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Prenatal cannabis exposure and infant outcomes: Overview of studies☆

A.C. Huizink *

Department of Developmental Psychology, VU University Amsterdam, Amsterdam, The Netherlands
Department of Clinical Child and Family Studies, VU University Amsterdam, Amsterdam, The Netherlands
EMGO + Institute for Health and Care Research, VU Medical Center, Amsterdam, The Netherlands

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ABSTRACT

Accumulating evidence from both human and preclinical studies indicates maternal substance use during pregnancy can affect fetal development, birth weight and infant outcomes. Thus, the prenatal period can be regarded as an important and potentially sensitive period of development. In this manuscript, an updated overview of studies on prenatal cannabis exposure in humans is presented, including recent studies conducted within the Generation R study. Findings on fetal growth, birth outcomes, early neonatal behavior and infant behavior and cognitive development are discussed in detail. Preclinical evidence and potential mechanisms are described as well, and recommendations for future studies are provided. It is concluded that evidence seems to suggest that fetal development is affected by prenatal maternal cannabis use, while findings on effects on infant behavior or cognition are inconsistent. Beyond infancy, subtle differences may be found in specific cognitive or behavioral outcomes, although replication studies in which pregnant women and their fetuses are exposed to current and probably higher levels of Δ9-tetrahydrocannabinol and novel designs are needed to come to firm conclusions.

1. Introduction

Currently, the scientific literature contains a wealth of studies and numerous reviews on the topic of prenatal maternal substance use and more particularly smoking and drinking, and offspring outcomes. From these studies, the general impression arises that there is converging and accumulating evidence for adverse effects of maternal smoking or drinking during pregnancy on her child's development and behavior from infancy onwards. This evidence thus indicates that the prenatal period lays an important fundament under the future prospective of a child, by shaping its development from pregnancy onwards. Nonetheless, not all studies are consistently in agreement with this suggestion, and some authors cautioned for claims that have been made regarding causality of prenatal substance use effects (for a review, see Huizink, 2009).

The striking increase of publications on prenatal exposures and possible affected offspring outcomes was a result of rising awareness of the potentially vulnerable pregnancy period, inspired by two lines of research based on specific frameworks. First, the identification of fetal alcohol syndrome (FAS) in the 1970s formed an important milestone in bringing the methods and relevance of the behavioral teratological approach to human studies. In the last decades, teratological studies have shown that exposure to agents that are relatively harmless to the mother may have adverse effects on the developing fetus (*e.g.* Annau and Eccles, 1986). These studies also assume that the central nervous system (CNS) is vulnerable to injury from fetal life onwards and all aspects of CNS development may be affected. Moreover, the consequence of such injury does not result in CNS malformations but rather in functional abnormalities that may not be evident at birth (Fried et al., 1998; Vorhees, 1989).

The second framework was built on the work of David Barker (1998), who was the first to explain the associations between prenatal environmental events, birth outcome and postnatal development using the concept of *prenatal* or *fetal programming*. His work focused mainly on prenatal malnutrition as a programming factor for adult cardiovascular health of the offspring (for an overview, see Barker, 2012). More recently, developmental origins of health and disease (DOHaD) researchers, with their own society (see www.mrc.soton.ac.uk/dohad), have broadened their interest towards mental health, which was already the focus of many behavioral teratological studies. The latter particularly focused on behavioral and cognitive outcomes (*e.g.* Barr et al., 1990; Streissguth

Abbreviations: FAS, fetal alcohol syndrome; CNS, central nervous system; DOHaD, developmental origins of health and disease; THC, delta9- tetrahydrocannabinol; OPPS, Ottawa Prenatal Prospective Study; MHPCD, Maternal Health Practices and Child Development Study; Generation R study, Generation Rotterdam Study; ALSPAC, Avon Longitudinal Study of Pregnancy; NBAS, Brazelton Neonatal Behavioral Assessment Scale; EEG, Electroencephalography; BSID, Bayley Scales of Infant Development; CBCL, Child Behavioral Checklist; PARCA, Parent Report of Children's Abilities; LDS, Language Development Survey; EF, executive functioning; CB1, cannabinoid receptor type 1; CB2, cannabinoid receptor type 2; GABA, gamma-aminobutyric acid; D2 receptor, Dopamine type 2 receptor.

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* Department of Developmental Psychology, VU University Amsterdam, Van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands. Tel.: +31 20 5988732.
E-mail address: a.c.huizink@vu.nl.

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et al., 1990) given their history in FAS research, a field that is now examined by DoHad researchers as well.

Several review articles have been published recently, summarizing findings from empirical studies conducted within those frameworks, with a focus on *in utero* exposure to maternal substance use and the offspring's behavioral outcomes. These reviews described mostly studies on maternal smoking or alcohol drinking during pregnancy (*e.g.* Driscoll et al., 1990; Ernst et al., 2001; Knopik, 2009; Linnet et al., 2003) and fewer on maternal cannabis use (*e.g.* Fried et al., 2002; Huizink and Mulder, 2006). Nonetheless, cannabis is the most commonly used illicit drug in pregnant women, with prevalence rates ranging between 3 and 4% in Western countries (Ebrahim and Gfroerer, 2003; el Marroun et al., 2008). Here, reference to cannabis represents any use of marijuana, hashish or sensimilla, which are all products of different parts of the *Cannabis sativa* plant. The active compound of cannabis, Δ9-tetrahydrocannabinol (THC), and its metabolites can freely pass through the placental barrier (Gomez et al., 2003; Little and VanBeveren, 1996) and hence, may affect fetal development. It has also been shown that local actions of endocannabinoids in the human placenta are already present in early pregnancy during fetal brain development (Helliwell et al., 2004), and may provide a mechanism by which cannabinoids exert an effect in the offspring (Gomez et al., 2003). Further research on potential mechanisms is described in Section 4. For now, it is important to recognize that there are potential mechanisms through which maternal cannabis use may have an impact on the developing fetus.

In the last couple of years, our group has published new findings on prenatal cannabis exposure in humans (El Marroun et al., 2008, 2009, 2010, 2011). Moreover, new trends in research methodology to examine prenatal influences on human development have emerged. Therefore, the purpose of this manuscript is to provide (1) an updated overview of studies on prenatal cannabis use exposure and infant and child outcomes and (2) recommendations for future studies, based on novel directions that can be observed in related lines of research.

2. Design of three prospective longitudinal human studies

As compared to the extensive number of studies on maternal smoking and drinking, there are only a few studies that examined the relation between prenatal exposure to cannabis use and offspring outcomes in humans. To date, three prospective longitudinal studies exist with follow-up assessments of the offspring beyond the early neonatal period.

The first study to be initiated in the late 1970s was the Ottawa Prenatal Prospective Study (OPPS) by Fried and colleagues (for a detailed description, see Fried, 1980; Fried et al., 1998), which included a low-risk, European-American, middle-class sample of pregnant women. Advertisement for the study through notices in doctors' offices and through the media resulted in an initial sample of n = 698 women participating in the study. Women were included with different gestational ages, but most of them were in their second trimester of pregnancy. By means of interviews, data were collected on drug use while pregnant, including cigarette, cannabis and alcohol use. The number of joints per week was used to describe cannabis use. Of the original n = 698 women, a sub-cohort was selected for follow-up, consisting of n = 140 women who reported any use of cannabis or a particular amount of alcohol per day (0.85 oz of absolute alcohol) or smoking at least 16 mg of nicotine per day. In addition to this sample, a smaller group of women (n = 50) who did not use any substances during pregnancy were randomly selected as a reference group. For this selected group of substance using women, prenatal maternal cannabis use was categorized into 3 groups, with levels averaged across pregnancy: (1) no use, (2) mild/moderate use up to 6 joints/week, and (3) heavy use of at least 6 joints/week. The heaviest using group was relatively small (n = 25), as was the moderately using group (n = 37). This study has resulted in many publications up to the offspring's age of 18–22 years, although the total number of cases dropped over time to a total of n = 49 of (any) prenatally cannabis-exposed offspring.

A couple of years later, in 1982, the Maternal Health Practices and Child Development Study (MHPCD) was started (Day and Richardson, 1991; Day et al., 1991). Their study included a completely different population as compared to the OPPS study and focused on high-risk pregnant women, with a low socioeconomic status, of mixed ethnicity (57% of African-American ethnicity) and often single (71%). Their recruitment strategy also differed from the OPPS study. All participants visited an inner-city outpatient prenatal clinic in Pittsburgh, USA, were at least 18 years old and were in their fourth month of pregnancy. Initially, a group of n = 1360 women was interviewed that fulfilled these criteria and agreed to participate. Pregnant women who were interviewed and who used two or more joints per month were then selected for the study. A random selection of women from the remaining subjects, equaling the number of cannabis-using women, was added to this selected group. In total, the study sample consisted of n = 564 women. Prenatal cannabis use was expressed as average daily joints for each trimester of pregnancy separately, though these groups showed overlap. In the first trimester, n = 103 women used one or more joints per day (defined as heavy use); in the second and third trimester, much smaller groups were defined as heavy users (n = 34 and 37, respectively). Light-to-moderate users in the first trimester (1–6.9 joints/week) summed up to n = 176, with reducing numbers in the second (n = 100) and third trimester (n = 93). Follow-up data of offspring have been reported up to the age of 14, at which time 79 adolescent offspring of mothers from the heaviest using group during first trimester of pregnancy participated.

More recently, in 2001, the Generation R study was started. Generation R is a multi-ethnic population-based prospective cohort study from fetal life until adulthood in the city of Rotterdam, the Netherlands (for details on the study protocol, see Hofman et al., 2004; Jaddoe et al., 2012). In total, n = 9778 mothers with a delivery date between April 2002 and January 2006 were enrolled in this study. Follow-up rates until age 6 years exceed 80% for most measures. A selection towards a higher socio-economic status was observed (Jaddoe et al., 2012), as is often seen in large-scaled cohort studies. The largest ethnic groups included were Dutch, Surinamese, Turkish and Moroccan. Embedded within this large-scaled cohort, we conducted several studies specifically focusing on maternal cannabis use during pregnancy and fetal and offspring behavioral outcomes. All participating women in Generation R filled out questionnaires on a variety of issues, including their substance use, repeatedly: during the first (<18 weeks of gestation), second (18–25 weeks of gestation) and third trimester (>25 weeks of gestation). In this population-based study, 220 women used cannabis during pregnancy, of whom the majority only used cannabis in the first trimester, and 43 of them continued their cannabis use throughout pregnancy. As cannabis is often combined with tobacco in the Netherlands, both rolled into and smoked as a joint, in all studies described here, cannabis-exposed offspring were compared with tobacco-exposed and non-exposed offspring.

These three prospective studies have used different populations to test the associations between prenatal cannabis exposure and offspring outcomes. Differences in findings between the studies may be partly due to their varying population characteristics. It is important to note that in the most recent study, Generation R, fetuses were most likely exposed to the highest levels of THC, as the levels of THC in cannabis have strongly increased over the last couple of decades. Specifically, the mean potency of cannabis products, in terms of the percentage of THC, has increased from 3.4% in 1993 to 8.8% in 2008 (Mehmedic et al., 2010) in the USA. Furthermore, because of improved breeding and greenhouse technology, Dutch cannabis products are known for their potency, with 17.7% of THC reported in *Nederweed* as opposed to 5.5% in other weed products sold in Dutch so-called coffee shops (Pijlman et al., 2005). About one third (30.9%) of the cannabis using pregnant women in the Generation R study reported daily use,

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Table 1
Overview of significant differences in cannabis exposed offspring as compared to non-exposed offspring in the three prospective studies.

Study	Population	Fetal development/birth outcome	Neonatal development	Infant behavior	Child behavior & cognitive development
OPPS — started in 1978	Low-risk, European-American, middle-class pregnant women	Gestational age reduced No differences in birth weight	Increased startles and tremors Reduced habituation to light	12 and 24 months BSID scores: no differences 36 months: more advanced motor skills 48 months: lower memory functioning and verbal scores	6 years: more impulsivity and hyperactivity 9–12 years: impaired visuo-perceptual functioning
MHPCD — started in 1982	High-risk pregnant women of mixed ethnicity (57% African-American), often single (71%), low socioeconomic status	Birth length reduced after first trimester exposure only Increased birth weight after third trimester exposure	No differences in neonatal behavior. Subtle differences in EEG sleep recordings in subsample	9 months: lower BSID scores 19 months: no differences on BSID scores 36 months: lower short-term memory functioning and verbal reasoning only in African-American offspring	6 years: more impulsivity, hyperactivity, delinquency 10 years: more problems in abstract and visual reasoning
Generation R — started in 2001	Multi-ethnic population cohort, slightly higher socioeconomic status.	Fetal growth reduced from second trimester onwards Birth weight reduced	Not examined	18 months: more aggression and inattention for exposed girls only 30 months: no differences in non-verbal cognition scores or vocabulary development 36 months: no differences in behavior for both sexes	Not yet examined

OPPS: Ottawa Prenatal Prospective Study (Fried, 1980); MHPCD: Maternal Health Practices and Child Development Study (Day and Richardson, 1991); Generation R (Hofman et al., 2004); BSID: Bayley Scales of Infant Development.

comparable to that of heavy users is the OPPS and MHPCD studies, another quarter (26%) reported weekly use (*i.e.*, moderate use), and the remaining proportion used cannabis once a month (light use).

3. Results: human studies

Findings from the OPPS, MHPCD and Generation R studies will be reviewed below. Table 1 presents a summary of the main findings of these three studies. As the Dutch Generation R study was initiated more recently, follow-up results of its offspring are only available until the first years of life, while the OPPS has published with offspring data up to age 18–22 years and the MHPCD until age 14 years. For the purpose of this review, results are restricted to the fetal period, infancy and childhood outcomes, so that findings between these three studies can be compared. For fetal and early neonatal outcomes observed after prenatal cannabis exposure, some other studies are reviewed as well, as their findings are relevant, but were restricted to these short-term effects.

3.1. Fetal development and birth outcomes

Of the three prospective cohorts, only Generation R examined fetal growth parameters, while MHPCD and OPPS assessed growth parameters within 48 h after birth. The Generation R study assessed fetal growth through fetal ultrasound assessments in early, mid-, and late pregnancy. Data were available from standardized techniques on femur length, abdominal and head circumference, and transcerebellar diameter. Fetal weight was estimated with femur length, head and abdominal circumference using Hadlock's formula (Hadlock et al., 1984). In total, 8880 mothers were enrolled during pregnancy and therefore eligible for fetal growth analyses. Fetal growth was reduced in mothers who used cannabis in early pregnancy only (n = 173) as compared to non-users and tobacco users, resulting in a 156 gram lower birth weight on average. Continued maternal cannabis use throughout pregnancy (n = 41) showed the largest growth reduction, resulting in a 277 gram lower birth weight on average. Head circumference also showed a growth reduction in fetuses of mothers using cannabis in early pregnancy only or continuously throughout pregnancy (−1.78 and −2.45 mm less growth on average, respectively, as compared to non-exposed fetuses), but transcerebellar diameter did not differ between groups. This latter finding is suggestive of brain sparing during intrauterine growth (Reece et al., 1987). Although similar findings were found for *in utero* exposure to continued maternal tobacco use, comparisons between cannabis exposure and tobacco exposure still showed larger growth reduction effects of *in utero* exposure to cannabis (El Marroun et al., 2009). Within a smaller subsample of the Generation R study, the Generation R Focus Study, early changes in fetal blood flow characteristics due to *in utero* cannabis exposure could be examined as well. It was hypothesized that cannabis exposure could result in adaptations of the vascular system, including a reduction in vascular resistance and an increase in vascular flow. Three groups were compared: (1) prenatal cannabis users (n = 23), (2) tobacco users (n = 177), and (3) a random selection of non-users (n = 85). Fetal circulation variables were assessed by means of pulsed-waved Doppler between 28 and 34 weeks of gestation (for more details, see El Marroun et al., 2010). Prenatal cannabis use was associated with an increased fetal pulsatility index and resistance index of the uterine artery, which suggests an increased placental resistance during pregnancy (Boito et al., 2002) that may partly explain fetal growth restriction. In addition, a smaller inner diameter of the aorta in cannabis-exposed fetuses was found (El Marroun et al., 2010), while no differences in blood flow of the cerebral arteries were observed. This is in line with the fetal growth findings that were suggestive of brain sparing reported above (El Marroun et al., 2009). Most of these changes in hemodynamic programming of the vascular system of the fetus were also present in the tobacco-exposed group. Thus, as yet, there is little evidence to suggest a specific cannabis exposure effect and replication studies (with larger sample sizes) are needed.

MHPCD examined mean differences in birth weight, birth length, gestational age and ponderal index (an indicator of leanness; Miller and Hassanei, 1973), among categories of cannabis use: heavy use (1 or more joints per day, n = 37 with data complete at the third trimester), moderate use (3–6.9 joints/week, n = 7), light use (<2.9 joints/week, n = 86) or non-users (n = 389). They also compared these parameters in the offspring of mothers who used cannabis in the first trimester only (n = 103) with abstainers. Only this latter comparison resulted in a significant difference in birth length (0.5 cm shorter in the exposed group). Many analyses were run and for instance, groups were made (not per definition mutually exclusive) of women using cannabis in a specific trimester. Of these multiple analyses, one appeared suggestive of a surprising increased birth weight (142 g) after cannabis exposure in third trimester (Day et al., 1991). This finding was not replicated in other studies.

In line with most of the other MHPCD findings on neonatal outcomes, the OPPS did not observe differences in birth weight, head

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circumference or ponderal index after prenatal cannabis exposure (Fried and O'Connell, 1987). Gestational length was reduced (with 5.6 days on average) after exposure to almost 1 joint/day throughout pregnancy, thus in the heavy exposed group only, as compared to the non-exposed group (Fried et al., 1984).

Besides these three prospective studies, several other human studies examined prenatal cannabis exposure and fetal or birth outcomes. In an Australian prospective study of 7301 births, a group of 36 women reported using cannabis 2 or more times a week. Of this group, 25% had premature births before 37 weeks of gestation (Gibson et al., 1983). A study of 1690 mother/child pairs at Boston City Hospital, of whom 2% (n = 33) reported cannabis use 3 or more times per week during pregnancy, found evidence for reduced birth weight in prenatally cannabis-exposed offspring, up to 139 g on average. A replication of this study in the same hospital also found evidence for lower birth weight (79 g on average) and slightly shorter birth length (0.5 cm) after prenatal exposure to cannabis, but only when urine screens of THC metabolite were used as the measure of exposure and not when only self-reported cannabis use (in the absence of a positive urine screen) was entered in their regression model (Zuckerman et al., 1989). Another impressive large-scaled study from Boston conducted interviews with over 12,000 women following delivery at their hospital, which included questions about cannabis use during pregnancy. Birth outcomes were derived from medical records. In their sample, 7.1% (n = 880) reported occasional use of cannabis, 1.8% (n = 229) reported weekly use and 1.1% (n = 137) reported daily use. In uncorrected analyses, there seemed to be a negative association between weekly or more frequent cannabis use and reduced gestational length and birth weight, but after correction for other risk factors these associations were no longer significant (Linn et al., 1983). A more recent study conducted among participants from the Avon Longitudinal Study of Pregnancy (ALSPAC) in the United Kingdom, including more than 12,000 pregnant women of whom 2.6% reported any cannabis use during pregnancy, reported similar findings: no significant effects on birth weight, birth length or head circumference after correction for confounding factors (Fergusson et al., 2002). In contrast with these findings, a study in the greater New Haven area reported a more than two-fold increased risk among European-American regular pregnant cannabis users (2–3 times a month or more) of delivering a low-birth-weight baby (<2500 g) or a two-fold increased risk of having a small-for-gestational-age infant (Hatch and Bracken, 1986). However, such a relationship was not observed for women of different ethnic backgrounds. Finally, more recently, Hurd et al. (2005) examined growth parameters in voluntarily aborted fetuses of women who used cannabis during early to mid pregnancy (*i.e.*, before abortion took place) in comparison to aborted fetuses with no exposure, and found some evidence for a small reduction in body weight and foot length of exposed fetuses.

In sum, a pattern of inconsistent findings seems to emerge when birth outcomes are examined, though fetal growth may be reduced from mid-pregnancy onwards, eventually leading to lower birth weight when exposure to the plausibly higher levels of THC in the more recent studies is considered.

3.2. Neonatal behavior

Both OPPS and MHPCD reported findings on early neonatal behavior. In the OPPS study, any cannabis use during pregnancy (n = 47) was related to subtle neonatal behavioral effects in the first week of life, as assessed with the Brazelton Neonatal Behavioral Assessment Scale (NBAS), including an increase in startles and tremors, and reduced habituation to light. The MHPCD study applied the same assessment instrument to prenatally cannabis-exposed neonates on the second day postpartum, but found no association between cannabis use throughout pregnancy and observed neonatal behavior (Richardson et al., 1989). It must be noted that temporary effects of delivery method and use of pain medication during delivery may be present when the NBAS is applied shortly after birth. Moreover, the correct neurological state (*i.e.*, awake and alert) is needed to elicit optimal responses (Hadders-Algra et al., 1993; Lenard et al., 1968). With small study samples, variation in these factors within exposed groups may mask any effects of prenatal substance exposure. In addition, the MHPCD study conducted a study on neonatal sleep patterns in the first two days of life in a smaller subset of prenatally cannabis-exposed infants (n = 11) by means of EEG-sleep recordings. Some subtle differences in sleep patterns were noted in exposed infants when compared to non-exposed infants (Scher et al., 1988). The Generation R study did not focus on these early outcomes, but assessed infant behavior from age 18 months onwards (see section 3.3).

In sum, the findings of OPPS and MHPCD do not give rise to a consistent pattern of adverse neonatal behavior after prenatal cannabis exposure. Perhaps, some minor signs of irritability may be found, resulting in slightly more tremors, startles, or different sleeping patterns, but repeated measures of larger groups, with adequate control of potential confounding factors are needed to come to a definite conclusion.

3.3. Infant behavior and cognitive development

All three studies examined behavior and/or cognitive development in prenatally cannabis-exposed infants, although different measures and methods were applied. The OPPS examined mental and motor development of prenatally cannabis-exposed infants at the ages of 12 and 24 months by means of the Bayley Scales of Infant Development (BSID), which also yield an infant behavior record through observation during test procedures. Additionally, they assessed expressive and receptive language development at the age of 24 months. They first examined linear associations between intensity of exposure (average joints per day during pregnancy) and infant outcomes within the total group of prenatal cannabis users (n = 54), and then tested whether a cut-off of using at least 5 joints/week (n = 17) was related to more adverse outcomes. None of these analyses yielded significant associations (Fried and Watkinson, 1988). In a follow-up study at ages 36 and 48 months, n = 31 (n = 12 moderately exposed, n = 19 heavily exposed) prenatally cannabis-exposed infants were re-assessed using the McCarthy Scales of Children's abilities, developmental language scales and some other specific tests (Fried and Watkinson, 1990). Only memory functioning and some verbal scores were significantly lower in heavily cannabis-exposed infants at the age of 48 months, while the motor skills of 36-month-olds of moderately cannabis-exposed infants were surprisingly more advanced, as compared to non-exposed or heavily exposed infants.

The MHPCD study examined mental and motor development of prenatally cannabis-exposed infants at ages 9 and 19 months using the BSID (Richardson et al., 1995). In total, approximately 40 exposed infants could be assessed, of whom 17 were exposed to cannabis throughout pregnancy. At age 9 months, lower mental development scores were present in infants whose mothers (also) used cannabis in the third trimester of pregnancy and smoked more than 1 joint/day, although exact age at examination was the most important (and logical) predictor. No relation with prenatal cannabis exposure was found for motor development at both assessments, or for mental development scores at age 19 months. At a follow-up assessment at the age of 3 years, the Stanford–Binet Intelligence Scale was applied resulting in a composite score of cognitive functioning, a short-term memory functioning score and a level of verbal reasoning (Day et al., 1994). The exposed group was further divided into ethnic groups, with 48.2% European-Americans and the remaining of African-American background in the total sample, but it is unclear how many prenatally cannabis-exposed infants were in each of the ethnicity groups. For offspring of African-American mothers, prenatal cannabis exposure was related to lower scores on short-term memory functioning and verbal reasoning. This negative effect was attenuated in European-American offspring when they attended preschool or day-care. When interpreting those findings, it is important to take into

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account the likelihood of very small groups being tested within the stratified analyses.

The Generation R study focused on infant behavioral outcomes, using the Child Behavioral Checklist at ages 18 and 36 months, but also conducted a non-verbal cognition test for 79 prenatally cannabis-exposed infants and a language development test at age 30 months for 51 prenatally cannabis-exposed infants. No evidence was found for a relation between prenatal exposure to cannabis and non-verbal cognition scores on the Parent Report of Children's Abilities (PARCA) or with phrase development or vocabulary development as assessed with the Language Development Survey (LDS) (El Marroun, 2010). CBCL scores at 18 months and 36 months were also not significantly different for the prenatally cannabis-exposed group when sexes were combined. Yet, a specific effect was found for girls only at age 18 months, with higher aggression and inattention scores for the exposed girls (El Marroun et al., 2011). This association was no longer significant at the age of 36 months (El Marroun, 2010).

In sum, there is little evidence for a negative effect of prenatal cannabis exposure on cognitive development in early infancy as only the MHPCD study found lower mental development scores in cannabis-exposed 9 month-olds, which disappeared almost a year later. When infants reached the age of 3–4 years, some small subgroup analyses in OPPS and MHPCD indicated a negative association between prenatal cannabis exposure and verbal and memory functioning, although the larger and more recent Generation R study did not find evidence for such an effect. Behavior was only assessed at infancy in the Generation R study and some temporary effects of prenatal cannabis exposure seemed evident for girls' aggression and inattention levels at this stage.

3.4. Child behavior and cognitive development

As only the OPPS and MHPCD studies have analyzed data of prenatally cannabis-exposed offspring beyond infancy, it is not possible to give a more recent overview of findings of child and adolescent behavioral and cognitive development than what has been already reviewed elsewhere (*e.g.* Fried, 2002b; Huizink and Mulder, 2006). In short, more symptoms of externalizing behavior were reported in children at ages 6 (OPPS and MHPCD) and 10 years (MHPCD) after prenatal cannabis exposure. These symptoms included impulsivity, hyperactivity or delinquency, but more delinquency was only reported in the high-risk MHPCD sample (Fried et al., 1992; Goldschmidt et al., 2000; Leech et al., 1999). With regard to cognitive development, Fried (2002a,b) implied that only after certain brain areas start to develop and to differentiate between individuals to a greater extent, it becomes possible to "unmask" longer-term effects of prenatal cannabis exposure. Thus, he particularly focused on tasks on executive functioning (EF) from preadolescence onwards, and found some preliminary evidence for impaired aspects of EF after prenatal cannabis exposure. This has not been examined in the MHPCD study yet and thus conclusions cannot be drawn. Some findings do suggest more problems in abstract and visual reasoning at age 10 in MPHCD prenatally cannabis-exposed offspring (Richardson et al., 2002) and impaired visuoperceptual functioning in 9–12-year old OPPS exposed offspring (Fried and Watkinson, 2000). However, at ages 13–16, prenatal cannabis exposure was not associated with aspects of EF such as attention, flexibility, encoding or focusing (Fried et al., 2003). The Generation R study will include specific neuropsychological testing of these functions in their follow-up measures and will thus be able to replicate these analyses in the years to come (Jaddoe et al., 2012).

4. Results: preclinical studies

Preclinical studies may increase our insight into the possible mechanisms through which prenatal cannabis exposure may affect the developing fetus and thereby developmental and behavioral outcomes after birth. They permit tighter control of environmental factors, which may become critical to validate findings in humans in which a complex of associated factors may at least partly account for presumed cannabis exposure effects. For instance, in a descriptive paper, we explored the covariates of prenatal cannabis use in the Generation R study and concluded that multiple demographic, emotional and social characteristics were associated with maternal cannabis use during pregnancy, all of which may pose a risk for adverse infant outcomes and should be considered when investigating prenatal cannabis exposure effects on offspring outcomes (El Marroun et al., 2008). These correlated factors complicate interpretations, as do the small subsamples studied in previous human studies (for an overview of these methodological challenges, see Huizink and Mulder, 2006).

Almost a decade ago, Navarro et al. (1995) reviewed *in utero* exposure to cannabinoids and rodent offspring's development. They concluded that the developmental pattern of spontaneous locomotor and exploratory behavior was altered after prenatal exposure to cannabinoids. Also, several behavioral alterations were observed when animals were exposed *in utero* or in the early neonatal periods, in which brain development was still ongoing, including less behavioral response to novelty, less active sexual approach behavior, lack of habituation and reactivity to a variety of stimuli, including different illumination conditions. In addition, visual developmental milestones were delayed after prenatal exposure to cannabis (Borgen and Davis, 1973; Fried, 1976). More recently, Mereu et al. (2003) found lower memory functioning, measured by disruption in the retention of a passive avoidance task when it was repeated 24 h later, and more motor hyperactivity that was observed in rats in which a cannabinoid receptor agonist was administered in utero. Thus, preclinical work does seem to suggest that prenatal cannabis exposure may affect fetal developmental and behavioral outcomes, and some findings, particularly those relating to hampered habituation in the early neonatal period, and affected memory functioning, related to relatively short-term learning capabilities and motor hyperactivity some time later in postnatal life, are in line with findings of the OPPS and MHPCD studies as discussed above.

More recently, Trezza et al. (2012) reviewed rodent studies that examined the impact of cannabinoid exposure in the prenatal and perinatal phases. They suggested that emotional reactivity may be altered after exposure to (synthesized) THC, as a result of effects on serotonin and dopamine release. In one of their own studies, they observed an increased rate of ultrasonic vocalizations, a sign of distress and anxiety, in rat offspring that were exposed in the perinatal period, a period, which mimics human prenatal exposure (Trezza et al., 2008). As yet, only the MPHCD study observed more depressive symptoms in children at age 10 after prenatal cannabis exposure (*e.g.* Goldschmidt et al., 2004). Another review of the same group (Campolongo et al., 2009) also pointed to a cognitive effect of prenatal exposure to cannabinoids in rodents, particularly impaired working memory functioning, which was also observed in some of the subsample analyses of infant offspring in the OPPS and MHPCD studies (*e.g.* Day et al., 1994; Fried and Watkinson, 1990).

4.1. Potential mechanisms

In preclinical studies, several potential mechanisms through which prenatal cannabinoid exposure may exert its impact on the developing fetus have been investigated. It has been estimated that one-third of THC in the plasma crosses the fetoplacental barrier in rats (Hutchings et al., 1989). Cannabinoid exposure in pregnant rats can affect the expression of key genes (*e.g.* related to the neural adhesion molecule L1) for fetal neural development, possibly resulting in neurotransmitter and behavioral disturbances (Gomez et al., 2003). One study showed an alteration in the development of nigrostriatal and mesolimbic dopaminergic neurons in prenatally cannabinoid-exposed rats (Defonseca et al., 1991). Other studies also found evidence for alterations in GABAergic, glutamatergic, dopaminergic, serotoninergic and opioidergic

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systems in rodent offspring (for a review, see Jutras-Aswad et al., 2009; Trezza et al., 2008).

In the rodent and human fetal brain, cannabinoid CB1 and CB2 receptors are present from early developmental stages onwards. There is evidence that the endocannabinoid system has a central signaling role in brain development of rodents (*e.g.* Galve-Roperh et al., 2009; Harkany et al., 2007; Wang et al., 2003). Exposure to exogenous cannabinoids during a precisely timed fetal brain developmental trajectory may thus, in theory, impact the normal developmental course, and lead to adverse outcomes (Wu et al., 2011). Yet, data on whether prenatal cannabis exposure actually alters the structural or molecular human fetal brain are scarce, though some preclinical evidence can be found (for a review, see Morris et al., 2011). One study of Hurd et al. (2005) in aborted prenatally cannabis-exposed human fetuses suggested that striatal encephalin/D2 receptors and the opioid system in the amygdala were affected. Major cannabinoid receptor sites can be found in the human prefrontal cortex and in the cerebellum (Glass et al., 1997), and if their functioning is affected through prenatal cannabis exposure, it could account for some of the executive functioning effects in humans that were noted in the OPPS study (Fried, 2002a; Smith et al., 2004).

Finally, cannabinoid receptors have also been found in the human placenta (Park et al., 2003), and hence, cannabinoid exposure may be able to affect placental functioning. This may perhaps explain some of the findings in the Generation R study on fetal growth reduction and fetal blood flow restriction.

5. Novel approaches to examine prenatal exposures in humans

As was briefly mentioned in Section 1, there is some ongoing debate on whether prenatal maternal substance use, in particular smoking or drinking, is causally related to adverse offspring outcomes. For instance, genetically sensitive designs (D'Onofrio et al., 2008; Thapar et al., 2009) showed that while prenatal maternal smoking is associated with lower birth weight, it does not appear to be causally related to adverse child behavior. Rather, they suggest that a heritable factor may be transmitted through the smoking mother, a gene-by-exposure interaction may be involved, or perhaps early family environment and maternal caregiving and mother–child-interaction are less optimal. They base these suggestions on their novel approaches to studying the effects of prenatal exposures on offspring outcomes. For instance, D'Onofrio et al. (2008) applied a Case-Crossover or Quasi-Experimental design, in which children born after subsequent pregnancies of the same mother, and with varying exposure to maternal substance use during each pregnancy, are compared with each other on behavioral outcomes. In this design, there is adequate control over within-family factors, behavior of the mother, genetic factors, and so on. No studies using this design are available for testing prenatal cannabis exposure effects, while they would be very informative when it comes to disentangling the true *in utero* biological effect of cannabis exposure from the inherited or associated family risk factors.

In the Generation R study, we applied a simpler design to obtain more insight into this matter. We compared the association between paternal cannabis use and fetal developmental and infant behavioral outcomes, with the association between maternal cannabis use during her pregnancy and the same outcomes. If the association between maternal use and fetal and infant outcomes is stronger than that of paternal cannabis use, there is evidence for the effect of *in utero* exposure, and hence for a direct biological effect, rather than for inherited or associated family risk effects. Indeed, maternal cannabis use during pregnancy was more strongly associated with fetal and offspring outcomes than paternal use (El Marroun et al., 2009, 2011), indicating that a biological effect of *in utero* exposure was observed. Other novel approaches may be useful as well and have been summarized elsewhere (Huizink, 2009). For instance, timing of exposure can be examined, to test whether the harmful effects are due to exposure *in utero* only. The easiest way of examining such timing effects in humans is by contrasting women who only used substances before pregnancy, and/or only after pregnancy, with women who continued using them while pregnant. Adoption studies, in which infants who were prenatally exposed to substance use of their biological mothers, and were raised by others, also provide the opportunity to unravel prenatal from postnatal influences. Finally, a Case-Crossover design, as previously discussed, also holds promise for testing true biological effects of *in utero* exposure.

6. Recommendations for future research

Firstly, some findings of the OPPS and MHPCD studies relating to longer-term outcomes in children and adolescents need to be replicated in larger and perhaps more recent studies, in which prenatal exposure to current levels of THC can be tested more adequately. To further develop this field of research, and gain more insight into the mechanisms underlying potential harmful effects of prenatal cannabis use exposure on human fetal development and offspring outcomes, different designs may be needed than those applied thus far. In fact, we will need more detailed studies focusing on prenatal cannabis exposure in particular, and should attempt to disentangle that effect from effects of other often-associated maternal substance use (*e.g.* tobacco use or alcohol use) or less-than-optimal prenatal circumstances (*e.g.* maternal malnutrition). We could then aim to investigate potential biological or psychobiological mechanisms to understand what is really going on during fetal development after prenatal cannabis exposure. Also, if possible, genetically sensitive designs could be applied to adequately account for inherited factors that may obscure relations between (antisocial) maternal and paternal behavior associated with prenatal maternal cannabis use and their offspring behavioral outcomes. Further, more insight is needed into the interaction between fetal exposure and early neonatal environment that may perhaps lead to cumulative and long-lasting consequences. For example, little is known about effects of second hand smoking of either tobacco or cannabis in early neonatal life, and exposure through breast-feeding. It is imperative to move beyond the longitudinal and epidemiological approaches to truly come to an understanding of what prenatal cannabis exposure might do to the child for the rest of its life, taking into account the context of its genes, its family environment and other risk and resilience factors. A promising method is to experimentally test interventions, aimed at substance use reduction or abstinence that improves either the prenatal or the early postnatal environment, or a combination of both. These interventions could then be tested for their effectiveness in altering the child's subsequent behavior and development. Recent insights into epigenetic processes that are not constant, but change according to the environmental circumstances, demonstrate the flexibility and adaptability of humans to their environment. These processes could be examined to a greater extent as well, as the findings thus far are not consistent across studies and may suggest differences in individual vulnerability and resilience to prenatal cannabis exposure and associated (postnatal) risk factors.

7. Conclusion

Three prospective longitudinal cohort studies have examined human prenatal cannabis exposure and fetal and infant outcomes thus far, two of which have longer-term follow-up data available as well, as they started their studies during the late 1970s or early 1980s. Some evidence points to an adverse effect of prenatal cannabis exposure on fetal developmental outcomes, but the pattern of findings regarding birth outcomes is rather inconsistent, as are the findings on early neonatal behavior and infant cognitive development. The more recent Generation R study, with levels of THC likely higher than other studies, reported more inattention and aggression in infant girls exposed to prenatal cannabis use, although this effect may be transient as it disappeared 1.5 years later. In sum, there is little evidence that prenatal cannabis exposure affects behavioral or cognitive outcomes in the early period

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of human life. Beyond infancy, there may be subtle effects on specific cognitive or behavioral outcomes, although more replication studies are needed. With the current evidence from both animal models and human research, in spite of inconsistencies between findings, the evidence does suggest a negative impact of prenatal exposure to cannabis on fetal growth and more subtle effects in infancy and childhood, which may turn into longer-lasting consequences such as altered executive functioning in adolescence. With that in mind, cannabis use during pregnancy may be regarded as potentially harmful to the developing fetus.

Indeed, most preclinical work does indicate the importance of the endocannabinoid system in modulating and fine-tuning brain development from fetal life onwards and found evidence for behavioral and developmental adverse outcomes also early in life. Yet, little is known about the molecular framework of endocannabinoid signaling and molecular changes due to prenatal cannabinoid exposures that may underlie behavioral and cognitive developmental changes observed in offspring, and more studies will be needed to gain insight into these pathways of effects. There is much better control over confounding factors in preclinical studies, and therefore, human studies may have to turn to applying novel approaches and different designs in order to disentangle true biological or direct *in utero* exposure effects from a range of associated risk factors.

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