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Effects of Prenatal Marijuana Exposure on Neuropsychological Outcomes in Children Aged 1–11 Years: A Systematic Review

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Abstract

Background.—Normalization of medicinal and recreational marijuana use has increased the importance of fully understanding effects of marijuana use on individual- and population-level health, including prenatal exposure effects on child development. We undertook a systematic review of the literature to examine the long-term effects of prenatal marijuana exposure on neuropsychological function in children aged 1–11 years.

Methods.—Primary research publications were searched from Medline, Embase, PsychInfo, CINAHL EbscoHost, Cochrane Library, Global Health, and ERIC (1980–2018). Eligible articles documented neuropsychological outcomes in children 1–11 years who had been prenatally exposed to marijuana. Studies of exposure to multiple prenatal drugs were included if results for marijuana exposure were reported separately from other substances. Data abstraction was independently performed by two reviewers using a standardized protocol.

Results.—The eligible articles (n=21) on data from seven independent longitudinal studies, had high quality based on the Newcastle-Ottawa Scale. Some analyses found associations (p<0.05) between prenatal marijuana exposure and decreased performance on memory, impulse control, problem solving, quantitative reasoning, verbal development, and visual analysis tests; as well as increased performance on attention and global motion perception tests. Limitations included concurrent use of other substances among study participants, potential underreporting and publication biases, non-generalizable samples, and limited published results preventing direct comparison of analyses.

Conclusions.—The specific effects of prenatal marijuana exposure remain unclear and warrant further research. The larger number of neuropsychological domains that exhibit decreased versus increased psychological and behavioral functions suggest that exposure to marijuana may be harmful for brain development and function.

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Keywords

cannabis; intrauterine; attention; memory; intellect; perception

Introduction

Marijuana is the most commonly used illicit drug in the United States, with an estimated 22.2 million past-month users aged 12 years or older in 2015. Since 1996, laws allowing medicinal marijuana use have been passed in 29 states, the District of Columbia (DC), Guam and Puerto Rico, and laws allowing recreational use and sales of marijuana for adults aged 21 and over have been passed in 8 states and DC since 2012. As more states consider legalizing marijuana use among adults, it is important to fully understand the effects of marijuana use on individual- and population-level health.

The growing availability and use of marijuana is important to consider among women of reproductive age. Among US women aged 18–44 years, self-reported past-30-day use of marijuana has increased from 2002 to 2014 from 2.4% to 3.9% among pregnant and from 6.3% to 9.3% among non-pregnant women. Given the increasing trends of marijuana use among women of reproductive age including pregnant women and the changing landscape of legal and medical marijuana in the US, a more robust understanding of the consequences of prenatal marijuana exposure on children is critical to inform individual decision making and public health policy, planning, and practice.

The use of marijuana during pregnancy could have implications for fetal brain development. Marijuana is lipid soluble and able to cross the placenta and blood-brain barrier to accumulate in fetal tissues including brain tissues. It is processed in the body through the endocannabinoid system, which may be involved in brain development through neurogenesis, differentiation, migration and neural circuit wiring. Data suggest that this system exists from the earliest stages of pregnancy, presenting multiple points of vulnerability to exposure of marijuana throughout gestation, although the exact processes of this system's development are still not completely understood in humans. Additionally, there is evidence of several adverse effects on the brain and cognition, including structural damage, learning and memory deficits, and impaired motor function in adolescents and adults who are active marijuana users. Therefore, marijuana exposure has potential adverse effects on brain development in prenatally exposed children.

The strongest evidence of adverse effects of prenatal marijuana exposure comes from animal studies. These studies demonstrated that even low doses of marijuana during pregnancy can result in adverse cognitive and developmental effects in offspring.⁷ In human studies, there are variations in the effect's direction, degree and duration. Moreover, it is often difficult to discern whether the effects are due solely to marijuana or to combination of marijuana with another substance the mother may have used concurrently. Syntheses of studies that have examined prenatal marijuana effects on children's brain development, while controlling for other substances use, are limited.

Existing systematic reviews have partially examined consequences of prenatal marijuana exposure in children; however, they have certain limitations. Among infants, a 2016 review found increased irritability, tremors and startles, and decreased stability scores in exposed neonates compared to unexposed neonates. Two systematic reviews from 2007 and 2012 examining cognitive functions in children with prenatal exposures to marijuana, alcohol, cocaine, tobacco, lead and mercury found evidence for long-term damage to attention resulting from prenatal marijuana exposure, attempting to control for use of other substances; however, these studies involved adolescents. By adolescence, subjects may have been subject to other potential developmental insults, including their own substance use, and it is difficult to distinguish consequences resulting from prenatal exposure. A 2011 summary article focused mainly on the endocannabinoid system and animal studies supporting evidence of marijuana's potential to interfere with the role of this system in development and did not employ systematic review methodology. Additionally, a recent consensus study by the National Academies of Sciences, Engineering, and Medicine noted the dearth of good or fair quality systematic reviews examining associations between maternal marijuana use and offspring's cognition or academic achievement. Given the abovementioned gaps in the scientific literature, this study presents the findings of a systematic review of the impact of prenatal marijuana exposure on neuropsychological functioning in children aged 1–11 years.

Methods

Literature searches for this review were conducted by a librarian specializing in systematic reviews. An initial literature search took place in August 2014 in the following databases: Medline, Embase, PsychInfo, Cumulative Index to Nursing and Allied Health Literature (CINAHL), EbscoHost, Cochrane Library, Global Health, and Education Resources Information Center (ERIC). Supplementary searches using the same terms were conducted in April 2015, September 2016, July 2017, and August 2018. Additionally, a cited reference search was conducted to identify articles missed in the searches. Appendix A of the supplemental materials provides an example of terms used in Medline. Search terms included terms for marijuana (e.g., cannabis, hash, ganja), pregnancy (e.g., pregnancy, pregnant women, in-utero), and outcomes (e.g., cognitive disorders, intelligence, learning, executive functions, attention). All terms were entered as subject headings, text words, and Medical Subject Headings (MESH) terms per requirements of each database. Detailed overview of the search and selection strategy is available in the supplemental materials (Appendix B).

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to track literature review results and to standardize the review process. The PRISMA flow diagram is displayed in Figure 1. Inclusion and exclusion criteria (the supplemental materials, Appendix C) were designed to include published or unpublished studies documenting neuropsychological outcomes in children aged 1–11 years who had been prenatally exposed to marijuana. Studies of prenatal exposure to multiple drugs were included if results for marijuana exposure and its associations with the outcomes were reported separately from results for other substance exposures. Grey literature, including conference abstracts, dissertations, white papers, and reports retrieved by the literature searches, was considered for eligibility. Reviewers identified 1 doctoral dissertation and 4

conference abstracts that met criteria for full text review. Authors of the conference abstracts were contacted in regards to potential pending publication of their studies. Full text review and further research lead to exclusion of these articles.

The literature search and selection consisted of 2 steps: (1) title and abstract screening, and (2) full text and reference review. A primary and a secondary reviewer independently reviewed all articles retrieved from the literature search. The articles were divided between nine reviewers who were either subject matter experts in child development and/or substance abuse (authors: SRS, KS, JK, RL, IR) or public health scientists (acknowledged: KA, RP, AJ, LP) trained to perform the review by the subject matter experts. A primary and a secondary reviewer screened each reference to determine if the reference met inclusion or exclusion criteria.

All articles that were found eligible during the full text review reported data from longitudinal studies. Additionally, it was found that some articles utilized data from a single study reporting results from different analyses or from different time points of the study. The reviewers utilized the list of authors and the methodology description of each eligible article, including references to publications reporting study methodology, in order to determine if articles belonged to a particular study.

The data abstraction instrument used by the Community Preventive Services Task Force was used to abstract data from the eligible articles. As the data abstraction instrument had been originally designed to assess public health interventions, it was adapted for assessing reports from longitudinal studies. The articles selected for the review, were divided between three reviewers (SRS, RP, and AJ) for data abstraction. Two reviewers independently coded qualitative and quantitative data from each selected article.

Study quality was graded using the Newcastle-Ottawa scale designed to assess longitudinal studies. It took into account factors of representativeness, comparability, and outcome. The scale included assessment of the suitability of study design and quality of study execution to determine each study's utility to answer the research questions. At any step of the review, when discrepancies occurred, primary and secondary reviewers discussed the discrepancy to achieve consensus. Additional reviewers were consulted if needed.

Results were synthesized qualitatively. Utilizing a conservative approach, only results that were statistically significant ($p < 0.05$) in analyses adjusted for potential confounders were considered to be different from the null. Negative association was defined as association between prenatal marijuana exposure and diminished neuropsychological function (e.g., lower score for verbal development and higher score for inattention). Positive association was defined as association between prenatal marijuana exposure and enhanced neuropsychological function (e.g., higher score for attention and lower score for impulsivity). High heterogeneity of assessment tools, analytical approaches and reported effect sizes precluded a quantitative assessment of publication bias and meta-analysis.

Results

Twenty-one articles were eligible for review and analysis (Table 1); the review process determined that these articles were based on data from 7 distinct longitudinal studies. There were 4 US studies: Maternal Health Practices and Child Development Project (MHPCD; 1982–1997) in Pennsylvania, a study of prenatal cocaine exposure in Ohio (1994–2003), a study of developmental effects of prenatal substance exposure in New Jersey and Pennsylvania (1993–2004), and the National Maternal and Infant Health Survey (NMIHS; 1988–1991). The other 3 studies included were the Ottawa Prenatal Prospective Study (OPPS; 1978–1995) in Canada; the Infant Development, Environment and Lifestyle Study (IDEAL; 2001–2008) in New Zealand; and a study in Jamaica (1983–1990). All the studies were of high quality (ranked 7 to 9 out of 9 stars) based on the Newcastle-Ottawa Scale (Table 2).

Each of the 7 studies utilized a variety of instruments to assess children's neuropsychological outcomes (Table 3). Instruments varied from very specific, measuring only one function (e.g., pegboard test measuring manual dexterity) to complex multi-scale tools assessing intelligence and various cognitive domains (e.g., Stanford-Binet Intelligence Scale measuring intelligence quotient (IQ), memory, visual reasoning, quantitative reasoning, and verbal reasoning). Six studies applied one of the commonly used comprehensive intelligence or academic achievement tests administered by trained professionals who were blinded to children's prenatal history. The tests included the following: Wechsler Intelligence Scale for Children (WISC) (OPPS, IDEAL and prenatal cocaine exposure study); the Stanford-Binet Intelligence Test (MHPCD and developmental effects of prenatal substance exposure studies); the McCarthy Scales of Children's Abilities (OPPS, Jamaica study and prenatal cocaine exposure study); and the Wide Range Achievement Test (OPPS and MHPCD). One study (NMIHS) relied only on parental reports based on the Denver Developmental Scale.

Most analyses found no associations between prenatal marijuana exposure and children's outcomes or found associations that were significant in bivariate analyses but not in adjusted analyses (Table 3). Table 1 lists comparison groups and covariates that each article used for adjusted analyses.

Ottawa Prenatal Prospective Study

Eight of the articles reported on results of OPPS (Tables 1, 2 and 3). This was a longitudinal study of the effects of prenatal marijuana, cigarette, and alcohol use in offspring in a mostly low-risk, middle class population of the Ottawa area, Ontario, Canada. Recruitment took place through advertisement in media and obstetricians' offices. Analyses of the children at ages 1 and 2 years found no associations of prenatal marijuana exposure and cognitive outcomes, but found that prenatal marijuana use was associated ($p < 0.05$) with higher scores on the 1-year-old Primary Composite score of the Infant Behavior Record that assessed interests and attitudes (i.e., that children exposed in utero had higher developmental levels than children who were not exposed). At ages 3 and 4 years, McCarthy quantitative scores were lower among children with heavy prenatal marijuana exposure before adjustment for confounding, but moderate marijuana exposure correlated to superior motor performance on

the McCarthy test, even after adjustment for confounders. There were no differences on a series of cognitive tasks (e.g., memory, verbal and perceptual scores) between 5–6 year-old children with and without prenatal marijuana exposure. For children aged 6–9 years, there was no statistically significant relationship after adjustment between prenatal marijuana exposure and parental ratings of behavior problems, visual-perceptual tasks, language comprehension, or distractibility. Prenatal marijuana exposure was not associated with deficits in reading, language, or psychometrically determined intelligence in children aged 9–11 years. Prenatal marijuana exposure was negatively associated with performance in visual problem solving situations as measured by WISC Perceptual Organization Index in children aged 9–11 years. The Perceptual Organization Index assesses non-verbal reasoning and hypotheses testing drawing upon visual-perceptual skills.

Maternal Health Practices and Child Development Project

MHPCD findings were reported in 6 articles (Tables 1, 2 and 3). Participants in MHPCD were women of lower socioeconomic status, recruited from an outpatient prenatal clinic in Pittsburgh, Pennsylvania. Day et al. found no associations between prenatal marijuana exposure and the Stanford-Binet Intelligence Test performance at age 3 years. Goldschmidt et al. found heavy prenatal marijuana use statistically significantly associated with lower verbal and quantitative reasoning and with decreased short-term memory at age 6 years. Leech et al. found a statistically significant negative association between prenatal marijuana exposure and measures of impulsivity at age 6 years using a continuous performance task, but a positive association ($p < 0.05$) with attention using this same task. At age 10 years, there were associations ($p < 0.05$) between prenatal exposure to marijuana and child behavior problems and school achievements. Specifically, first and third trimester exposure to marijuana was associated with increased hyperactivity, inattention and impulsivity, and heavy second and third trimester exposure was associated with increased delinquency and externalizing behavior problems. Associations were reported between first trimester prenatal marijuana exposure and lower predicted reading and spelling scores, and between second trimester exposure and deficits in reading comprehension and underachievement, all at age 10 years ($p < 0.05$). A similar analysis by Richardson and colleagues suggested that prenatal marijuana exposure was associated with increased impulsivity in ten-year-olds based on continuous performance task.

Prenatal cocaine exposure study

Two eligible articles used data from a longitudinal prospective study of the developmental effects of prenatal cocaine exposure conducted in Ohio (Tables 1, 2 and 3). Study participants were patients of a large urban hospital who had clinical indications of illicit drug use and had no private health insurance. At age 4 years, there was no relationship between prenatal marijuana exposure and performance on the tapping inhibition test, a measure of ability to resist acting impulsively; however, heavier prenatal marijuana use was associated with lower ability to maintain sustained attention.

Developmental effects of prenatal substance exposure study

Two articles reported on results of the study of developmental effects of prenatal substance exposure with the focus on maternal cocaine use. This study recruited women from hospital-

based prenatal clinics or hospitals in Trenton, NJ, or at the Medical College of Pennsylvania Hospital in Philadelphia, PA (Tables 1, 2 and 3). Neither article found statistically significant associations between marijuana exposure and child IQ, attention, or impulsivity at ages 6, 9 and 11 years.

Jamaica study

One article examined data from a longitudinal study of children born to mothers living in rural areas of Jamaica and having low income. The women were recruited through fieldwork with the assistance of nurses from the Jamaican Ministry of Health antepartum clinics (Tables 1, 2 and 3). This study differed from the others as marijuana use was not confounded by use of other substances. In a sample of 4 and 5 year olds, Hayes and colleagues found no association between prenatal marijuana exposure and McCarthy Scales of Children's Abilities scores measuring IQ, memory, verbal development, perception, and quantitative abilities.

National Maternal and Infant Health Survey

One article by Faden and colleagues analyzed data from NMIHS. This longitudinal follow-up survey was conducted by the Centers for Disease Control and Prevention. The survey sampled participants from live births occurring in 1988, based on race and/or birthweight strata, to look at poor pregnancy outcomes. Women from the 1988 survey were re-contacted and interviewed in 1991. Faden's study differed from the others included in this review as child outcome was determined by self-report from the mothers via detailed questionnaires mailed after the birth and when the child reached age 3 years rather than by direct assessment (Tables 1, 2 and 3). Prenatal marijuana use was associated with increased fear, poorer gross motor development and shorter length of play at age 3 years, which impeded overall ability to get along with peers.

Infant Development, Environment, and Lifestyle (IDEAL) Study

IDEAL is a prospective, controlled longitudinal study of prenatal methamphetamine exposure from birth to 36 months, conducted in the US and New Zealand (Tables 1, 2 and 3). Independent and hospital-based midwives recruited mothers. Among 4.5- year-olds from the New Zealand study population, prenatal marijuana exposure was found to be associated with improved global motion perception compared to non-exposed children ($p=0.001$). Global motion perception is ability to recognize speed and direction of moving objects and is linked to cognitive skills and social competence.

Comment

Principal findings

Among the 21 reports completed from seven longitudinal studies, results varied on the association between prenatal marijuana exposure and child's neuropsychological functioning. Several analyses found statistically significant associations between prenatal marijuana exposure and both decreased and increased neuropsychological functions, while others found no significant associations. These findings indicate that the specific effects of prenatal marijuana exposure remain unclear. However, while more research is warranted to

clarify the specific effects of prenatal marijuana exposure, there were more instances of negative than positive associations among the articles, suggesting that exposure to marijuana may be harmful to neuropsychological functioning.⁷

The analyses that found positive associations suggested improved aspects of attention and perceptive abilities in exposed children aged 1 to 6 years. While the positive findings were statistically significant, it is important to note that cognitive testing on children aged 5 years, is typically not as reliable as testing performed when children are older and better able to communicate and understand the tasks presented to them.⁷ In contrast, the significant negative associations were mostly drawn from testing of children over 6 years old, and the majority of studies without statistically significant results still showed decrease in neuropsychological functions. These results suggest some potential adverse effects of prenatal marijuana exposure on attention and perceptive abilities, in addition to decreased general cognitive function, memory, impulse control, IQ, and reading comprehension especially in children aged >6 years.

Strengths of the study

While majority of data on prenatal marijuana exposure and neuropsychological outcomes in children come from only a few longitudinal studies, they are methodologically sound, with standardized outcome assessment, and high response and participant retention rates.^{7,8} Each study provides some higher level measure of the marijuana exposure: as average marijuana use per day/week (MHPCD, NMIHS, and developmental effects of prenatal exposure study) or smoking frequency (OPPS, prenatal cocaine study, and IDEAL). One study additionally provided timing of the exposure by trimester of pregnancy (MHPCD). These measures allowed distinction of a dose-response relationship of marijuana use. Heavy marijuana use had stronger associations and larger effect sizes compared to moderate and light use.⁷

Limitations of the data

However, despite these strengths, all of the studies used in this review were subject to several limitations. First, concurrent use of other substances was present among study participants, except the single Jamaican study of participants who used marijuana almost exclusively.⁷ Tobacco and alcohol were the most frequent. Prenatal nicotine exposure is a known determinant of negative health outcomes for children, and tends to be a significant confounder for marijuana research.⁷ Smoking tobacco during pregnancy can cause tissue damage affecting fetal brain development, and has been associated with negative behavioral and cognitive outcomes throughout the lifetime, including conduct disorder, attention-deficit/hyperactivity disorder, poor academic achievement, and cognitive impairment.⁷ Alcohol use may also be a source of confounding in this research, as fetal alcohol spectrum disorders (FASDs) can cause a variety of physical and cognitive impairments. Prenatal alcohol exposure is associated with deficits in memory, attention span, verbal learning, motor function, and a lower overall IQ. The prenatal cocaine exposure study and the developmental effects of prenatal substance exposure study examined concurrent use of cocaine, and the IDEAL study examined methamphetamine. Only three articles reported that self-reported drug use was confirmed by toxicology tests.⁷ While all of the articles in the review attempted to control for other substances use in their analyses, variation in

measurements of other substance exposures, such as tobacco use, may skew outcomes attributable to marijuana, and statistical controls might not account for all potential confounding of the other substances since the interactive effects of exposures to different or multiple substances are not fully understood.

A second limitation is not controlling for postnatal maternal marijuana use and thus potentially mixing effects of prenatal and postnatal exposures. Only 6 of the reviewed articles explicitly stated adjusting analyses for postnatal maternal marijuana use.^{51–55} Five more articles listed postnatal maternal marijuana use as a potential confounder that did not meet requirements for inclusion into final analytic models.^{51–55} However, in future research postnatal maternal marijuana use might be better conceptualized as a mediator rather than a confounder. Temporal and causal relationships between prenatal and postnatal maternal marijuana use prenatally and neuropsychological functioning in children are plausible for mediation conceptualization.

A third limitation is the potential for bias arising from sample selection and response. For example, the MHPCD study consisted of mostly low-income women and the OPPS study consisted of a low-risk predominantly middle class sample. Moreover, with the exception of NIMS, no samples were representative of the general US population. Additionally, the pregnancies took place when recreational use was illegal and medicinal use was illegal in the locations of data collection, thus potentially resulting in underreporting.

A fourth limitation is publication bias due to possible selective publication of results. More specifically, comparability of the test results is limited by several factors, including the fact that tests were administered selectively utilizing subscales and adaptations in different age groups, and test results were not reported in a consistent manner. Moreover, at least three studies conducted WISC; however, not all presented the results of this particular test in association with marijuana exposure. Publishing WISC measures from all or most of the analyses, would have allowed for an individual patient data (IPD) meta-analysis. Employing IPD meta-analysis would have enabled researchers to more reliably compare individual outcomes of prenatal marijuana exposure across the different studies, independent of the specific intent of the 21 published works. Finally, we were unable to conduct a formal assessment of publication bias due to heterogeneity of the data. However, as with any systematic review, issues of publication bias may have influenced the results and led to overestimates of effect. Although we allowed for the inclusion of non-peer-reviewed papers, none met the inclusion criteria. The results are thus reflective of the published literature.

Finally, there are additional concerns about the reported growing potency of marijuana and increasing variety of marijuana products and modes of administration that may potentially increase severity of dependence and have stronger effects on the brain.^{81–}

Interpretation of findings

When interpreting the findings of this review, it is important to note that neuropsychological functioning is a multidimensional construct. The children in our review were tested at a wide variety of ages. Testing at different ages changes the tools available to measure ability, as younger children will not be able to complete the same tasks that older children can. While

there are some effects of prenatal marijuana exposure on neuropsychological functions in children, one has to exercise caution interpreting these effects. On one hand, though cognitive function effects due to prenatal marijuana exposure may be small in magnitude and often are not statistically significant, they may still have a significant impact on social outcomes for an individual in later life. Thus, it is important to fully understand the risks of exposure in light of the changing culture and political climate surrounding marijuana. On the other hand, additional factors, including genetics, maternal cognitive abilities, medical conditions, such as preterm birth or nutritional deficits, and environmental influences, such as parenting, preschool attendance, or lead exposure, may influence the detectable effects of prenatal marijuana exposure.

Conclusions

This systematic review suggest possible negative associations of prenatal marijuana exposure and neuropsychological functions, such as attention, memory, and impulse control in older children. However, the available literature shows mixed results and does not allow us to confidently exclude other explanations, including confounding and publication bias. More mixed results were found for the association with prenatal marijuana exposure and language development, reading, and composite IQ scores. More complete reporting of the findings made by existing studies could facilitate data accumulation and meta-analyses, allowing for a more robust assessment of these associations. More recent data capturing the effects of marijuana in the absence of polysubstance use and changing dynamics in use could also be beneficial. While data are beginning to accumulate, educating the public about potential dangers of marijuana use during pregnancy is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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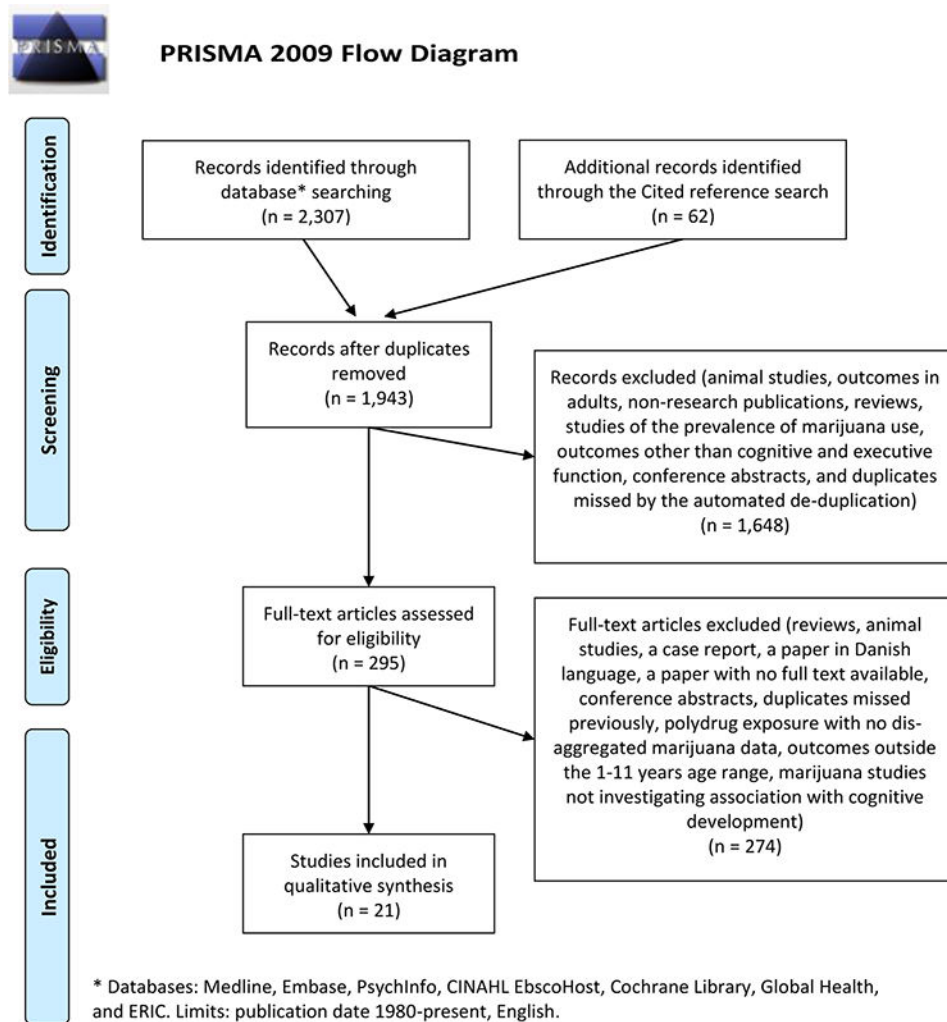
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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 1. Flow chart of literature review

Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. (<http://www.bmj.com/content/339/bmj.b2535>)

Table 1.

Methodology summary of the eligible articles.

Author, year Study	Sample sizes (at follow-up/ recruited) Age at follow-up	Analyses comparison groups by marijuana exposure	Prenatal exposure to substances other than marijuana and other covariates that analyses controlled for.	Study biases and limitations (reported by the authors and additionally identified by the reviewers)
Hayes, 1991 Jamaica study	54/59 4 and 5 years	Non-users Light users (<10 marijuana cigars or 'spliffs' per week) Moderate (11–20) Heavy (21–70)	Quality of Housing Index	(a) Results may not be generalizable as sample consisted of lower income rural women. (b) Impossible to distinguish between exposure effects of marijuana and child's environment. (c) Authors do not provide results of the analyses for 5-year-olds.
Fried, 1988 OPPS	153/217 1 year and 2 years	Joints per week (range 0–153, mean 15 in 12-month sample, and 18 in 24-month sample) Heavy use (>5 joints/week).	Cigarettes, alcohol Family income, maternal age and education, maternal caffeine, protein, and caloric intake during pregnancy, difficulties during pregnancy, maternal and paternal health history, exposure to X-rays or rubella, gestation, birth weight, parity, method of feeding, and the HOME scale.	(a) Prenatal marijuana use was confounded by nicotine and alcohol use. (b) Study results may not be generalizable.
Fried, 1990 OPPS	133/190 3 and 4 years	Infrequent/ no use Moderate (> 1 - < 6 joints/ week) Heavy (6 joints/week)	Cigarettes, alcohol Family income, mother's weight and pregnancy weight gain, age, education, nutrition, and the two drugs not of primary interest. Perinatal controls were sex, parity, gestation, birth weight, and HOME scale	(a) Volunteer subjects are a low risk sample which may represent a conservative estimate of drug effects. (b) Variance explained by maternal drug use was relatively small compared with the HOME test.
Fried, 1992 OPPS	139/190 5 and 6 years	Infrequent/no use (1 joint/ week) Moderate (>1 - <6 joints/week) Heavy (6 joints/week)	Cigarettes, alcohol Family income, mother's pregnancy weight and pregnancy weight gain, mother's age at delivery, average level of parental education, parental relationship, predominant language spoken by the child, child's gender, HOME scale, and the two drugs not of primary interest	(a) Instruments that provide a general description of cognitive abilities may not be capable of identifying nuances in neuro-behavior that may discriminate between marijuana and non-marijuana exposed children. (b) Very low risk sample which may represent a conservative estimate of drug effects. (c) Potency of marijuana preparations has increased several fold since the entrance of pregnant women in the study.
Fried, 1992 OPPS	127/190 6 years	Infrequent/no use Moderate (>1 - <6 joints/week) Heavy (6 joints/week)	Cigarettes, alcohol Family income, mother's pre-pregnancy weight, mother's caffeine intake and nutrition during pregnancy, pregnancy difficulties, mother's age at delivery, average level of parental education, parity, child's sex, predominant language spoken by child, parental relationship, the two drugs not of primary interest and the HOME scale	(a) Fetal drug exposure measurements do not distinguish timing of exposure or account for sporadic heavy use during pregnancy. (b) Measures of home environment were not statistically associated with attention-related outcomes, other postnatal factors not assessed may influence child's performance on these tasks. (c) Interaction between drug exposure and parenting and/or personality is currently being investigated in this sample.
O'Connell, 1991 OPPS	56/56 6–9 years	Non-users Users (>1 joint/week) Reported range 1.5–50 joints/week (mean=14.4, standard deviation=15)	Cigarettes, alcohol Mother's age at delivery, mother's education level, father's education level, highest occupational status of parents, family income, number of parents in the home, the number of parents working outside the home, the number of children in the family, the birth order of the subject child, the principal language of the home, the principal language of instruction in school, presence of problems in school, history of eye and/or	(a) Home environment measures are viewed as legitimate outcomes, rather than potential confounders. (b) Low risk sample which may represent a conservative estimate of drug effects. (c) Potency of marijuana preparations has increased since the entrance of pregnant women in the study.

Author, year Study	Sample sizes (at follow-up/ recruited) Age at follow-up	Analyses comparison groups by marijuana exposure	Prenatal exposure to substances other than marijuana and other covariates that analyses controlled for:	Study biases and limitations (reported by the authors and additionally identified by the reviewers)
Fried, 1997 OPPS	146/190 9–12 years	Infrequent/no use (< 1 joints/ week) Moderate (>1 - <6 joints/week) Heavy (> 6 joints/week)	Cigarettes, alcohol Family income, mother's age at delivery, mother's weight before pregnancy, mother's total pregnancy weight gain, average level of parental education, other maternal drug use, and prenatal passive smoke exposure. Postnatal variables: sex of the child, the home environment, the mother's personality, child's level of depression and anxiety, secondhand smoke exposure of child, and current maternal sociodemographic characteristics and marijuana use at the time of child's testing.	(a) Small number of subjects in the group of children exposed to moderate marijuana use limits confidence in the results.
Fried, 1998 OPPS	146/190 9–12 years	No use Infrequent/moderate (>0 - <6 joints/week) Heavy (> 6 joints/week)	Cigarettes, alcohol Family income, mother's age at delivery, mother's weight before pregnancy, average level of parental education, other maternal drug use, and prenatal passive smoke exposure. Postnatal variables: sex of the child, home environment, mother's personality, child's level of depression and anxiety, secondhand smoke exposure of the child, current maternal sociodemographic characteristics and marijuana use at the time of child's testing.	(a) Some mothers continued to use marijuana after the pregnancy (b) Data had extreme univariate outliers (z score >4); 2 marijuana and alcohol, one nicotine value.
Fried, 2000 OPPS	146/190 9–12 years	No use Infrequent/moderate (>0 - <6 joints/week) Heavy (> 6 joints/week)	Cigarettes, alcohol Average level of parental education, other maternal drug use, prenatal passive smoke exposure, and sex of the baby. Postnatal variables: home environment, current socioeconomic status, child's gender, and the environmental tobacco smoke exposure of the child.	(a) Could not categorize marijuana use into three levels due to inadequate cell size (delineated into heavy use and infrequent or moderate or no use). (b) Unclear whether deficits observed in visuosperceptual tasks are due to the perceptual demands of these tests or due to one or more non-perceptual requirements that are necessary for their successful performance.
Day, 1994 MHPCD	672/763 3 years	Average daily number of joints (ranges: 0–8.8 in first trimester, 0–6.5 in second trimester, and 0–9.4 in third trimester)	Alcohol, tobacco, amphetamines, tranquilizers, heroin, cocaine Maternal education, current work status, family income, home environment, number and distance in age between siblings, maternal levels of: depression, anxiety, hostility, self-esteem, mother's perception of how difficult the child was	(a) Only 55% of the children completed the quantitative reasoning subscale. (b) Significant differences between non-completion and age at assessment were found, but not by prenatal marijuana exposure. (c) The effects reported are not clinically significant for an individual.
Leech, 1999 MHPCD	608/763 6 years	Abstainers >0 to <0.4 joint/day 0.4 to <1 joint/day 1 joint/day	Alcohol, tobacco, amphetamines, tranquilizers, heroin, cocaine Child Characteristics: age at assessment, gender, number of hospitalizations, number of illnesses, race Environmental Characteristics: Home Screening Questionnaire, male in household, maternal work/school status Maternal Characteristics: Hostility, life events, maternal age	(a) The Continuous Performance Test varies across studies in terms of modality (visual, auditory), type of stimulus (color, letter, number, animal), and difficulty of task. It may not have been difficult enough, did not allow comparison of different types of commission errors, and did not include a measure of reaction time. (b) All subjects were assessed by Stanford-Binet test but results were not reported by marijuana exposure status.
Goldschmidt, 2008 MHPCD	648/763 6 years	Abstainers/light/ moderate (< 0 and <1 joint/day) Heavy (> 1 joint/day)	Alcohol, tobacco, amphetamines, tranquilizers, heroin, cocaine. Maternal variables: cognitive ability, age at delivery, ethnicity, current level of education, income, work status, marital status, depression, hostility, social support, number of life events	(a) The sample was predominantly of lower socio- economic status.

Author, year Study	Sample sizes (at follow-up/ recruited) Age at follow-up	Analyses comparison groups by marijuana exposure	Prenatal exposure to substances other than marijuana and other covariates that analyses controlled for:	Study biases and limitations (reported by the authors and additionally identified by the reviewers)
Goldschmidt, 2000 MHPDC	636/763 10 years	<i>First trimester users:</i> Abstainers Light/moderate (0–0.89 joints/ day) Heavy (>0.89 joints/day) <i>Second/third trimester users:</i> No use Light use (0–0.4 joints/day) Moderate/heavy (>0.4 joints/ day)	Environmental variables: total number of people in the household, drug and alcohol problems of the man in the household, current home environment Child variables: sex, nutrition, number of siblings, poor speech/vision/hearing, number of injuries, hospitalizations, and illnesses Alcohol, tobacco, amphetamines, tranquilizers, heroin, cocaine Maternal variables: Number of years of education, working/ studying outside the home, monthly family income, race/ ethnicity, presence of husband or boyfriend in the household, depression, hostility, and number of reported life events Child’s environment variables: cognitive stimulation and emotional support provided by the child’s family, level of overt aggression among family members, number of siblings, child in maternal custody, gender, age, number of illnesses, number of injuries	(a) Mothers reported 21 children (3.3%) taking medication for attention deficit/hyperactivity disorder.
Richardson, 2001 MHPDC	636/763 10 years	No use Light (0–0.4 joints/day) Moderate (>0.4–0.89 joints/ day) Heavy (>0.89 joints/day)	Alcohol, tobacco, amphetamines, tranquilizers, heroin, cocaine Maternal variables: education, monthly family income, race Child characteristics: Age, anxiety, gender, cognitive stimulation and emotional support provided by the child’s family, uncorrected vision problems	(a) Magnitude of marijuana effects was small and limited to only a few aspects of functioning. (b) Difficult to compare Continuous Performance Test measure of inattention to parental reports of inattention. (c) Possible that marijuana effects on these and additional domains may be found when the children reach 14 years of age.
Goldschmidt, 2004 MHPDC	636/763 10 years	Light/moderate (<1 joints/day) Heavy (1 joints/day).	Alcohol, tobacco, amphetamines, tranquilizers, heroin, cocaine Maternal variables: age, education, family income, presence of an adult male in the household, ethnicity, working status, depression, hostility, number of life events, and support from friends and relatives Child characteristics: home environment, child in maternal custody, number of siblings, age between oldest and youngest child, child’s gender	(a) Variables such as motivation, social skills, and parent involvement in child’s education were not taken into account. (b) Generalizability is somewhat limited as cohort is low-income and only women who had received prenatal care.
Faden, 2000 NMIHS	8285/9953 3 years	No use <1/month 1–3/month 1–2/week >3/week	Alcohol, tobacco (cocaine use collected but too rare to be analyzed) Birthweight, child’s exact age in months, child’s sex, mother’s race, mother’s level of education, and mother’s Hispanic status	(a) Parental report and self-report of marijuana use may cause reporting bias. (b) Biased estimates of effects from exposure – important covariates left out or incorrectly modeled in the regression analysis.
Noland, 2003 Prenatal cocaine exposure study	316/415 4 years	Exposed Unexposed No/light use Heavier use (>5 joints per week)	Cocaine, alcohol, tobacco Race, gender, birth mother characteristics (age, education, verbal ability, block design and picture completion, SES, psychiatric symptoms, and marital status), and current caregiver characteristics (education, verbal ability score, block design and picture completion, SES, psychiatric symptoms, marital status, and HOME interview).	(a) Prenatal marijuana exposure effect on speeded and organized responding may not be apparent until subsystem develops more fully. (b) Atypical levels of gestational stress associated with sample may limit generalizability.

Author, year Study	Sample sizes (at follow-up/ recruited) Age at follow-up	Analyses comparison groups by marijuana exposure	Prenatal exposure to substances other than marijuana and other covariates that analyses controlled for.	Study biases and limitations (reported by the authors and additionally identified by the reviewers)
Noland, 2008 Prenatal cocaine exposure study	330/415 4 years	Exposed Unexposed No/light use Heavier use (>5 joints per week)	Cocaine, alcohol, tobacco Gender, African-American ethnicity of birth mother, maternal age at birth, parity, prenatal care visit(s), maternal years of education, marital status, low socioeconomic status, biological and current caregiver mental functioning variables	(a) Prenatal substance exposure accounts for a very small percent of the variance in performance.
Bennett, 2008 Developmental effects of prenatal substance exposure study	185/231 4, 6 and 9 years	0 joints/day 0.01–0.5/day 0.51–1/day >1/day	Cocaine, alcohol, cigarettes, opiates, phenylethylamine, tranquilizers, amphetamines, barbiturates Environmental risk, maternal verbal intelligence, gender, and neonatal health problems	(a) Main focus of study was cocaine exposure. (b) Maternal marijuana use was associated with cocaine, alcohol and tobacco use. (c) Results are not generalizable as study enrolled a convenience sample of urban, predominantly African American and low socio- economic status population. (d) Other environmental factors may have affected children's IQ but were not controlled for in this study.
Carmody, 2011 Developmental effects of prenatal substance exposure study	210/321 6, 9 and 11 years	Joints/day (range 0.022–0.497)	Cocaine, alcohol, cigarettes, opiates, phenylethylamine, tranquilizers, amphetamines, barbiturates Environmental risk, medical complications, and gender	(a) Main focus of study was cocaine exposure. (b) Maternal marijuana use was associated with cocaine, alcohol and tobacco use. (c) Results are not generalizable as study enrolled a convenience sample of urban, predominantly African American and low socio- economic status population. (d) Other environmental factors may have affected children's IQ but were not controlled for in this study.
Chakraborty, 2015 IDEAL	165/170 4.5 years	<i>Frequency of use (days per week):</i> <1 1–4 5–7 <i>Amount of drug (joint per occasion):</i> Light (<1) Moderate (1–2) Heavy (>2)	Methamphetamine, nicotine, alcohol Sex, ethnicity, stereoacuity, visual acuity, and verbal IQ	(a) Results cannot be extrapolated beyond global motion perception or interpreted as marijuana having beneficial effects on fetal development. (b) Average motion coherence thresholds reported for non-drug exposed children are slightly elevated (worse) compared to previous studies of global motion perception in preschool children. (c) Study has a small sample size in which the majority of participants were poly drug users.

OPPS – Ottawa Prenatal Prospective Study, Canada

MHPCD – Maternal Health Practices and Child Development Project, USA, Pennsylvania

NMIHS – National Maternal and Infant Health Survey, USA

IDEAL – Infant Development, Environment, and Lifestyle study, New Zealand

IQ – Intelligence quotient

Table 2.

Newcastle-Ottawa scale assessment of the eligible studies.

# (by study/year of publication)	Star categories	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Study or location		Jamaica	OPIS ^a	AMPC ^b	MMHS	MMHS	MMHS	MMHS	MMHS	MMHS	MMHS	MMHS	MMHS	MMHS	MMHS	MMHS	MMHS	MMHS	MMHS	MMHS	MMHS	MMHS		
Author, year		Hayes, 1991	Fried, 1988	Fried, 1990	Fried, 1990	Fried, 1992	Fried, 1992	O'Connell, 1991	Fried, 1997	Fried, 1998	Fried, 2000	Day, 1994	Leach, 1999	Goldschmidt, 2008	Goldschmidt, 2000	Richardson, 2001	Goldschmidt, 2004	Fuden, 2000	Noland, 2003	Noland, 2005	Bennett, 2008	Cumody, 2011	Chakraborty, 2015	
1) Representativeness of the exposed cohort																								
a) Truly representative of the average demographics in the community	*																							
b) Somewhat representative of the average demographics in the community	*	*									*							*					*	
c) Selected group of users, e.g. nurses, volunteers																								
d) No description of the derivation of the cohort																								
2) Selection of the non-exposed cohort																								
a) Drawn from the same community as the exposed cohort	*	*									*										*		*	
b) Drawn from a different source																								
c) No description of the derivation of the non-exposed cohort																								
3) Ascertainment of exposure																								
a) Secure record (e.g. surgical records)	*																							
b) Structured interview	*										*										*		*	
c) Written self-report																								
d) No description																								
4) Demonstration that outcome of interest was not present at start of study^c																								
a) Yes	*	*									*										*		*	
b) No																								
Comparability																								
1) Comparability of cohorts on the basis of the design or analysis																								
a) Study controls for exposure to tobacco...	*	*									*										*		*	
b) Study controls for any additional factor	*	*									*										*		*	
Outcome																								
1) Assessment of outcome																								
a) Independent blind assessment	*	*									*										*		*	
b) Record linkage	*																							
c) Self-report																								
d) No description																								

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# (by study/year of publication)	Star categories	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Study or location		Jamaica	OPPS																				IDEAL
2) Was follow-up long enough for outcomes to occur?																							
a) Yes	*	*	*	(1-2)	*	(3-4)	*	(5-6)	*	(6)	*	(6-9)	*	(0-12)	*	(0-12)	*	(6)	*	(6)	*	(10)	8 (4.5)
b) No																							65%
3) Adequacy of follow up of cohorts																							
a) Complete follow up - all subjects recruited for	*	*																					
b) Subjects lost to follow up unlikely to introduce bias - small number lost - >80% follow ups or description provided of those lost	*	*	(92%)																				8 (97%)
c) Follow up rate < 80% and no description of those lost			71%	70%	73%	67%	77%	77%	77%	77%													
d) No statement																							
Total score:		8.5	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7

* Article has met requirement to be awarded a star (1 score point)

0- Article's standing in an assessment category, when no star is awarded

a- When all articles belonging to a single study received same score, the cells were combined to save space.

b- Study has met the requirement to be awarded the star, however, this information was not in the reviewed article, and was found in a different publication that did not meet eligibility criteria for this review (.5 score point)

c- As outcome of interest is affected cognitive development, all articles were awarded star for this question since all studies had enrolled participants at birth.

OPPS – Ottawa Prenatal Prospective Study, Canada

MHPCD – Maternal Health Practices and Child Development Project, Pennsylvania, USA

NMHS – National Maternal and Infant Health Survey, USA

OH – Prenatal cocaine exposure study, Ohio, USA

NJ/PA – Developmental effects of prenatal substance exposure study, New Jersey/Pennsylvania, USA

IDEAL - Infant Development, Environment, and Lifestyle study, New Zealand

Table 3.

Scope of diagnostic tests and outcomes in the eligible studies.

Diagnostic instrument	Outcomes measured	Reported associations with prenatal marijuana exposure ^a	Age at assessment	Article (Study, first author, year)
Bayley Scale of Infant Development	Mental Development Index: sensory/perceptual abilities, acquisition of object constancy, memory, learning, problem solving, vocalization and beginning of verbal communication Psychomotor Development Index: degree of body control, large muscle coordination, finer manipulatory skills of the hands and fingers, dynamic movement, postural imitation, and the ability to recognize objects by sense of touch (stereognosis)	No significant associations	1 year and 2 years	OPPS, Fried, 1988
Infant Behavior Record	Primary Cognition Composite Score: object orientation, goal directedness, attention span, reactivity, and vocalization Extraversion Score: social orientation to the examiner, cooperativeness, and general emotional tone Visual and auditory sensory systems	Positive association No results reported. No associations	1 year 2 years 1 year and 2 years	OPPS, Fried, 1988 OPPS, Fried, 1988 OPPS, Fried, 1988
Reynell Developmental Language Scale	Comprehension Expression	Negative association No associations	2 years 2, 3, and 4 years	OPPS, Fried, 1988 OPPS, Fried, 1988; 1990
Denver Developmental Scale	Gross motor development Adaptive functioning, language, and fine motor development	Negative association No associations	3 years	NMHS, Faden, 2000
McCarthy Scales of Children's Abilities	General Cognitive Index (memory, verbal development, perception, and quantitative abilities)	No associations Negative association No associations	3 years 4 years 4, 5 and 6 years	OPPS, Fried, 1990 OPPS, Fried, 1990 Jamaica study, Hayes, 1991; OPPS, Fried, 1992
	Motor performance score	Positive association in moderately exposed children compared to unexposed and heavily exposed No associations	3 years 4, 5 and 6 years	OPPS, Fried, 1990 OPPS, Fried, 1990; 1992; Jamaica study, Hayes, 1991
	Memory score	No associations Negative association No associations	3 years 4 years 4, 5 and 6 years	OPPS, Fried, 1990 OPPS, Fried, 1990 Jamaica study, Hayes, 1991; OPPS, Fried, 1992

Diagnostic instrument	Outcomes measured	Reported associations with prenatal marijuana exposure ^a	Age at assessment	Article (Study, first author, year)	
McCarthy Scales of Children's Abilities subset adapted for use with children 3 to 12 years of age, truncated.	Verbal score	No associations	3 years	OPPS, Fried, 1990	
		Negative association	4 years	OPPS, Fried, 1990	
	Quantitative score	No associations	4, 5 and 6 years	Jamaica study, Hayes, 1991; OPPS, Fried, 1992	
		Negative association	3 years	OPPS, Fried, 1990	
	Perceptual score	No associations	4 years	OPPS, Fried, 1990	
		No associations	4, 5 and 6 years	Jamaica study, Hayes, 1991; OPPS, Fried, 1992	
		No associations	3 years	OPPS, Fried, 1990	
		Negative association	4 years	OPPS, Fried, 1990	
	Stanford-Binet Intelligence Scale, 4 Ed.	Category fluency (language development)	No associations	4 years	Prenatal cocaine exposure study, Noland, 2003
			Negative association	3 years	MHPCD, Day, 1994
Composite score (IQ)		No associations	4, 6 and 9 years	Developmental effects of prenatal substance exposure study, Bennett, 2008	
		Not reported	6 years	MHPCD, Leech, 1999	
Short-term memory		Negative association	6 years	MHPCD, Goldschmidt, 2008	
		Negative association	3 years	MHPCD, Day, 1994	
		No associations	4, 6 and 9 years	Developmental effects of prenatal substance exposure study, Bennett, 2008	
		Negative association	6 years	MHPCD, Goldschmidt, 2008	
Verbal reasoning		Negative association	3 years	MHPCD, Day, 1994	
		No associations	4, 6 and 9 years	Developmental effects of prenatal substance exposure study, Bennett, 2008	
	Negative association	6 years	MHPCD, Goldschmidt, 2008		
	No associations	3 years	MHPCD, Day, 1994		
Quantitative reasoning	No associations	4, 6 and 9 years	Developmental effects of prenatal substance exposure study, Bennett, 2008		
	Negative association	3 years	MHPCD, Day, 1994		

Diagnostic instrument	Outcomes measured	Reported associations with prenatal marijuana exposure ^d	Age at assessment	Article (Study, first author, year)
	Abstract/visual reasoning	Negative association	6 years	MHPCD, Goldschmidt, 2008
		Negative association	3 years	MHPCD, Day, 1994
		No associations	4, 6 and 9 years	Developmental effects of prenatal substance exposure study, Bennett, 2008
Wechsler Preschool and Primary Scale of Intelligence, III	Verbal IQ, attention	No associations	6 years	MHPCD, Goldschmidt, 2008
		Not reported	4 years	Prenatal cocaine exposure study, Noland, 2003; 2005
		No associations	4.5 years	IDEAL, Chakraborty, 2015
Finger sequencing task adapted by Welsh for use with children.	Motor planning	No associations	4 years	Prenatal cocaine exposure study, Noland, 2003
Pegboard test	Manual dexterity and bimanual coordination	No associations	4 years	OPPS, Fried, 1990
Picture deletion task for preschoolers-modified (Corkum)	Attention	Non-significant negative association	4 years	Prenatal cocaine exposure study, Noland, 2005
Tactile Form Recognition Task	Stereognosis	No associations	4 years	OPPS, Fried, 1990
Tapping Inhibition (test of frontal lobe functioning (Luria) adapted by Diamond and Taylor for use with children 3.5 through 7 years of age)	Inhibitory control (Ability to override their natural, habitual, or dominant behavioral response to a stimulus in order to implement more adaptive goal-oriented behaviors)	No associations	4 years	Prenatal cocaine exposure study, Noland, 2003
Peabody Picture Vocabulary Test	Vocabulary	Negative association	4 years	OPPS, Fried, 1990
		No associations	5 years, 6 years and 9–12 years	OPPS, Fried, 1992; 1997
Random Dot Kinematograms	Global motor perception (higher-level processing in visual cortex)	Positive association in children who were not prenatally exposed to alcohol.	4.5 years	IDEAL, Chakraborty, 2015
Conners Parent Questionnaire	Impulsivity hyperactivity	Non-significant negative association	6 years	OPPS, Fried, 1992
		No associations	6–9 years	OPPS, O'Connell, 1991
	Hyperactivity index, learning problems, and psychosomatic problems	No associations	6–9 years	OPPS, O'Connell, 1991
	Anxiety, conduct problems	Non-significant negative association	6–9 years	OPPS, O'Connell, 1991
Gordon Diagnostic System	Sustained attention and self-control	Negative association	6 years	OPPS, Fried, 1992
	Impulsivity	Negative association	9–12 years	OPPS, Fried, 1998
Continuous Performance Task	Errors of commission (impulsivity)	Not reported	4 years	Prenatal cocaine exposure study, Noland, 2005

Diagnostic instrument	Outcomes measured	Reported associations with prenatal marijuana exposure ^d	Age at assessment	Article (Study, first author, year)
	Errors of omission (inattentiveness)	Negative association	6 years and 10 years	MHPCD, Leech, 1999; Richardson, 2001
The Sentence Memory Test	Immediate auditory memory and auditory attention for sentences	Not reported	4 years	Prenatal cocaine exposure study, Noland, 2005
The Target Test	Visual-spatial memory	Positive association	6 years	MHPCD, Leech, 1999
The Yale Child Study Center Attention Task	Attention and inhibitory control	No associations	6 years	OPPS, Fried, 1992
	Visual-spatial memory	No associations	6 years	OPPS, Fried, 1992
	Attention and inhibitory control	No associations	6, 9, and 11 years	Developmental effects of prenatal substance exposure study, Carmody, 2011
Test of Visual-Perceptual Skills	Perceptual Quotient, Visual Discrimination, Visual Sequential Memory	Non-significant negative association	6-9 years	OPPS, O'Connell, 1991
	Visual Closure, Visual Figure Ground, Visual Form Constancy, Visual Memory, and Visual Spatial Relations	No associations	9-12 years	OPPS, Fried, 2000
Trail Making Test	Visual scanning, visuospatial sequencing, attention, mental flexibility, and motor function	No associations	6-9 and 9-12 years	OPPS, O'Connell, 1991; Fried, 2000
	Reading, arithmetic, spelling	Non-significant negative association	6-9 years	OPPS, O'Connell, 1991
Wide Range Achievement Test-revised	Reading, arithmetic, spelling	No associations	9-12 years	OPPS, Fried, 2000
	Reading	Negative association	6-9 years	OPPS, O'Connell, 1991
	Reading	Negative association	10 years	MHPCD, Goldschmidt, 2004
Knox Cube Test	Visual attention, visual memory and visual sequencing	No associations	6-9 and 9-12 years	OPPS, O'Connell, 1991; Fried, 1997
	Visual attention, visual memory and visual sequencing	No associations	6-9 and 9-12 years	OPPS, O'Connell, 1991; Fried, 2000
Woodcock Reading Mastery Test	Passage comprehension	No associations	6-9 and 9-12 years	OPPS, O'Connell, 1991; Fried, 1997
Beery Developmental Test of Visual Motor Integration	Visual-motor integration (copy geometric forms into a notepad)	No significant associations	6-9 years	OPPS, O'Connell, 1991
	Visual-motor integration (copy geometric forms into a notepad)	No associations	9-12 years	OPPS, Fried, 2000
Draw a man	Intelligence (score is based on detail, proportion and coordination)	No significant associations	6-9 years	OPPS, O'Connell, 1991
Finger tapping	Motor control, speed and lateral coordination	No significant associations	6-9 years	OPPS, O'Connell, 1991
Stroop Interference	Tests the ability to sort and selectively react to information: e.g. word 'red' is printed in green ink. The child must say loudly the color of the text and not the word.	No significant associations	6-9 years	OPPS, O'Connell, 1991
	Tests the ability to sort and selectively react to information: e.g. word 'red' is printed in green ink. The child must say loudly the color of the text and not the word.	Non-significant negative association	6-9 years	OPPS, O'Connell, 1991

Diagnostic instrument	Outcomes measured	Reported associations with prenatal marijuana exposure ^d	Age at assessment	Article (Study, first author, year)
Test of Language Development (Primary syntax quotient score)	Ability to generate acceptable sentences	Non-significant negative association	6–9 years	OPPS, O'Connell, 1991
Auditory Working Memory	Working memory	Non-significant negative association	9–12 years	OPPS, Fried, 1998
Category Test	Problem-solving capacity	Negative association	9–12 years	OPPS, Fried, 1998
Fluency Test	Verbal fluency (number of words starting with 'C' and 'P' produced in 60 sec)	No associations	9–12 years	OPPS, Fried, 1997; 1998
Oral Cloze Task	Ability to understand the basic grammatical structure of English based on auditory process	No associations	9–12 years	OPPS, Fried, 1997
Pseudoword Task	Reading and decoding abilities	Non-significant negative association in children with moderate exposure compared to children with no or heavy exposure	9–12 years	OPPS, Fried, 1997
Seashore Rhythm Test	Rhythm discrimination	No associations	9–12 years	OPPS, Fried, 1997
Tactile Performance Task	Motor abilities and motor memory (blindfolded, place wooden blocks into properly shaped holes)	No associations	9–12 years	OPPS, Fried, 1998
Wechsler Intelligence Scale for Children, 3rd ed.	Full scale IQ	No associations	6–9 and 9–12 years	OPPS, O'Connell, 1991; Fried, 1997; 1998; 2000
	Information	No associations	9–12 years	OPPS, Fried, 1997
	Verbal IQ, Verbal Comprehension Index	Non-significant negative association	9–12 years	OPPS, Fried, 1998
	Similarities, Vocabulary	No associations	6–9 and 9–12 years	OPPS, O'Connell, 1991; Fried, 1997; 1998
	Performance IQ	No associations	9–12 years	OPPS, Fried, 1997; 1998
	Arithmetic, Processing Speed Index	No associations	6–9 and 9–12 years	OPPS, O'Connell, 1991; Fried, 1998
	Freedom from Distractibility Index	No associations	9–12 years	OPPS, Fried, 1998
	Coding (discrimination and memory of visual symbols); Symbol Search (visual scanning), and Digit Span (memory)	No associations	6–9 and 9–12 years	OPPS, O'Connell, 1991; Fried, 1998; 2000
	Comprehension	Negative association	9–12 years	OPPS, Fried, 1998
	Mazes (rudimentary planning)	Negative association	9–12 years	OPPS, Fried, 1998
		No associations	9–12 years	OPPS, Fried, 2000
	Perceptual Organization Index (a summary index of picture completion, picture	No association	6–9 and 9–12 years	OPPS, O'Connell, 1991; Fried, 1998

Diagnostic instrument	Outcomes measured	Reported associations with prenatal marijuana exposure ^a	Age at assessment	Article (Study, first author, year)
	arrangement, block design, and object assembly)	Negative association	9–12 years	OPPS, Fried, 2000
	Object Assembly	Negative association	9–12 years	OPPS, Fried, 1998; 2000
	Block Design	Negative association	9–12 years	OPPS, Fried, 1998; 2000
	Picture Arrangement	No associations	9–12 years	OPPS, Fried, 1998; 2000
	Picture Completion	No associations	9–12 years	OPPS, Fried, 1998; 2000
Child Behavior Checklist	Attention problems	No associations	10 years	MHPCD, Goldschmidt, 2000
Severe discrepancy between ability (Stanford-Binet Intelligence Scale, 4ed.)	Underachieving	Negative association	10 years	MHPCD, Goldschmidt, 2004
Swanson, Noland, and Pelham Assessment	Impulsivity, hyperactivity, inattention symptoms	Negative association	10 years	MHPCD, Goldschmidt, 2000
Teacher's Report Form	Attention problems	No associations	10 years	MHPCD, Goldschmidt, 2000
Teacher's assessment of the child in language arts, history, math, and science.	Educational performance	Negative association	10 years	MHPCD, Goldschmidt, 2004
Peabody Individual Achievement Test-revised	Reading comprehension	Negative association	10 years	MHPCD, Goldschmidt, 2004
Wide Range Assessment of Memory and Learning	Design memory, screening index	Negative association	10 years	MHPCD, Richardson, 2001
	Story memory, verbal learning	No association	10 years	MHPCD, Richardson, 2001

^a**Negative** associations were defined as statistically significant association in analyses adjusted for potential confounders between prenatal marijuana exposure and diminished neuropsychological function, e.g. lower scores on reading comprehension or memory; or higher scores on errors, impulsivity, inattention, or underachievement ($p < 0.05$), regardless of the trimester of exposure. **Positive** associations were defined as statistically significant associations in adjusted analyses between prenatal marijuana exposure and enhanced neuropsychological function, e.g. higher scores on reading comprehension or memory; or lower scores on errors, impulsivity, inattention, or underachievement ($p < 0.05$), regardless of the trimester of exposure. **Non-significant negative and positive associations** were defined as statistically significant negative or positive associations found in bivariate analyses but not in adjusted analyses ($p < 0.05$). **No association** the analyses did not find associations between prenatal marijuana exposure and neuropsychological functions in bivariate and adjusted analyses.