatotoxicity affecting enzymes involved in cortisol metabolism such as CYP3A4 (Zendulka et al., 2016). These subsequent higher cortisol concentrations may then affect fetal development (Cottrell and Seckl, 2009). Despite the placenta has the ability to convert cortisol into less active cortisone using the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which is present abundantly in syncytiotrophoblast. The activity of placental 11β-HSD2 shows inter-individual variations and seems to be dynamically regulated by maternal stress, anxiety, pro-inflammatory cytokines and malnutrition (Chapman et al., 2013; O'Donnell et al., 2012). The capacity of 11β-HSD2 in higher maternal cortisol concentrations may be oversaturated or overruled leading to active transfer of maternal cortisol into fetal circulation (Cottrell et al., 2014; O'Donnell et al., 2012). Excess of cortisol in utero acts to program the fetal HPA-axis, permanently altering basal and stress response of HPA-axis in offspring (Cottrell and Seckl, 2009; Jensen Peña et al., 2012; Seckl and Meaney, 2004). Also, both mechanisms may potentiate each other, generating adverse consequences on HPA-axis fetal programming, and disruption of HPA-axis functioning throughout life.

Table 3
Associations of maternal and paternal tobacco use with childhood hair cortisol and cortisone concentrations at age 6 years.

	Childhood hair cortisol concentrations (log10-transformed)							Childhood hair cortisone concentrations (log10-transformed)						
			Basic model[a]		Adjusted model[b]					Basic model[a]		Adjusted model[b]		
	N	Difference	(95 % CI)	p	Difference	(95 % CI)	p	N	Difference	(95 % CI)	p	Difference	(95 % CI)	p
Maternal tobacco use only during pregnancy														
No	1691	Reference		–	Reference		–	1663	Reference		–	Reference		–
First trimester only	190	−0.06	(-0.13;0.01)	0.10	−0.05	(-0.12;0.02)	0.16	188	−0.05	(-0.09; -0.01)	0.02	−0.04	(-0.08;0.00)	0.07
Continued during pregnancy	306	0.02	(-0.04;0.08)	0.54	0.00	(-0.06;0.06)	0.93	297	0.00	(-0.03;0.04)	0.93	−0.01	(-0.04;0.03)	0.64
<5 per day	140	0.08	(-0.00;0.17)	0.05	0.05	(-0.03;0.14)	0.21	134	−0.00	(-0.05;0.05)	0.86	−0.02	(-0.07;0.03)	0.46
≥5 per day	166	−0.04	(-0.11;0.04)	0.35	−0.04	(-0.12;0.04)	0.31	163	0.01	(-0.04;0.05)	0.78	0.00	(-0.05;0.05)	0.99
Paternal tobacco use only during pregnancy														
No	1255	Reference		–	Reference		–	1238	Reference		–	Reference		–
Yes	817	−0.01	(-0.06;0.03)	0.53	−0.03	(-0.08;0.01)	0.11	806	0.02	(-0.00;0.05)	0.09	0.01	(-0.01;0.04)	0.28

Note. Values are regression coefficients and 95 % confidence interval (95 % CI). In models of regression analysis were used log10-transformed of hair cortisol and cortisone concentrations (pg/mg).
[a] Basic model was corrected for child sex and child age.
[b] Adjusted model was corrected for maternal age, maternal alcohol use, maternal education, maternal ethnicity, maternal psychopathology score, child sex, and child age.

4.3. Strengths and limitations

The strengths of our study were the population-based the prospective design, the multiethnic composition of the cohort, the combination of self-reported information and urinalysis to determine cannabis use, the ability to adjust for many sociodemographic confounders (including parental psychopathology) and the assessment of long-term child hair cortisol and cortisone concentrations using LC–MS/MS (Noppe et al., 2015). In children, hair cortisol levels are age-dependent (de Kruijff et al., 2020). Therefore, it is a strength that there was a narrow age range in this study. Some limitations that need to be discussed. First, although assessing of smoking during pregnancy by questionnaires appears to be a valid method, non-differential misclassification is possible, potentially causing an underestimation of our association of the observed. Nevertheless, information was obtained in different trimesters of pregnancy, the prevalence of tobacco use was also similar among the Dutch population aged 15–64 years in the same period (Statistics Netherlands, 2006), and previous studies have reported a high correlation between cotinine levels and reporting smoking habits (McDonald et al., 2005). Second, non-response analysis showed mothers who were not in the analyses were lower educated, and had higher alcohol use than ones include in the analyses. Based on these characteristics, the excluded mothers may have a higher risk for using cannabis and tobacco. Finally, although we have adjusted for several sociodemographic and lifestyle factors (including alcohol use during pregnancy) in our models, residual confounding might still be possible due to observational design of the study.

5. Conclusion

In conclusion, the results from this study cautiously suggest that children exposed to maternal cannabis use during pregnancy, in combination with tobacco, have altered HPA-axis function reflected by higher hair cortisol concentrations. These results may have implications in the fetal programming of HPA-axis delineating pathways to long-term adverse outcomes, such as cardiovascular, metabolic, immune and neurodevelopmental outcomes in offspring. These findings should be considered as hypothesis generating and need further replication. Future studies are needed to elucidate the causality and mechanisms underlying the observed associations.

Role of the founding source

The general design of the Generation R Study was supported by Erasmus Medical Center, Erasmus University Rotterdam, the Netherlands, the Organization for Health Research and Development (ZonMw) and the Ministry of Health, Welfare and Sport. VWVJ was supported by a Consolidator Grant from the European Research Council [ERC-2014-CoG-648916]. EFCvR and ELTvdA were supported by the Elisabeth Foundation, and EFCvR was supported by the Netherlands Organization of Scientific Research NWO [Vidi Grant Number 91716453]. HEM was supported by Stichting Volksbond Rotterdam, the Dutch Brain Foundation [De Hersenstichting, project number GH2016.2.01], the NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation [grant number 27853], and the European Union's Horizon 2020 Research and Innovation Program [LifeCycle, grant agreement 733206]. KNCT was supported by Peruvian Scholarship [547-2018-SERVIR]. The founding sources had no role in the study design, collection, analysis and interpretation of data, writing of the report, or in the decision to submit the paper for publication.

Contributors

Kim N. Cajachagua-Torres was involved conception and design of the study, analysis and interpretation of data, wrote the paper, critical revision and final approval of the manuscript. Vincent W.V. Jaddoe and

Hanan El Marroun were involved in conception and design of the study, data acquisition, analysis and interpretation of data, critical revision and final approval of the manuscript. Yolanda B. de Rijke, Erica L.T. van den Akker, Irwin K.M. Reiss and Elisabeth F.C. van Rossum were involved in the interpretation of data, critical revision and final approval of the manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

The Generation R study is conducted by the Erasmus Medical Centre Rotterdam in collaboration with the Faculty of Social Sciences of the Erasmus University Rotterdam, the Municipal Health Service Rotterdam, the Rotterdam Homecare Foundation and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR), Rotterdam. We gratefully acknowledge the contribution of general practitioners, hospitals, midwives and pharmacies in Rotterdam.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2021.108751.

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