Received: 24 May 2018 | Revised: 1 August 2018 | Accepted: 17 August 2018

DOI: 10.1111/ppe.12505

REVIEW ARTICLE

WILEY Paediatric and Perinatal Epidemiology

Effects of prenatal marijuana exposure on neuropsychological outcomes in children aged 1-11 years: A systematic review

Saida R. Sharapova[1] | Elyse Phillips[1] | Karen Sirocco[2] | Jennifer W. Kaminski[3] | Rebecca T. Leeb[3] | Italia Rolle[1]

[1]Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia

[2]Division of Epidemiology, Services and Prevention, Prevention Research Branch, National Institute on Drug Abuse, National Institutes of Health, Bethesda, Maryland

[3]Division of Human Development and Disability, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia

Correspondence
Saida R. Sharapova, Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA.
Email: ssharapova@cdc.gov

Abstract

Background: Normalisation 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 standardised 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 under-reporting and publication biases, non-generalisable 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 behavioural functions suggests that exposure to marijuana may be harmful for brain development and function.

KEYWORDS

attention, cannabis, intellect, intrauterine, memory, perception

1 | 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.[1] 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.[2,3] As more states consider legalising marijuana use among adults, it is important to fully understand the effects of marijuana use on individual- and population-level health.[3]

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.[4] 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 United States, 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.[5,6]

The use of marijuana during pregnancy could have implications for foetal brain development.[7-12] Marijuana is lipid soluble and able to cross the placenta and blood-brain barrier to accumulate in foetal tissues including brain tissues.[13,14] 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.[15,16] 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.[15,17] 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.[18-25] Therefore, marijuana exposure has potential adverse effects on brain development in prenatally exposed children.[26]

The strongest evidence of adverse effects of prenatal marijuana exposure comes from animal studies.[7-9] These studies demonstrated that even low doses of marijuana during pregnancy can result in adverse cognitive and developmental effects in offspring.[7-9] In human studies, there are variations in the effect's direction, degree and duration.[11,12] Moreover, it is often difficult to discern whether the effects are due solely to marijuana or to a combination of marijuana with another substance the mother may have used concurrently.[27-29] Syntheses of studies that have examined prenatal marijuana effects on children's brain development, while controlling for other substances use, are limited.[6]

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.[30] 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.[31,32] By adolescence, subjects may have been affected by other potential developmental insults, including their own substance use, and it is difficult to distinguish consequences resulting from prenatal exposure.[33] 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.[15] 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.[34] 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.

2 | METHODS

Literature searches for this review were conducted by a librarian specialising 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.[35] Appendix S1 of the supplemental materials provides an example of terms used in Medline. Search terms included terms for marijuana (eg, cannabis, hash, ganja), pregnancy (eg, pregnancy, pregnant women, in utero) and outcomes (eg, 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 S1).

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to track literature review results and to standardise the review process.[36] The PRISMA flow diagram is displayed in Figure 1. Inclusion and exclusion criteria (the supplemental materials, Appendix S1) 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

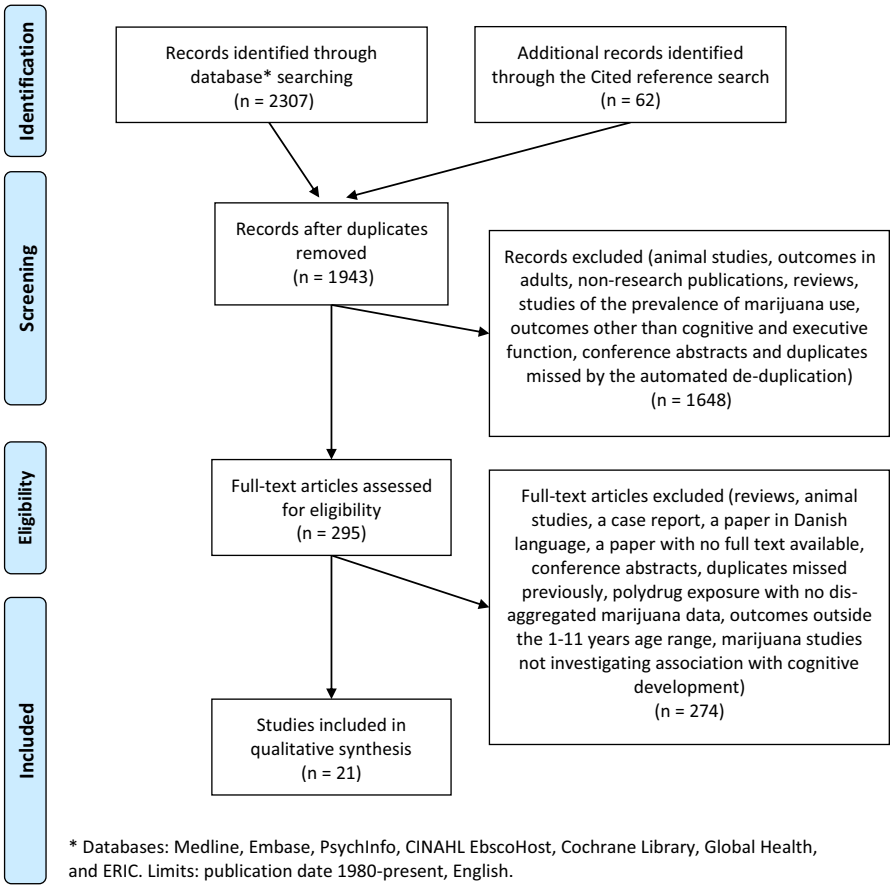

FIGURE 1 Flow chart of literature review
Note: Adapted from Moher et al[36] (http://www.bmj.com/content/339/bmj.b2535)

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 regard 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 two steps: (a) title and abstract screening, and (b) 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 whether 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 utilised data from a single study reporting results from different analyses or from different time points of the study. The reviewers utilised the list of authors and the methodology description of each eligible article, including references to publications reporting study methodology, in order to determine whether articles belonged to a particular study.

The data abstraction instrument developed by the Community Preventive Services Task Force was used to abstract data from the eligible articles.[37] 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 among 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.[38] 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 synthesised qualitatively. Utilising 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 (eg, lower score for verbal development and higher score for inattention). Positive association

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 y	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 generalisable 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-y-olds
Fried, 1988 OPPS	153/217 1 and 2 y	Joints per week (range 0-153, mean 15 in 12-mo sample, and 18 in 24-mo sample) Heavy use (>5 joints/wk)	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, birthweight, 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 generalisable
Fried, 1990 OPPS	133/190 3 and 4 y	Infrequent/no use Moderate (>1 - <6 joints/wk) Heavy (≥6 joints/wk)	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, birthweight 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 y	Infrequent/no use (≤1 joint/wk) Moderate (>1 - <6 joints/wk) Heavy (≥6 joints/wk)	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-behaviour 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 folds since the entrance of pregnant women in the study
Fried, 1992 OPPS	127/190 6 y	Infrequent/no use Moderate (>1 - <6 joints/wk) Heavy (≥6 joints/wk)	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) Foetal 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, and 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

(Continues)

TABLE 1 (Continued)

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)
O'Connell, 1991 OPPS	56/56 6-9 y	Non-users Users (>1 joint/wk) Reported range 1.5-50 joints/wk (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 ear infections, the need for visual correction, the presence of special conditions at the time of testing and HOME scale	(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
Fried, 1997 OPPS	146/190 9-12 y	Infrequent/no use (≤1 joints/wk) Moderate (>1 - <6 joints/wk) Heavy (≥6 joints/wk)	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, second-hand 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 y	No use Infrequent/moderate (>0 - <6 joints/wk) Heavy (≥6 joints/wk)	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, second-hand 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 y	No use Infrequent/moderate (>0 - <6 joints/wk) Heavy (≥6 joints/wk)	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 socio-economic status, child's gender and the environmental tobacco smoke exposure of the child	(a) Could not categorise 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 visuoperceptual 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

(Continues)

TABLE 1 (Continued)

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)
Day, 1994 MHPCD	672/763 3 y	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, tranquilisers, 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 y	Abstainers >0 to <0.4 joint/d 0.4 to <1 joint/d ≥1 joint/d	Alcohol, tobacco, amphetamines, tranquilisers, heroin, cocaine Child Characteristics: age at assessment, gender, number of hospitalisations, 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 (colour, 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 y	Abstainers/light/ moderate (≥0 and <1 joint/d) Heavy (≥1 joint/d)	Alcohol, tobacco, amphetamines, tranquilisers, 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 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, hospitalisations and illnesses	(a) The sample was predominantly of lower socio-economic status
Goldschmidt, 2000 MHPCD	636/763 10 y	*First trimester users:* Abstainers Light/moderate (0-0.89 joints/d) Heavy (>0.89 joints/d) *Second-/third-trimester users:* No use Light use (0-0.4 joints/d) Moderate/heavy (>0.4 joints/d)	Alcohol, tobacco, amphetamines, tranquilisers, 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 attention-deficit/ hyperactivity disorder

(Continues)

TABLE 1 (Continued)

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)
Richardson, 2001 MHPCD	636/763 10 y	No use Light (0-0.4 joints/d) Moderate (>0.4-0.89 joints/d) Heavy (>0.89 joints/d)	Alcohol, tobacco, amphetamines, tranquilisers, 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 y of age
Goldschmidt, 2004 MHPCD	636/763 10 y	Light/moderate (<1 joints/d) Heavy (≥1 joints/d)	Alcohol, tobacco, amphetamines, tranquilisers, 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) Generalisability is somewhat limited as cohort is low income and only women who had received prenatal care
Faden, 2000 NMIHS	8285/9953 3 y	No use <1/mo 1/mo 2-3/mo 1-2/wk >3/wk	Alcohol, tobacco (cocaine use collected but too rare to be analysed) 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 modelled in the regression analysis.
Noland, 2003 Prenatal cocaine exposure study	316/415 4 y	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, block design and picture completion, SES, psychiatric symptoms, marital status and HOME interview)	(a) Prenatal marijuana exposure effect on speeded and organised responding may not be apparent until subsystem develops more fully. (b) Atypical levels of gestational stress associated with sample may limit generalisability
Noland, 2005 Prenatal cocaine exposure study	330/415 4 y	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 socio-economic status, biological and current caregiver mental functioning variables	(a) Prenatal substance exposure accounts for a very small per cent of the variance in performance

(Continues)

TABLE 1 (Continued)

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)
Bennett, 2008 Developmental effects of prenatal substance exposure study	185/231 4, 6 and 9 y	0 joints/d 0.01-0.5/d 0.51-1/d >1/d	Cocaine, alcohol, cigarettes, opiates, phencyclidine, tranquilisers, 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 generalisable 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 y	Joints/d (range 0.022-0.497)	Cocaine, alcohol, cigarettes, opiates, phencyclidine, tranquilisers, 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 generalisable 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 y	Frequency of use (days per week): <1 1-4 5-7 Amount of drug (joint per occasion): 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 foetal 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 polydrug users

IDEAL, Infant Development, Environment and Lifestyle study, New Zealand; IQ, Intelligence quotient; MHPCD, Maternal Health Practices and Child Development Project, USA, Pennsylvania; NMIHS, National Maternal and Infant Health Survey, USA; OPPS, Ottawa Prenatal Prospective Study, Canada.

was defined as association between prenatal marijuana exposure and enhanced neuropsychological function (eg, 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.

3 | 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 7-9 out of nine stars) based on the Newcastle-Ottawa Scale (Table 2).[38]

Each of the seven studies utilised a variety of instruments to assess children's neuropsychological outcomes (Table 3). Instruments varied from very specific, measuring only one function (eg, pegboard test measuring manual dexterity) to complex multiscale tools assessing intelligence and various cognitive domains (eg, 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);[39] the Stanford-Binet Intelligence Test (MHPCD and developmental effects of prenatal substance exposure studies);[40] the McCarthy Scales of Children's Abilities (OPPS, Jamaica study and prenatal cocaine exposure study);[41] and the Wide Range Achievement Test (OPPS and MHPCD).[42] One study (NMIHS) relied only on parental reports based on the Denver Developmental Scale.[43]

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.

3.1 | Ottawa prenatal prospective study

Eight of the articles reported on results of OPPS (Tables 1-3). 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.[44-51] Recruitment took place through advertisement in media and obstetricians' offices. Analyses of the children at ages 1 and 2 years found no associations between 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 (ie, that children exposed in utero had higher developmental levels than children who were not exposed).[44] 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 with superior motor performance on the McCarthy test, even after adjustment for confounders.[45] There were no differences on a series of cognitive tasks (eg, memory, verbal and perceptual scores) between 5- and 6-year-old children with and without prenatal marijuana exposure.[46,47] For children aged 6-9 years, there was no statistically significant relationship after adjustment between prenatal marijuana exposure and parental ratings of behaviour problems, visual-perceptual tasks, language comprehension or distractibility.[48] Prenatal marijuana exposure was not associated with deficits in reading, language or psychometrically determined intelligence in children aged 9-11 years.[49,50] 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.[51] The Perceptual Organization Index assesses non-verbal reasoning and hypotheses testing drawing upon visual-perceptual skills.

3.2 | Maternal health practices and child development project

MHPCD findings were reported in six articles (Tables 1-3).[52-57] Participants in MHPCD were women of lower socio-economic status, recruited from an outpatient prenatal clinic in Pittsburgh, Pennsylvania. Day et al[52] found no associations between prenatal marijuana exposure and the Stanford-Binet Intelligence Test performance at age 3 years. Goldschmidt et al[53] 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[54] 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 behaviour 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 externalising behaviour problems.[55] Associations were reported between first-trimester prenatal marijuana exposure and lower predicted reading and spelling scores, and between second trimester exposure

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
Study or location		Jamaica	OPPS[a]							
Author, year		Hayes, 1991	Fried, 1988	Fried, 1990	Fried, 1992	Fried, 1992	O'Connell, 1991	Fried, 1997	Fried, 1998	Fried, 2000
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	*	*(Rural lower income community)								
c) Selected group of users, for example nurses, volunteers			Volunteers responding to advertisement of the study, low-risk sample							
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 (eg, surgical records)	*	*[b]								
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										
2) Was follow-up long enough for outcomes to occur?										
a) Yes	*	* (5y)	* (1-2y)	* (3-4y)	* (5-6y)	* (6y)	* (6-9y)	* (9-12y)	* (9-12y)	* (9-12y)
b) No										
3) Adequacy of follow-up of cohorts										
a) Complete follow-up—all subjects accounted for	*						*			
b) Subjects lost to follow-up unlikely to introduce bias—small number lost - >80% follow-up, or description provided of those lost (%)	*	* (92)								
c) Follow-up rate <80% and no description of those lost (%)			71	70	73	67		77	77	77
d) No statement										
Total score:		8.5	7	7	7	7	8	7	7	7

IDEAL, Infant Development, Environment and Lifestyle study, New Zealand; MHPCD, Maternal Health Practices and Child Development Project, Pennsylvania, USA; NJ/PA, Developmental effects of prenatal substance exposure study, New Jersey/Pennsylvania, USA; NMIHS, National Maternal and Infant Health Survey, USA; OH, Prenatal cocaine exposure study, Ohio, USA; OPPS, Ottawa Prenatal Prospective Study, Canada.
0—Article's standing in an assessment category, when no star is awarded.
*Article has met requirement to be awarded a star (1 score point).
[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.

10	11	12	13	14	15	16	17	18	19	20	21
MHPCD[a]						NMIHS	OH[a]		NJ/PA[a]		IDEAL
Day, 1994	Leech, 1999	Goldschmidt, 2008	Goldschmidt, 2000	Richardson, 2001	Goldschmidt, 2004	Faden, 2000	Noland, 2003	Noland, 2005	Bennett, 2008	Carmody, 2011	Chakraborty, 2015
						*					
*(Lower income population)							*(Lower income)				*(Lower income and education)
									Volunteers		
*						*	*		*		*
							*		*		*
*						*					
*						*	*		*		*
*						*	*		*		*
*						*	*		*		*
*						*	*		*		*
* (3y)	* (6y)	* (6y)	* (10y)	* (10y)	* (10y)	* (3y)	* (4y)	* (4y)	* (4-9y)	* (6-11y)	8 (4.5y)
* (88)	* (80)	* (85)	* (83)	* (83)	* (83)	* (83)		* (80)	* (80)		* (97)
							76			65	
9	9	9	9	9	9	9	8	9	8	7	7

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, vocalisation 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 recognise objects by sense of touch (stereognosis)	No significant associations	1 and 2 y	OPPS, Fried, 1988
Infant Behavior Record	Primary Cognition Composite Score: object orientation, goal directedness, attention span, reactivity and vocalisation	Positive association	1 y	OPPS, Fried, 1988
		No results reported	2 y	OPPS, Fried, 1988
	Extraversion Score: social orientation to the examiner, cooperativeness, and general emotional tone Visual and auditory sensory systems	No associations	1 and 2 y	OPPS, Fried, 1988
Reynell Developmental Language Scale	Comprehension	Negative association	2 y	OPPS, Fried, 1988
	Expression	No associations	2, 3 and 4 y	OPPS, Fried, 1988; 1990
Denver Developmental Scale	Gross motor development	Negative association	3 y	NMIHS, Faden, 2000
	Adaptive functioning, language and fine motor development	No associations		
McCarthy Scales of Children's Abilities	General Cognitive Index (memory, verbal development, perception and quantitative abilities)	No associations	3 y	OPPS, Fried, 1990
		Negative association	4 y	OPPS, Fried, 1990
		No associations	4, 5 and 6 y	Jamaica study, Hayes, 1991; OPPS, Fried, 1992
	Motor performance score	Positive association in moderately exposed children compared to unexposed and heavily exposed	3 y	OPPS, Fried, 1990
		No associations	4, 5 and 6 y	OPPS, Fried, 1990; 1992; Jamaica study, Hayes, 1991
	Memory score	No associations	3 y	OPPS, Fried, 1990
		Negative association	4 y	OPPS, Fried, 1990
		No associations	4, 5 and 6 y	Jamaica study, Hayes, 1991; OPPS, Fried, 1992
	Verbal score	No associations	3 y	OPPS, Fried, 1990
		Negative association	4 y	OPPS, Fried, 1990
		No associations	4, 5 and 6 y	Jamaica study, Hayes, 1991; OPPS, Fried, 1992
	Quantitative score	Negative association	3 y	OPPS, Fried, 1990
		No associations	4 y	OPPS, Fried, 1990
		No associations	4, 5 and 6 y	Jamaica study, Hayes, 1991; OPPS, Fried, 1992
	Perceptual score	No associations	3 y	OPPS, Fried, 1990
		Negative association	4 y	OPPS, Fried, 1990
		No associations	4, 5 and 6 y	Jamaica study, Hayes, 1991; OPPS, Fried, 1992

(Continues)

TABLE 3 (Continued)

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 3-12 y of age, truncated.	Category fluency (language development)	No associations	4 y	Prenatal cocaine exposure study, Noland, 2003
Stanford-Binet Intelligence Scale, 4 Ed	Composite score (IQ)	Negative association	3 y	MHPCD, Day, 1994
		No associations	4, 6 and 9 y	Developmental effects of prenatal substance exposure study, Bennett, 2008
		Not reported	6 y	MHPCD, Leech, 1999
		Negative association	6 y	MHPCD, Goldschmidt, 2008
	Short-term memory	Negative association	3 y	MHPCD, Day, 1994
		No associations	4, 6 and 9 y	Developmental effects of prenatal substance exposure study, Bennett, 2008
		Negative association	6 y	MHPCD, Goldschmidt, 2008
	Verbal reasoning	Negative association	3 y	MHPCD, Day, 1994
		No associations	4, 6 and 9 y	Developmental effects of prenatal substance exposure study, Bennett, 2008
		Negative association	6 y	MHPCD, Goldschmidt, 2008
	Quantitative reasoning	No associations	3 y	MHPCD, Day, 1994
		No associations	4, 6 and 9 y	Developmental effects of prenatal substance exposure study, Bennett, 2008
		Negative association	6 y	MHPCD, Goldschmidt, 2008
	Abstract/visual reasoning	Negative association	3 y	MHPCD, Day, 1994
		No associations	4, 6 and 9 y	Developmental effects of prenatal substance exposure study, Bennett, 2008
		No associations	6 y	MHPCD, Goldschmidt, 2008
Wechsler Preschool and Primary Scale of Intelligence, III	Verbal IQ, attention	Not reported	4 y	Prenatal cocaine exposure study, Noland, 2003; 2005
		No associations	4.5 y	IDEAL, Chakraborty, 2015
Finger sequencing task adapted by Welsh for use with children.	Motor planning	No associations	4 y	Prenatal cocaine exposure study, Noland, 2003
Pegboard test	Manual dexterity and bimanual coordination	No associations	4 y	OPPS, Fried, 1990
Picture deletion task for preschoolers-modified (Corkum)	Attention	Non-significant negative association	4 y	Prenatal cocaine exposure study, Noland, 2005

(Continues)

TABLE 3 (Continued)

Diagnostic instrument	Outcomes measured	Reported associations with prenatal marijuana exposure [a]	Age at assessment	Article (Study, first author, year)
Tactile Form Recognition Task	Stereognosis	No associations	4 y	OPPS, Fried, 1990
Tapping Inhibition (test of frontal lobe functioning (Luria) adapted by Diamond and Taylor for use with children 3.5 through 7 y of age)	Inhibitory control (Ability to override their natural, habitual or dominant behavioural response to a stimulus in order to implement more adaptive goal-oriented behaviours)	No associations	4 y	Prenatal cocaine exposure study, Noland, 2003
Peabody Picture Vocabulary Test	Vocabulary	Negative association	4 y	OPPS, Fried, 1990
		No associations	5, 6 and 9-12 y	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 y	IDEAL, Chakraborty, 2015
Conners Parent Questionnaire	Impulsivity hyperactivity	Non-significant negative association	6 y	OPPS, Fried, 1992
		No associations	6-9 y	OPPS, O'Connell, 1991
	Hyperactivity index, learning problems and psychosomatic problems	No associations	6-9 y	OPPS, O'Connell, 1991
	Anxiety, conduct problems	Non-significant negative association	6-9 y	OPPS, O'Connell, 1991
Gordon Diagnostic System	Sustained attention and self-control	Negative association	6 y	OPPS, Fried, 1992
	Impulsivity	Negative association	9-12 y	OPPS, Fried, 1998
Continuous Performance Task	Errors of commission (impulsivity)	Not reported	4 y	Prenatal cocaine exposure study, Noland, 2005
		Negative association	6 and 10 y	MHPCD, Leech, 1999; Richardson, 2001
	Errors of omission (inattentiveness)	Not reported	4 y	Prenatal cocaine exposure study, Noland, 2005
		Positive association	6 y	MHPCD, Leech, 1999
The Sentence Memory Test	Immediate auditory memory and auditory attention for sentences	No associations	6 y	OPPS, Fried, 1992
The Target Test	Visual-spatial memory	No associations	6 y	OPPS, Fried, 1992
The Yale Child Study Center Attention Task	Attention and inhibitory control	No associations	6, 9, and 11 y	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 y	OPPS, O'Connell, 1991
		No associations	9-12 y	OPPS, Fried, 2000
	Visual Closure, Visual Figure Ground, Visual Form Constancy, Visual Memory and Visual Spatial Relations	No associations	6-9 and 9-12 y	OPPS, O'Connell, 1991; Fried, 2000
Trail Making Test	Visual scanning, visuospatial sequencing, attention, mental flexibility and motor function	Non-significant negative association	6-9 y	OPPS, O'Connell, 1991
		No associations	9-12 y	OPPS, Fried, 2000

(Continues)

TABLE 3 (Continued)

Diagnostic instrument	Outcomes measured	Reported associations with prenatal marijuana exposure [a]	Age at assessment	Article (Study, first author, year)
Wide Range Achievement Test-revised	Reading, arithmetic, spelling	No associations	6-9 y	OPPS, O'Connell, 1991
		Negative association	10 y	MHPCD, Goldschmidt, 2004
	Reading	No associations	6-9 and 9-12 y	OPPS, O'Connell, 1991; Fried, 1997
Knox Cube Test	Visual attention, visual memory and visual sequencing	No associations	6-9 and 9-12 y	OPPS, O'Connell, 1991; Fried, 2000
Woodcock Reading Mastery Test	Passage comprehension	No associations	6-9 and 9-12 y	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 y	OPPS, O'Connell, 1991
		No associations	9-12 y	OPPS, Fried, 2000
Draw a man	Intelligence (score is based on detail, proportion and coordination)	No significant associations	6-9 y	OPPS, O'Connell, 1991
Finger tapping	Motor control, speed and lateral coordination	No significant associations	6-9 y	OPPS, O'Connell, 1991
Stroop Interference	Tests the ability to sort and selectively react to information: for example, word "red" is printed in green ink. The child must say loudly the colour of the text and not the word.	Non-significant negative association	6-9 y	OPPS, O'Connell, 1991
Test of Language Development (Primary syntax quotient score)	Ability to generate acceptable sentences	Non-significant negative association	6-9 y	OPPS, O'Connell, 1991
Auditory Working Memory	Working memory	Non-significant negative association	9-12 y	OPPS, Fried, 1998
Category Test	Problem-solving capacity	Negative association	9-12 y	OPPS, Fried, 1998
Fluency Test	Verbal fluency (number of words starting with "C" and "P" produced in 60 sec)	No associations	9-12 y	OPPS, Fried, 1997; 1998
Oral Cloze Task	Ability to understand the basic grammatical structure of English based on auditory process	No associations	9-12 y	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 y	OPPS, Fried, 1997
Seashore Rhythm Test	Rhythm discrimination	No associations	9-12 y	OPPS, Fried, 1997
Tactile Performance Task	Motor abilities and motor memory (blind-folded, place wooden blocks into properly shaped holes)	No associations	9-12 y	OPPS, Fried, 1998

(Continues)

TABLE 3 (Continued)

Diagnostic instrument	Outcomes measured	Reported associations with prenatal marijuana exposure [a]	Age at assessment	Article (Study, first author, year)
Wechsler Intelligence Scale for Children, 3rd ed.	Full-scale IQ	No associations	6-9 and 9-12 y	OPPS, O'Connell, 1991; Fried, 1997; 1998; 2000
	Information	No associations	9-12 y	OPPS, Fried, 1997
		Non-significant negative association	9-12 y	OPPS, Fried, 1998
	Verbal IQ, Verbal Comprehension Index	No associations	6-9 and 9-12 y	OPPS, O'Connell, 1991; Fried, 1997; 1998
	Similarities, Vocabulary	No associations	9-12 y	OPPS, Fried, 1997; 1998
	Performance IQ	No associations	6-9 and 9-12 y	OPPS, O'Connell, 1991; Fried, 1998
	Arithmetic, Processing Speed Index	No associations	9-12 y	OPPS, Fried, 1998
	Freedom from Distractibility Index	No associations	6-9 and 9-12 y	OPPS, O'Connell, 1991; Fried, 1998; 2000
	Coding (discrimination and memory of visual symbols); Symbol Search (visual scanning) and Digit Span (memory)	No associations	9-12 y	OPPS, Fried, 1998; 2000
	Comprehension	Negative association	9-12 y	OPPS, Fried, 1998
	Mazes (rudimentary planning)	Negative association	9-12 y	OPPS, Fried, 1998
		No associations	9-12 y	OPPS, Fried, 2000
	Perceptual Organization Index (a summary index of picture completion, picture arrangement, block design, and object assembly)	No association	6-9 and 9-12 y	OPPS, O'Connell, 1991; Fried, 1998
		Negative association	9-12 y	OPPS, Fried, 2000
	Object Assembly	Negative association	9-12 y	OPPS, Fried, 1998; 2000
	Block Design	Negative association	9-12 y	OPPS, Fried, 1998; 2000
	Picture Arrangement	No associations	9-12 y	OPPS, Fried, 1998; 2000
	Picture Completion	No associations	9-12 y	OPPS, Fried, 1998; 2000
Child Behavior Checklist	Attention problems	No associations	10 y	MHPCD, Goldschmidt, 2000
Severe discrepancy between ability (Stanford-Binet Intelligence Scale, 4ed.)	Underachieving	Negative association	10 y	MHPCD, Goldschmidt, 2004
Swanson, Noland, and Pelham Assessment	Impulsivity, hyperactivity, inattention symptoms	Negative association	10 y	MHPCD, Goldschmidt, 2000
Teacher's Report Form	Attention problems	No associations	10 y	MHPCD, Goldschmidt, 2000
Teacher's assessment of the child in language arts, history, math, and science	Educational performance	Negative association	10 y	MHPCD, Goldschmidt, 2004
Peabody Individual Achievement Test-revised	Reading comprehension	Negative association	10 y	MHPCD, Goldschmidt, 2004

(Continues)

TABLE 3 (Continued)

Diagnostic instrument	Outcomes measured	Reported associations with prenatal marijuana exposure [a]	Age at assessment	Article (Study, first author, year)
Wide Range Assessment of Memory and Learning	Design memory, screening index	Negative association	10 y	MHPCD, Richardson, 2001
	Story memory, verbal learning	No association	10 y	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, for example 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, for example 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 ($P \geq 0.05$). No association—the analyses did not find associations between prenatal marijuana exposure and neuropsychological functions in bivariate and adjusted analyses.

and deficits in reading comprehension and underachievement, all at age 10 years ($P < 0.05$).[56] A similar analysis by Richardson and colleagues[57] suggested that prenatal marijuana exposure was associated with increased impulsivity in 10-year-olds based on continuous performance task.

3.3 | 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 1-3).[58,59] 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;[58] however, heavier prenatal marijuana use was associated with lower ability to maintain sustained attention.[59]

3.4 | 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 1-3).[60,61] Neither article found statistically significant associations between marijuana exposure and child IQ, attention or impulsivity at ages 6, 9 and 11 years.[60,61]

3.5 | 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 1-3).[62] 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[62] found no association between prenatal marijuana exposure and McCarthy Scales of Children's Abilities scores measuring IQ, memory, verbal development, perception and quantitative abilities.

3.6 | National maternal and infant health survey

One article by Faden and colleagues analysed data from NMIHS.[63] 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.[64] 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 1-3).[63] 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.[63]

3.7 | 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 United States and New Zealand (Tables 1-3).[65] 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 ($P = 0.001$).[66] Global motion perception is ability to recognise speed and direction of moving objects and is linked to cognitive skills and social competence.[67]

4 | COMMENT

4.1 | 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.[18-21]

The analyses that found positive associations suggested improved aspects of attention and perceptive abilities in exposed children aged 1-6 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.[68,69] 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.

4.2 | Strengths of the study

While the majority of data on prenatal marijuana exposure and neuropsychological outcomes in children come from only a few longitudinal studies, they are methodologically sound, with standardised outcome assessment, and high response and participant retention rates.[44-63,66,70,71] 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.[45,53,55]

4.3 | 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.[62,72] 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.[69,73] Smoking tobacco during pregnancy can cause tissue damage affecting foetal brain development and has been associated with negative behavioural and cognitive outcomes throughout the lifetime, including conduct disorder, attention-deficit/hyperactivity disorder, poor academic achievement and cognitive impairment.[74-77] Alcohol use may also be a source of confounding in this research, as foetal alcohol spectrum disorders (FASDs) can cause a variety of physical and cognitive impairments.[78] Prenatal alcohol exposure is associated with deficits in memory, attention span, verbal learning, motor function and a lower overall IQ.[79] 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.[58,59,61] 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.[49,50,54,55,58,59] Five more articles listed postnatal maternal marijuana use as a potential confounder that did not meet requirements for inclusion into final analytic models.[51-53,56,57] However, in future research postnatal maternal marijuana use might be better conceptualised 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 conceptualisation.

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 under-reporting.

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 utilising 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.[80] Finally, we were unable to conduct a formal assessment of publication bias due to the 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 the severity of dependence and have stronger effects on the brain.[81-84]

4.4 | 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.[85,86] Thus, it is important to fully understand the risks of exposure in the light of the changing culture and political climate surrounding marijuana. On the other hand, additional factors, including genetics, maternal cognitive abilities,[87] 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.[56,62]

5 | CONCLUSIONS

This systematic review suggests possible negative associations between 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.

ACKNOWLEDGEMENTS

We are grateful to Joanna Taliano for her invaluable contribution to composing the literature search strategy, running literature searches and keeping us updated on new publications. We also acknowledge Paul Cheh, Sara Kennedy and Derrick Beasley for conceptualising the systematic review and preparing a foundation for this project. We thank Kat Asman for reviewing literature to summarise the state of the science. Roshni Patel and Amal Jama have our gratitude for their assistance with screening thousands of titles retrieved by the literature searches, collecting full-text articles and abstracting data. We also would like to thank Linda Pederson for helping to sort and review titles and abstracts from the literature search.

ORCID

Saida R. Sharapova http://orcid.org/0000-0002-1097-2204

REFERENCES

1. Center for Behavioral Health Statistics and Quality. *Key substance use and mental health indicators in the United States: results from the 2015 National Survey on Drug Use and Health*. 2016. HHS Publication No. SMA 16-4984, NSDUH Series H-51.
2. National Conference of State Legislatures. *National Conference of State Legislatures. State medical marijuana laws*. 2016; http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx. Accessed August 19, 2017.
3. Carliner H, Brown QL, Sarvet AL, Hasin DS. Cannabis use, attitudes, and legal status in the U.S.: a review. *Prev Med*. 2017;104:13-23.
4. Brown QL, Sarvet AL, Shmulewitz D, Martins SS, Wall MM, Hasin DS. Trends in marijuana use among pregnant and nonpregnant reproductive-aged women, 2002-2014. *JAMA*. 2017;317:207-209.
5. Chasnoff IJ. Medical marijuana laws and pregnancy: implications for public health policy. *Am J Obstet Gynecol*. 2017;216:27-30.
6. Mark K, Terplan M. Cannabis and pregnancy: maternal child health implications during a period of drug policy liberalization. *Prev Med*. 2017;104:46-49.
7. Benevenuto SG, Domenico MD, Martins MA, et al. Recreational use of marijuana during pregnancy and negative gestational and fetal outcomes: an experimental study in mice. *Toxicology*. 2016;376:94-101.
8. Calvigioni D, Hurd YL, Harkany T, Keimpema E. Neuronal substrates and functional consequences of prenatal cannabis exposure. *Eur Child Adolesc Psychiatry*. 2014;23:931-941.
9. de Salas-Quiroga A, Diaz-Alonso J, Garcia-Rincon D, et al. Prenatal exposure to cannabinoids evokes long-lasting functional alterations by targeting CB1 receptors on developing cortical neurons. *Proc Natl Acad Sci USA*. 2015;112:13693-13698.
10. Wang GS. Pediatric concerns due to expanded cannabis use: unintended consequences of legalization. *J Med Toxicol*. 2016;13:99-105.
11. Carter RC, Wainwright H, Molteno CD, et al. Alcohol, methamphetamine, and marijuana exposure have distinct effects on the human placenta. *Alcohol Clin Exp Res*. 2016;40:753-764.
12. Chabarria KC, Racusin DA, Antony KM, et al. Marijuana use and its effects in pregnancy. *Am J Obstet Gynecol*. 2016;215:506.e1-506.e7.

13. Blackard C, Tennes K. Human placental transfer of cannabinoids. *N Engl J Med*. 1984;311:797-797.
14. Lee CC, Chiang CN. Maternal-fetal transfer of abused substances: pharmacokinetic and pharmacodynamic data. *NIDA Res Monogr*. 1985;60:110-147.
15. Wu CS, Jew CP, Lu HC. Lasting impacts of prenatal cannabis exposure and the role of endogenous cannabinoids in the developing brain. *Fut Neurol*. 2011;6:459-480.
16. Sobrian SK. Developmental cannabinoid exposure: new perspectives on outcomes and mechanisms. *Neurotoxicol Teratol*. 2016;58:1-4.
17. Volkow ND, Compton WM, Wargo EM. The risks of marijuana use during pregnancy. *JAMA*. 2017;317:129-130.
18. Batalla A, Bhattacharyya S, Yucel M, et al. Structural and functional imaging studies in chronic cannabis users: a systematic review of adolescent and adult findings. *PLoS ONE*. 2013;8:e55821.
19. Hill SY, Sharma V, Jones BL. Lifetime use of cannabis from longitudinal assessments, cannabinoid receptor (CNR1) variation, and reduced volume of the right anterior cingulate. *Psychiatry Res*. 2016;255:24-34.
20. Jakabek D, Yucel M, Lorenzetti V, Solowij N. An MRI study of white matter tract integrity in regular cannabis users: effects of cannabis use and age. *Psychopharmacology*. 2016;233:3627-3637.
21. Solowij N, Stephens RS, Roffman RA, et al. Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA*. 2002;287:1123-1131.
22. Lorenzetti V, Alonso-Lana S, Youssef GJ, et al. Adolescent cannabis use: what is the evidence for functional brain alteration? *Curr Pharm Des*. 2016;22:6353-6365.
23. Gonzalez R, Swanson JM. Long-term effects of adolescent-onset and persistent use of cannabis. *Proc Natl Acad Sci USA*. 2012;109:15970-15971.
24. Schweinsburg AD, Brown SA, Tapert SF. The influence of marijuana use on neurocognitive functioning in adolescents. *Curr Drug Abuse Rev*. 2008;1:99-111.
25. Meier MH, Caspi A, Ambler A, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci USA*. 2012;109:E2657-E2664.
26. Alpar A, Di Marzo V, Harkany T. At the tip of an iceberg: prenatal marijuana and its possible relation to neuropsychiatric outcome in the offspring. *Biol Psychiatry*. 2016;79:e33-e45.
27. Huizink AC. Prenatal cannabis exposure and infant outcomes: overview of studies. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014;52:45-52.
28. Irner TB, Teasdale TW, Nielsen T, Vedal S, Olofsson M. Substance use during pregnancy and postnatal outcomes. *J Addict Dis*. 2012;31:19-28.
29. Greydanus DE, Hawver EK, Greydanus MM, Merrick J. Marijuana: current concepts. *Front Public Health*. 2013;1:42.
30. Gunn JK, Rosales CB, Center KE, et al. Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis. *BMJ Open*. 2016;6:e009986.
31. Irner TB. Substance exposure in utero and developmental consequences in adolescence: a systematic review. *Child Neuropsychol*. 2012;18:521-549.
32. Williams JH, Ross L. Consequences of prenatal toxin exposure for mental health in children and adolescents: a systematic review. *Eur Child Adolesc Psychiatry*. 2007;16:243-253.
33. Hasin DS, Wall M, Keyes KM, et al. Medical marijuana laws and adolescent marijuana use in the USA from 1991 to 2014: results from annual, repeated cross-sectional surveys. *Lancet Psychiatry*. 2015;2:601-608.
34. National Academies of Sciences, Engineering, Medicine. *The Health Effects of Cannabis and Cannabinoids: the Current State of Evidence and Recommendations for Research*. Washington, DC: National Academies Press; 2017.
35. Reavie KT. Mining the research literature in systems biology. In: Krawetz S, ed., *Bioinformatics for Systems Biology*. Totowa, NJ: Humana Press; 2009:369-383.
36. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews*. 2015;4:1.
37. Zaza S, Wright-De Agüero LK, Briss PA, et al. Data collection instrument and procedure for systematic reviews in the guide to community preventive services. *Am J Prev Med*. 2000;18:44-74.
38. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2014; http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed October 21, 2015.
39. Wechsler D. *Wechsler Preschool and Primary Scale of Intelligence*. 3rd ed., San Antonio, TX: The Psychological Corporation; 2002.
40. Thorndike R, Hagen E, Sattler J. *The Stanford-Binet Intelligence Scale*. Chicago: Riverside Publishing; 1986.
41. MacCarthy D. *Manual for the McCarthy Scales of Children's Abilities*. New York: Psychological Corporation; 1972.
42. Wilkinson G. *Wide Range Achievement Test Administration Manual*. Wilmington, DE: Wide Range Inc; 1993.
43. Frankenburg WK, Dodds J, Archer P, Shapiro H, Bresnick B. The Denver II: a major revision and restandardization of the denver developmental screening test. *Pediatrics*. 1992;89:91-97.
44. Fried PA, Watkinson B. 12- and 24-month neurobehavioural follow-up of children prenatally exposed to marihuana, cigarettes and alcohol. *Neurotoxicol Teratol*. 1988;10:305-313.
45. Fried PA, Watkinson B. 36- and 48-month neurobehavioral follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol. *J Dev Behav Pediatr*. 1990;11:49-58.
46. Fried PA, Watkinson B, Gray R. A follow-up study of attentional behavior in 6-year-old children exposed prenatally to marihuana, cigarettes, and alcohol. *Neurotoxicol Teratol*. 1992;14:299-311.
47. Fried PA, O'Connell CM, Watkinson B. 60- and 72-month follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol: cognitive and language assessment. *J Dev Behav Pediatr*. 1992;13:383-391.
48. O'Connell CM, Fried PA. Prenatal exposure to cannabis: a preliminary report of postnatal consequences in school-age children. *Neurotoxicol Teratol*. 1991;13:631-639.
49. Fried PA, Watkinson B, Siegel LS. Reading and language in 9- to 12-year olds prenatally exposed to cigarettes and marijuana. *Neurotoxicol Teratol*. 1997;19:171-183.
50. Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marihuana. *Neurotoxicol Teratol*. 1998;20:293-306.
51. Fried PA, Watkinson B. Visuoperceptual functioning differs in 9- to 12-year olds prenatally exposed to cigarettes and marihuana. *Neurotoxicol Teratol*. 2000;22:11-20.
52. Day NL, Richardson GA, Goldschmidt L, et al. Effect of prenatal marijuana exposure on the cognitive development of offspring at age three. *Neurotoxicol Teratol*. 1994;16:169-175.
53. Goldschmidt L, Richardson GA, Willford J, Day NL. Prenatal marijuana exposure and intelligence test performance at age 6. *J Am Acad Child Adolesc Psychiatry*. 2008;47:254-263.
54. Leech SL, Richardson GA, Goldschmidt L, Day NL. Prenatal substance exposure: effects on attention and impulsivity of 6-year-olds. *Neurotoxicol Teratol*. 1999;21:109-118.
55. Goldschmidt L, Day NL, Richardson GA. Effects of prenatal marijuana exposure on child behavior problems at age 10. *Neurotoxicol Teratol*. 2000;22:325-336.

56. Goldschmidt L, Richardson GA, Cornelius MD, Day NL. Prenatal marijuana and alcohol exposure and academic achievement at age 10. *Neurotoxicol Teratol*. 2004;26:521-532.
57. Richardson GA, Ryan C, Willford J, Day NL, Goldschmidt L. Prenatal alcohol and marijuana exposure: effects on neuropsychological outcomes at 10 years. *Neurotoxicol Teratol*. 2002;24:309-320.
58. Noland JS, Singer LT, Arendt RE, Minnes S, Short EJ, Bearer CF. Executive functioning in preschool-age children prenatally exposed to alcohol, cocaine, and marijuana. *Alcohol Clin Exp Res*. 2003;27:647-656.
59. Noland JS, Singer LT, Short EJ, et al. Prenatal drug exposure and selective attention in preschoolers. *Neurotoxicol Teratol*. 2005;27:429-438.
60. Bennett DS, Bendersky M, Lewis M. Children's cognitive ability from 4 to 9 years old as a function of prenatal cocaine exposure, environmental risk, and maternal verbal intelligence. *Dev Psychol*. 2008;44:919-928.
61. Carmody DP, Bennett DS, Lewis M. The effects of prenatal cocaine exposure and gender on inhibitory control and attention. *Neurotoxicol Teratol*. 2011;33:61-68.
62. Hayes JS, Lampart R, Dreher MC, Morgan L. Five-year follow-up of rural Jamaican children whose mothers used marijuana during pregnancy. *West Indian Med J*. 1991;40:120-123.
63. Faden VB, Graubard BI. Maternal substance use during pregnancy and developmental outcome at age three. *J Subst Abuse*. 2000;12:329-340.
64. US Department of Health and Human Services, National Center for Health Statistics. National Maternal and Infant Health Survey, 1988: Longitudinal Follow-up, 1991. In: Inter-university Consortium for Political and Social Research (ICPSR) [distributor]; 1995.
65. LaGasse LL, Wouldes T, Newman E, et al. Prenatal methamphetamine exposure and neonatal neurobehavioral outcome in the USA and New Zealand. *Neurotoxicol Teratol*. 2011;33:166-175.
66. Chakraborty A, Anstice NS, Jacobs RJ, et al. Prenatal exposure to recreational drugs affects global motion perception in preschool children. *Sci Rep*. 2015;5:16921.
67. Pavlova MA. Biological motion processing as a hallmark of social cognition. *Cereb Cortex*. 2012;22:981-995.
68. Anderson P. Assessment and development of executive function (EF) during childhood. *Child Neuropsychol*. 2002;8:71-82.
69. Riley AW. Evidence that school-age children can self-report on their health. *Ambul Pediatr*. 2004;4:371-376.
70. Kane-Wineland M. The relationship between prenatal substance exposure and neuromotor development in children from birth to three years. *Diss Abstr Int*. 2002;63:860.
71. Stein MT, Drahota A, Chavira DA. Ian: a 7-year old with prenatal drug exposure and early exposure to family violence. *J Dev Behav Pediatr*. 2008;29:512-515.
72. Dreher MC, Hayes JS. Triangulation in cross-cultural research of child development in Jamaica. *West J Nurs Res*. 1993;15:216-229.
73. Huizink AC, Mulder EJ. Maternal smoking, drinking or cannabis use during pregnancy and neurobehavioral and cognitive functioning in human offspring. *Neurosci Biobehav Rev*. 2006;30:24-41.
74. Ekblad M, Korkeila J, Lehtonen L. Smoking during pregnancy affects foetal brain development. *Acta Paediatr*. 2015;104:12-18.
75. El Marroun H, Schmidt MN, Franken IH, et al. Prenatal tobacco exposure and brain morphology: a prospective study in young children. *Neuropsychopharmacology*. 2014;39:792-800.
76. Zhou S, Rosenthal DG, Sherman S, Zelikoff J, Gordon T, Weitzman M. Physical, behavioral, and cognitive effects of prenatal tobacco and postnatal secondhand smoke exposure. *Curr Probl Pediatr Adolesc Health Care*. 2014;44:219-241.
77. Rose-Jacobs R, Richardson MA, Buchanan-Howland K, et al. Intrauterine exposure to tobacco and executive functioning in high school. *Drug Alcohol Depend*. 2017;176:169-175.
78. Khoury JE, Milligan K, Girard TA. Executive functioning in children and adolescents prenatally exposed to alcohol: a meta-analytic review. *Neuropsychol Rev*. 2015;25:149-170.
79. Coriale G, Fiorentino D, Di Lauro F, et al. Fetal Alcohol Spectrum Disorder (FASD): neurobehavioral profile, indications for diagnosis and treatment. *Riv Psichiatr*. 2013;48:359-369.
80. Clarke MJ. Individual patient data meta-analyses. *Best Pract Res Clin Obstet Gynaecol*. 2005;19:47-55.
81. Psychoyos D, Vinod KY. Marijuana, Spice 'herbal high', and early neural development: implications for rescheduling and legalization. *Drug Test Anal*. 2013;5:27-45.
82. ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC. Changes in cannabis potency over the last 2 decades (1995-2014): analysis of current data in the United States. *Biol Psychiatry*. 2016;79:613-619.
83. Freeman TP, Winstock AR. Examining the profile of high-potency cannabis and its association with severity of cannabis dependence. *Psychol Med*. 2015;45:3181-3189.
84. Schauer GL, King BA, Bunnell RE, Promoff G, McAfee TA. Toking, vaping, and eating for health or fun: marijuana use patterns in adults, U.S., 2014. *Am J Prev Med*. 2016;50:1-8.
85. Lester BM, LaGasse LL, Seifer R. Cocaine exposure and children: the meaning of subtle effects. *Science*. 1998;282:633-634.
86. Goldschmidt L, Richardson GA, Larkby C, Day NL. Early marijuana initiation: the link between prenatal marijuana exposure, early childhood behavior, and negative adult roles. *Neurotoxicol Teratol*. 2016;58:40-45.
87. McGue M. Classical and molecular genetic research on general cognitive ability. *Hastings Center Rep*. 2015;45:S25-S31.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Sharapova SR, Phillips E, Sirocco K, Kaminski JW, Leeb RT, Rolle I. Effects of prenatal marijuana exposure on neuropsychological outcomes in children aged 1-11 years: A systematic review. *Paediatr Perinat Epidemiol*. 2018;00:1–21. https://doi.org/10.1111/ppe.12505