

The Impact of Maternal Prenatal Methamphetamine Exposure on Child Behavioural  
Development: A systematic review

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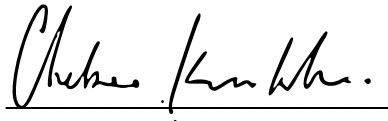
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*I declare that this research report is my own account of my research and contains as its main content work which has not previously been submitted for a degree at any tertiary educational institution.*

A handwritten signature in black ink, appearing to read "Chelsea Kunkler", is written over a horizontal line.

Chelsea Kunkler

### Abstract

Methamphetamine (MA) use during pregnancy is associated with a range of adverse neurodevelopmental implications for a developing fetus. This systematic review examines studies which report the effects of prenatal MA exposure *in utero* on infant and child behavioural development. A systematic search of PSYCINFO, Scopus, PubMed and ERIC databases was conducted and 839 records were identified. A total of 15 articles met inclusion criteria, examining behavioural outcomes in children from birth to nine years of age. This review found consistent reports of behavioural dysregulation in neonates and children prenatally exposed to MA. Furthermore, the results indicate that children with prenatal MA exposure display more pronounced behavioural difficulties as they age. However, the small number of longitudinal studies and the narrow breadth of populations sampled limits the interpretation and generalisability of these findings. Future research should consider these limitations and conduct longitudinal studies, with a broader range of population samples, to determine the temporal association between prenatal MA exposure and behavioural outcomes. These findings have implications for early identification and prevention of later behavioural dysfunction as a result of prenatal MA exposure. It is crucial to prevent maternal MA use during pregnancy and to provide postnatal service care for parents of children with prenatal MA exposure; so they have the ability to support and promote a more adaptive developmental trajectory for their child.

*Keywords:* methamphetamine, prenatal drug exposure, fetal behaviour, child behaviour

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## Table of Contents

Neurotoxicity of Methamphetamine .....	7
Modes of Prenatal Methamphetamine Exposure .....	9
Neurodevelopmental Effects of Prenatal Methamphetamine Exposure Via Maternal Use.	10
The Present Review .....	11
Method .....	12
Preliminary Search Strategy .....	12
Inclusion and Exclusion Criteria.....	12
Implementation of Search Strategy and Data Extraction.....	13
Risk of Bias and Quality Assessment .....	14
Results.....	14
Eligible Studies .....	14
Study Characteristics .....	16
Neurobehavioural Outcomes .....	26
Neonate neurobehavioural dysfunction. ....	26
Infant and child neurobehavioural dysfunction. ....	26
Discussion.....	30
Limitations and Directions for Future Research.....	32
Implications for Health Professionals, Policy Makers and Parents .....	33
References.....	35

## List of Figures and Tables

## Figures

1. PRISMA flow diagram of identification of studies for inclusion in systematic review.....15

## Tables

1. Summary of the Study Characteristics of the Behavioural Studies Included in the Systematic Review..... 17

The Impact of Maternal Prenatal Methamphetamine Exposure on Child Behavioural  
Development: A systematic review

The growing use of amphetamine-type substances (ATS) is a world-wide concern. The United Nations Office on Drugs and Crime (UNODC) reported that in 2016, an estimated 34.2 million people world-wide had used an ATS in the past year (UNODC, 2018). One specific type of amphetamine, methamphetamine (MA), is of growing concern to health professionals (UNODC, 2018). In the U.S. alone, 1.39 million people reported MA use in the year of 2016 (Substance Abuse and Mental Health Service Administration, 2017). Furthermore, women account for a substantial amount of MA users, with data showing that 44% of the 1.39 million people were women (SAMHSA, 2017). The use of MA has noticeable effects on the behaviour of its users; including, aggression, behavioural disinhibition, poor impulse control, inattention, anxiety, depression and irritability (Brown & Hohman, 2006; Cruickshank & Dyer, 2009; Murray, 1998).

This review is focused on the use of MA by women during pregnancy. There is little information detailing the outcomes for children exposed to MA *in utero*. The most recent Treatment Episode Data Set (TEDS) from the U.S reported that in 2016, 20% of pregnant women admitted to federally funded substance abuse centres were there for MA exposure (SAMHSA, 2016). The current review examines studies reporting on the impact of prenatal methamphetamine exposure (PME) on a child's behavioural development.

### **Neurotoxicity of Methamphetamine**

Methamphetamine is a central nervous system (CNS) stimulant that predominantly acts on the sympathetic nervous system (Courtney & Ray, 2014). It causes a release of dopamine, serotonin and norepinephrine, and inhibits the reuptake of these transmitters. Initially, increased dopamine in the brain's reward centre results in intense euphoria, arousal

and behavioural disinhibition (Cruickshank & Dyer, 2009). However, prolonged MA abuse can result in impairments in motor control, memory, learning and behavioural function (Barr et al., 2006; Meredith, Jaffe, Ang-Lee, & Saxon, 2005; Volkow et al., 2001). It is postulated that these impairments are associated with the neurotoxic effects of MA (Barr et al., 2006; Meredith et al., 2005). The term ‘neurotoxicity’ indicates any adverse changes in the structure and/or function of the nervous system as a result of a biological, physical or chemical agent. (Cho & Melega, 2002; Erinoff, 1995). Animal models have demonstrated the neurotoxicity of methamphetamine; showing distinct anatomic deterioration of dopaminergic pathways in the striatum of MA-exposed mice (Barr et al., 2006; Miller & O’Callaghan, 2003) and a long-term decrease in dopamine transporter (DAT) density in non-human primates (Villemagne et al., 1998).

Although the mechanisms of action of MA are not completely understood, researchers investigating the neurotoxic effects of MA in human studies suggest that prolonged MA abuse has similar adverse effects on the dopaminergic systems as in the animal models (Cho & Melega, 2002; Ernst, Chang, Leonido–Yee & Speck, 2000; Wilson et al., 1996). Volkow et al. (2001) used positron emission tomography (PET) to demonstrate a reduction in striatal DAT density is associated with long-term MA abuse in adult users. Several studies have also shown MA-induced structural and metabolic alterations to a number of brain areas, including the hippocampus (Thompson et al., 2004), thalamus (Volkow et al., 2001) and basal ganglia (Chang et al., 2005) in both current and abstinent MA users. Furthermore, researchers have demonstrated an association between MA-induced neurostructural damage and altered cognitive and affective function in adult users (Tanabe et al., 2009; Thompson et al., 2004; Volkow et al., 2001).



### **Modes of Prenatal Methamphetamine Exposure**

Given the neurotoxic effects of long-term MA exposure in adults, researchers have proposed that prenatal MA exposure may also induce similar effects on fetal neurodevelopment (Frost, 2000; Salisbury, Ponder, Padbury, & Lester, 2009; Warton et al., 2018). The term 'neurodevelopment' refers to the brain's development of neurological pathways which impact on an individual's performance and functioning (Neurodevelopment, n.d.). It has been established that MA readily crosses the placenta and blood-brain barrier (Garcia-Bournissen, Rokach, Karaskov, & Koren, 2007; Joya, Pacifici, Salat-Batlle, García-Algar, & Pichini, 2015). Furthermore, preclinical models have demonstrated the vasoconstrictive effects of MA exposure *in utero* (Burchfield, Lucas, Abrams, Miller, & DeVane, 1991; Stek et al., 1993), resulting in decreased placental blood flow and fetal hypoxia (Stek, Baker, Fisher, Lang, & Clark, 1995), which can have adverse effects on a developing fetus (Thompson, Crimmins, Telugu, & Turan, 2015).

Fetal exposure to MA can occur in a number of different ways. First, a fetus can be directly exposed to MA *in utero* via maternal use (i.e. direct exposure). Second, an infant can be exposed by inhaling fumes from MA use while family members are using the drug within the child's environment in the postnatal period (i.e. passive exposure via second-hand smoke inhalation). Also an infant could be passively exposed through MA-contaminated clothing or surfaces in the home (Brown & Hohman, 2006). Third, children born to women who use MA are likely to also be exposed to a suboptimal home environment and reduced parental care (Derauf, LaGasse, et al., 2012; Nguyen et al., 2010). Therefore, these would be considered indirect effects of MA-exposure, for example, neglect or domestic violence in the home (Dowling & Morgan, 2018). While it is imperative to understand the evidence detailing how different modes of exposure might impact on fetal and child development, given the scope of

the current paper, only studies assessing the effects of direct MA exposure will be included in the review.

### **Neurodevelopmental Effects of Prenatal Methamphetamine Exposure Via Maternal Use**

The literature in this area of research uses the term ‘neurodevelopment’ as an overarching concept which encompasses a number of different domains relating to growth and development. These include; cognitive (e.g. memory, attention and IQ), language (e.g. receptive and expressive language) behavioural and emotional (e.g. emotional regulation, internalising and externalising behaviours), psychomotor (e.g. gross and fine motor skills) and neuroanatomical (e.g. development of CNS and brain structures) domains.

It is reasonable to postulate that exposure to methamphetamine *in utero*, during a neurologically vulnerable period, might produce serious neurostructural alterations, which might subsequently lead to neurodevelopmental impairments in a developing fetus (Salisbury et al., 2009; Sowell et al., 2010). Previous research investigating the neurodevelopmental implications of PME have found changes in infant brain structures when they are prenatally exposed to MA. A recent study by Warton et al. (2018) investigated the potential changes of white-matter integrity in the striatal-orbitofrontal circuit in neonates prenatally exposed to MA. They utilised a case-control design with 23 infants (11 exposed) and found that increased MA use was associated with reduced white-matter connections in the striatum, midbrain and orbitofrontal cortex. There were some limitations to this particular study, including a small sample size and inconsistent *p* values used for the statistical analyses. Nonetheless, this paper is one of several neurological studies which report neurostructural changes in an infant’s brain following MA exposure. Other studies have found reduced caudate volume (Sowell et al., 2010; Warton et al., 2018); and smaller subcortical volumes, which were associated with attention and verbal memory deficits (Chang et al., 2004).

In addition, researchers have observed a number of neuropsychological and behavioural differences between infants exposed to MA *in utero* and healthy controls, including; reduced fine motor control (Smith et al., 2011); deficits in inhibitory control (Derauf, LaGasse, et al., 2012); and increased emotional reactivity and externalising behaviours (LaGasse et al., 2012). Considering the widespread use of MA in pregnancy (SAMHSA, 2016), the influence of PME on fetal development and child neurodevelopmental outcomes is of particular clinical importance.

### **The Present Review**

In order to provide health professionals, policy makers and parents with an accurate and informative education on the effects of PME on fetal and child development, it is imperative to systematically examine and understand this area of research. However, given the volume of studies produced by researchers in this field, the current review will be limited to behavioural outcomes.

Behavioural dysfunction has the potential to permeate and negatively influence many aspects of daily life; for example, high levels of externalising behaviours have been associated with poor school performance and educational attainment (Breslau, Lane, Sampson, & Kessler, 2008). Furthermore, it is essential to examine behavioural outcomes specifically, given that behavioural difficulties are more perceptible in the early years of a child's life, prior to school entrance (van Dyk, Ramanjam, Church, Koren, & Donald, 2014), and may therefore be used as an early marker to identify children who may later experience other deficits as a result of MA exposure (Abar et al., 2013). As such, early detection of behavioural dysfunction allows for early intervention to support more adaptive functioning.

At this time, to our knowledge, there are no systematic reviews investigating how pregnancy-related MA exposure impacts on infant and child behavioural outcomes only. Therefore, the purpose of the following review was to examine and synthesise the available

literature to provide this area of research with a comprehensive understanding of how PME effects infants and child behavioural development. The results of the review indicate where additional research is required and provide considerations to improve future studies.

## **Method**

### **Preliminary Search Strategy**

The primary objective of the current search strategy was to identify all published peer-reviewed studies reporting the prevalence of behavioural outcomes in a population of infants and/or children prenatally exposed to methamphetamine, through maternal use. A systematic search strategy was developed by two independent researchers. The search of abstracts and titles of peer-reviewed articles was conducted using PSYCINFO, PubMed, Scopus and ERIC databases including papers up to *September 2019*. Search results were not limited to a specific date range. In order to identify studies investigating prenatal exposure to methamphetamine and behavioural outcomes the following terms were used to systematically search databases: “prenatal OR maternal,” AND “methamphetamine OR meth,” AND “exposure,” AND “neurodevelopment\* OR ‘child development’ OR neurobehavioural”.<sup>1</sup> Furthermore, the reference lists of all relevant studies were searched to identify any additionally relevant studies not found in the search.

### **Inclusion and Exclusion Criteria**

For inclusion in the review, studies had to: 1) involve human subjects only, 2) be peer reviewed, 3) conduct formal assessment of at least one behavioural outcome using a validated test, 4) assess the behavioural outcomes of children and/or infants exposed to

<sup>1</sup> While the current review only focused on behavioural outcomes, previous studies (Dixon, Kurtz, & Chin, 2008) have used the terms ‘neurodevelopmental’ and ‘neurobehavioural’ interchangeably, encompassing ‘behavioural’ outcomes as well. Therefore, broad search terms (i.e. ‘neurodevelopment\*’ and ‘neurobehavioural’) were used to ensure that all relevant studies could be identified in the database search.

methamphetamine in the prenatal period through maternal use, and 5) adhere to an observational study methodology. Observational study designs included were cohort studies, case-control studies and cross-sectional studies, whereas intervention studies were excluded. Papers published in a language other than English were translated by a native speaker and reviewed. Studies that included a cohort of individuals prenatally exposed to methamphetamine via maternal use, that were part of a single larger study, were included if the analysis of this particular sub-cohort was reported separately. Studies were excluded if: 1) they involved non-human subjects, 2) they were grey literature, 3) outcome measures assessed neurodevelopmental outcomes only, and 4) study design was experimental.

### **Implementation of Search Strategy and Data Extraction**

One independent reviewer ran the search using the key terms described above. Using the inclusion and exclusion criteria, each study was screened for relevance based on the title and abstract. If the researcher could not ascertain the studies' relevance from the title and abstract, the full text was assessed independently. The eligibility of the resulting studies was then assessed by reading the full text articles based on the inclusion and exclusion criteria. At this point, if the researcher could not establish an article's eligibility, a second independent reviewer was consulted. Discrepancies were resolved through review and discussion with all authors until consensus was achieved. All excluded articles and reasons detailing their exclusion were documented (see Figure 1). A hand search of the reference lists from relevant papers produced no further relevant papers.

For the eligible studies, data were collected regarding characteristics including author, study year, study design, groups compared, method identifying methamphetamine exposure, study sample size, infant age at testing, sex of the infant, outcome measure(s) assessing

neurobehavioural outcomes, covariates and statistical analysis. For group comparisons, Cohen's *d* was calculated using *M* and *SD* where reported.

### **Risk of Bias and Quality Assessment**

A quality assessment of all eligible studies meeting full inclusion and exclusion criteria was conducted using the Newcastle-Ottawa Quality Assessment Scale (NOQAS) (Wells et al., 2009). Each study was given a star rating in three categories by one reviewer (selection, comparability and exposure/outcome) using either the case control assessment scale, the cohort studies assessment scale or the cross-sectional studies assessment scale, depending on the study's methodology. The first category assessed the selection of study groups (cases or cohorts); the second category assessed the comparability of cases and controls (or cohorts); and the third category assessed exposure (for case control studies) or outcome (for cohort studies). The quality of the studies was rated (good, fair and poor) by awarding stars in each domain. Table 1 shows the quality rating score awarded to each study.

## **Results**

### **Eligible Studies**

The search outlined above yielded a total of a total of 839 articles from four databases. After 55 duplicates were removed, the remaining 784 articles were screened for relevance firstly by title and abstract. Following extensive title and abstract screening, 762 articles were excluded, which left 22 articles to be assessed for full-text eligibility. Of the papers assessed for full-text eligibility, a total of seven articles were excluded; four articles reported other outcomes of interest, two articles had other study methodologies, and one article was of poor quality as assessed by the NOS. Finally, 15 papers met all of the inclusion and exclusion criteria (see Figure 1).

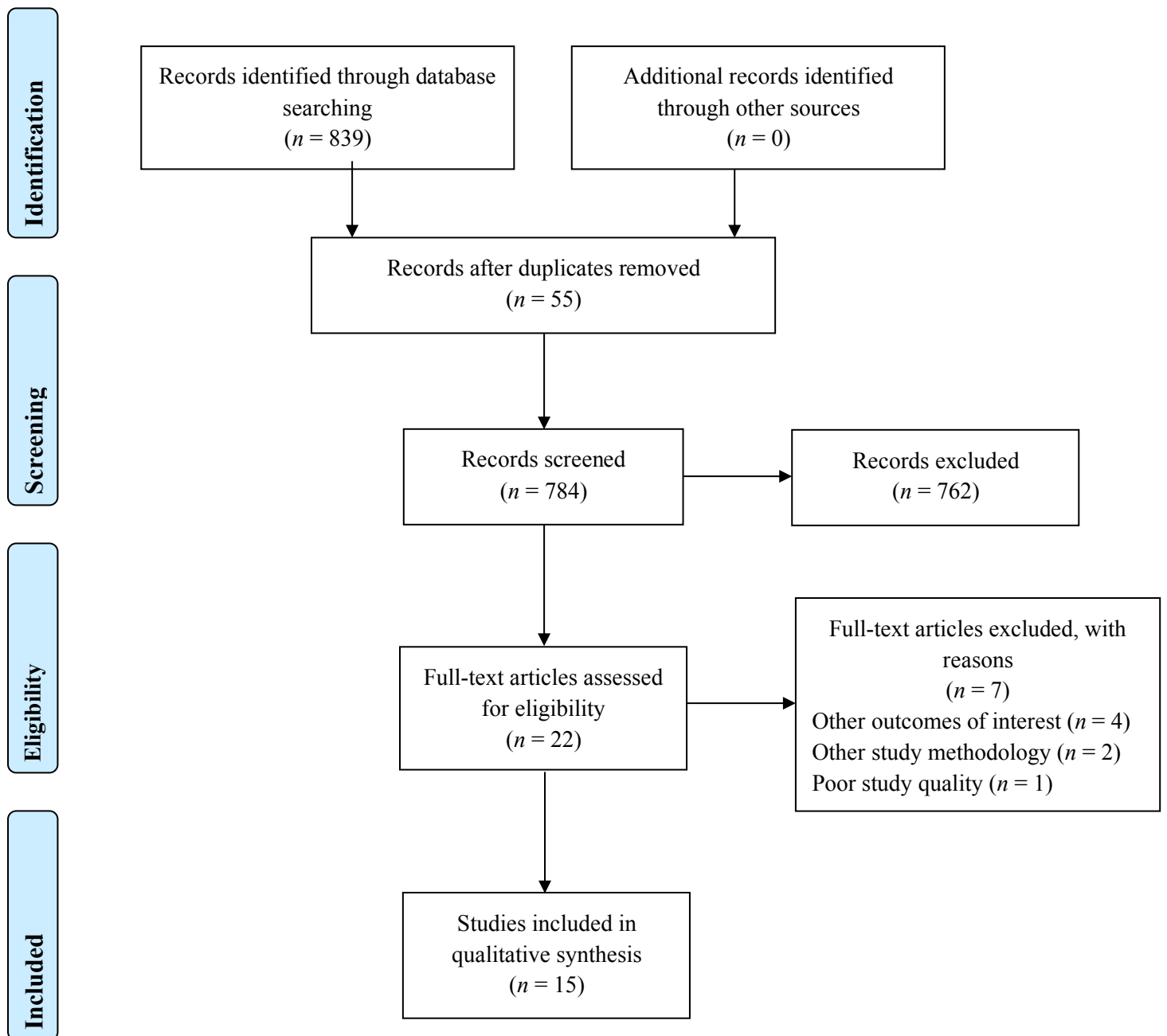


Figure 1. Identification of studies for inclusion in systematic review.

### **Study Characteristics**

The characteristics of each study are summarised in Table 1. Studies took place in the USA, South Africa and New Zealand. 13 of the 15 articles were a part of a single larger study, called the Infant Development, Environment, and Lifestyle (IDEAL) Study, while the remaining two articles were conducted independent of the IDEAL Study. This does introduce important limitations to the breadth of populations sampled and will be discussed further below. To identify MA exposure, the IDEAL studies used the Substance Use Inventory (self-report maternal exposure to MA) and positive meconium screening confirmed by positive gas chromatography-mass spectrometry, the van Dyk et al. (2014) paper used self-report only and the Piper et al. (2011) paper used medical records only. The sample sizes ranged from 35 to 559 total participants and child assessments ranged in age from birth to nine years. 13 studies reported roughly equal participants sex ratios, with the exception of van Dyk et al., (2014) reporting 36% female and Galland, Mitchell, Thompson and Wouldes (2013) not reporting participant sex ratio. Outcome measures included the NICU Neonatal Neurobehavioural Scale (NNNS), the Child Behaviour Checklist (CBCL), the Connors Kiddie Continuous Performance Test (K-CPT), Connors Behaviour Rating Scale (CBRS-R), The Behaviour Rating Inventory of Executive Function (BRIEF), and endocrine measures of stress reactivity in the form of cortisol reactivity and arousal thresholds. In general, the quality scores were of fair to good quality; with ratings ranging between 5 and 9 out of a maximum of 9 stars for cohort and case-control studies, and 8 out of a maximum of 10 for cross-sectional studies.



Table 1.

*Summary of the Study Characteristics of the Behavioural Studies Included in the Systematic Review.*

<b>Study</b>	<b>Study Design and Location</b>	<b>Groups Compared</b>	<b>Method identifying exposure</b>	<b>N (exposed)</b>	<b>Infant age at testing</b>	<b>Infant female sex (%)</b>	<b>Outcome measures</b>	<b>Covariates</b>	<b>Analysis</b>	<b>NOS Rating</b>
Smith et al. (2008)	Case-control IDEAL study - USA	Exposed Group: Prenatal methamphetamine exposed (PME) mother-infant dyads  Control group: mother-infant dyads not exposed to MA during pregnancy (exposed to other drug combinations during pregnancy, excluding PCP, cocaine, LSD, opiates and hallucinogens)	Substance Use Inventory (self-report maternal exposure) and positive meconium screening confirmed by positive gas chromatography-mass spectrometry (GC/MS).	N = 166 (74 exposed)	Between birth and 5 days	46.40%	NNNS	Birth weight; SES; and 3-level alcohol, tobacco, marijuana use (Heavy/Some/No Use); assessment > 5 days postpartum; first born; and study site	Multivariate linear regression	8

LaGasse et al. (2011)	Case-control study – USA and NZ	US and NZ cohorts Exposed group: PME mother-infant dyads  Control group: mother-infant dyads not exposed to MA during pregnancy (exposed to other drug combinations during pregnancy, excluding PCP, cocaine, LSD, opiates and hallucinogens)	Substance Use Inventory (self-report maternal exposure) and positive meconium screening confirmed by positive GC/MS.	US: $n = 379$ (183 exposed) NZ: $n = 180$ (85 exposed)  $N = 559$ (268 exposed)	Between birth and 5 days	US: 46.7% NZ: 48%	NNNS	Birth weight; SES; prenatal alcohol, tobacco and marijuana use; and first born.	Multivariate linear regression	8
Piper et al. (2011)	Case-control USA	PME mother-infant dyads and Nonexposed control group	Medical records	$N = 66$ (31 exposed)	Between 7 and 9 years	48.10%	BRIEF  Connors K-CPT	ADHD diagnosis; prenatal alcohol, nicotine or marijuana use	ANOVA and t tests	6

Derauf et al. (2012)	Case-control IDEAL study - USA	Exposed group: PME mother-infant dyads (excluding alcohol)  Control group: Prenatal tobacco exposed (PTE) mother-infant dyads not exposed to MA during pregnancy (exposed to other drug combinations during pregnancy, excluding alcohol, PCP, cocaine, LSD, opiates and hallucinogens)	Substance Use Inventory (self-report maternal exposure) and positive meconium screening confirmed by positive GC/MS.	<i>N</i> = 35 (20 exposed)	3 years	46%	CBCL  Connors K-CPT	No covariates adjusted for	Multivariate linear regression	6
LaGasse et al. (2012)	Prospective longitudinal study IDEAL study - USA	Exposed group: PME mother-infant dyads  Control group: mother-infant dyads not exposed to MA during pregnancy (exposed to other drug combinations during pregnancy, excluding PCP, cocaine, LSD, opiates and hallucinogens)	Substance Use Inventory (self-report maternal exposure) and positive meconium screening confirmed by positive GC/MS.	<i>N</i> = 330 (166 exposed)	3 years and 5 years	48.50%	CBCL	Sex; prenatal tobacco, alcohol and marijuana exposures; low SES; birth weight; maternal age; primary caregiver change; DV; postnatal caregiver use of MA, alcohol, tobacco and marijuana; caregiver psychological symptoms; quality of home and reported child abuse	Multivariate linear regression	8

Abar et al. (2013)	Prospective longitudinal study  IDEAL Study - USA	Exposed group: PME mother-infant dyads  Control group: mother-infant dyads not exposed to MA during pregnancy (exposed to other drug combinations during pregnancy, excluding PCP, cocaine, LSD, opiates and hallucinogens)	Substance Use Inventory (self-report maternal exposure) and positive meconium screening confirmed by positive GC/MS.	<i>N</i> = 320 (162 exposed) at 5 years  <i>N</i> = 290 (unclear number of exposed) at 6.5 years	5 years and 6.5 years	48%	CBCL	Sex; gestational age at birth; head circumference at birth; maternal age at birth and maternal quantity of self-reported use of tobacco, alcohol and marijuana while pregnant.	Mediation	6
Galland et al. (2013)	Case-control  IDEAL study - NZ	Exposed group: PME mother-infant dyads  Control group: mother-infant dyads not exposed to MA during pregnancy (exposed to other drug combinations during pregnancy, excluding PCP, cocaine, LSD, opiates and hallucinogens)	Substance Use Inventory (self-report maternal exposure) and positive meconium screening confirmed by positive GC/MS.	<i>N</i> = 99 (42 exposed)	3 months old	Not reported	Arousal thresholds measured by EEG recordings	Other substance use (alcohol, marijuana and tobacco).	Intraclass correlations	7

Kiblawi et al. (2013)	Case-control IDEAL study - USA	Exposed group: PME mother-infant dyads  Control group: mother-infant dyads not exposed to MA during pregnancy (exposed to other drug combinations during pregnancy, excluding PCP, cocaine, LSD, opiates and hallucinogens)	Substance Use Inventory (self-report maternal exposure) and positive meconium screening confirmed by positive GC/MS.	<i>N</i> = 301 (153 exposed)	5.5 years	48.50%	Connors K-CPT	Prenatal exposure to alcohol, tobacco, and marijuana; child's age at assessment; gender; caregiver IQ, caretaker change, caregiver depressive symptoms, maternal education, partner status, postnatal use of tobacco, alcohol and marijuana, HOME score, SES and study site.	Hierarchical linear regression model and logistic regression	9
Kirlic et al. (2013)	Cross-sectional IDEAL study - USA	Exposed group: PME mother-infant dyads  No control group	Substance Use Inventory (self-report maternal exposure) and positive meconium screening confirmed by positive GC/MS.	<i>N</i> = 123 (123 exposed)	2 years	44.70%	Cortisol stress reactivity measured by saliva	Child's sex; birth weight; time since last meal; baseline saliva collection time; baseline saliva collection emotional state; behavioural dysregulation and measures of potential stress (caregiver's postnatal MA, alcohol, marijuana or alcohol use, psychopathology and potential for physical abuse).	Hierarchical linear regression model	8/10

Twomey et al. (2013)	Case-control IDEAL study - USA	Exposed group: PME mother-infant dyads  Control group: mother-infant dyads not exposed to MA during pregnancy (exposed to other drug combinations during pregnancy, excluding PCP, cocaine, LSD, opiates and hallucinogens)	Substance Use Inventory (self-report maternal exposure) and positive meconium screening confirmed by positive GC/MS.	<i>N</i> = 214 (97 exposed)	5 years	48.20%	CBCL	Study site; primary caregiver's age; partner status (partnered vs. not); medical insurance status (public vs. other); education (<high school vs. other); prenatal exposure of the following drugs (yes vs. no): tobacco, alcohol, marijuana, cocaine, or MA; low child birthweight (<2500 g); and child gender; and at 36 months, PC experience of physical abuse; CPS involvement; and use of tobacco, alcohol, or illicit drugs; quality of the child's home environment; parenting stress, and psychological symptom assessments.	Multivariate logistic regression	8
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Diaz et al. (2014)	Case-control IDEAL study - USA	Exposed group: PME mother-infant dyads  Control group: mother-infant dyads not exposed to MA during pregnancy (exposed to other drug combinations during pregnancy, excluding PCP, cocaine, LSD, opiates and hallucinogens)	Substance Use Inventory (self-report maternal exposure) and positive meconium screening confirmed by positive GC/MS.	<i>N</i> = 298 (151 exposed)	7.5 years	53%	CPRS-R:S	Prenatal exposure to alcohol, tobacco, and marijuana; prematurity; sex; single (no partner); postnatal use of tobacco, alcohol and marijuana; caregiver psychological symptoms; quality of the home; PPVT; age at assessment; average SES and study site.	Multivariate regression (linear and logistic regression)	8
van Dyk et al. (2014)	Case-control South Africa	Prenatal methamphetamine exposed (PME) mother-infant dyads and  Control group: non-MA exposed mother-infant infants (exposed only to alcohol and/or nicotine. Other illicit drugs excluded)	Self-report maternal exposure obtained by NICU admission logs or records of referrals to a social worker	<i>N</i> = 36 (15 exposed)	Between 2 and 4 years	36.11%	CBCL	No covariates adjusted for	T-tests	5

Himes et al. (2014)	Case-control IDEAL study - USA	Exposed group: PME mother-infant dyads  Control group: mother-infant dyads not exposed to MA during pregnancy (exposed to other drug combinations during pregnancy, excluding PCP, cocaine, LSD, opiates and hallucinogens)	Prenatal MA exposure: Substance Use Inventory (self-report maternal exposure) and positive meconium screening confirmed by positive GC/MS.  Postnatal MA exposure: Positive hair toxicology results.	<i>N</i> = 264 (133 exposed)	Between 6.5 and 7.5 years (unclear)	51.90%	CBCL  CPRS-R	Study site; IQ; low birth weight (<2500g); prenatal care; child sex; prenatal tobacco, alcohol and marijuana exposures; caregiver SES; maternal BSI responses averaged through 3 years; physical abuse; DV and neighbourhood violence through 6.5 years	Hierarchical linear regression model	8
Kiblawi et al. (2014)	Prospective longitudinal study IDEAL study - USA	Exposed group: PME mother-infant dyads  Control group: mother-infant dyads not exposed to MA during pregnancy (exposed to other drug combinations during pregnancy, excluding PCP, cocaine, LSD, opiates and hallucinogens)	Substance Use Inventory (self-report maternal exposure) and positive meconium screening confirmed by positive GC/MS.	<i>N</i> = 380 (185 exposed)	Birth and 1 month	47%	NNNS	Birth weight, first born, SES, heavy prenatal tobacco, alcohol and marijuana exposures, and study site	Mixed model ANOVA	9



Eze et al. (2016)	Case-control IDEAL study - USA	Exposed group: PME mother-infant dyads  Control group: mother-infant dyads not exposed to MA during pregnancy (exposed to other drug combinations during pregnancy, excluding PCP, cocaine, LSD, opiates and hallucinogens)	Substance Use Inventory (self-report maternal exposure) and positive meconium screening confirmed by positive GC/MS.	<i>N</i> = 290 (146 exposed)	7.5 years	47.20%	CBCL	Sex, prenatal tobacco, alcohol and marijuana exposures, and study site	Mediation (PROCESS macro) and multivariate linear regression	9
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*Note.* IDEAL = Infant Development, Environment and Lifestyle, PME = prenatal methamphetamine exposure, PCP = phencyclidine, LSD = Lysergic acid diethylamide, GC/MS = gas chromatography-mass spectrometry, NNNs = NICU Neonatal Neurobehavioural Scale, BRIEF = Behavioural Regulation Inventory of Executive Function, Connors K-CPT = Connors Kiddie Continuous Performance Test, ADHD = Attention Deficit/Hyperactivity Disorder, ANOVA = Analysis of Variance, PTE = prenatal tobacco exposure, EEG = electroencephalogram, CPS = Child Protective Services, CPRS-R:S = Revised Connors Parent Rating Scale

## Neurobehavioural Outcomes

### **Neonate neurobehavioural dysfunction.**

*The NICU Neonatal Neurobehavioural Scale.* In a sample of 166 mothers recruited from the U.S. and in another sample of 559 mothers recruited from the U.S. ( $N = 379$ ) and New Zealand ( $N = 180$ ), Smith et al. (2008) and LaGasse et al. (2011) assessed neonatal outcomes between birth and 5 days. Smith et al. (2008) found PME to be associated with greater physiological stress in neonates (Cohen's  $d = .21$ ). LaGasse et al. (2011) reported that neonates with PME exhibited poorer quality of movement (Cohen's  $d = .31$ ), greater total stress abstinence (Cohen's  $d = .18$ ), greater physiological stress (Cohen's  $d = .23$ ) and greater CNS stress (Cohen's  $d = .12$ ). In a sample of 380 mothers recruited from the U.S., Kiblawi et al. (2014) assessed neurobehavioural outcomes in neonates between birth and one month. They did not report any significant differences between MA-exposed and comparison neonates solely based on exposure status (Cohen's  $d$ 's  $\leq .32$ ). However, for MA-exposed neonates, they reported a significant increase in arousal levels (Cohen's  $d = .27$ ) and an overall decrease in stress levels (Cohen's  $d = .40$ ) in MA-exposed neonates between birth and one month. Therefore, infants with PME were less drowsy and stressed by one month of age.

### **Infant and child neurobehavioural dysfunction.**

*Endocrine measures of stress reactivity.* Galland et al. (2013) used EEG recordings to assess sleep arousal thresholds in a sample of 99 three-month-old infants. They reported no significant differences in arousal thresholds between MA-exposed infants and the comparison groups. These results indicated that PME was not associated with adverse neurobehavioural outcomes in relation to sleep-wakefulness patterns in infants aged three months old. However, as effect sizes could not be calculated these results were interpreted with caution. Kirlic and colleagues (2013) assessed cortisol reactivity using saliva samples in

123 MA-exposed children aged two years. They found that PME predicted increased cortisol reactivity, therefore higher stress levels, after a stress inducing situation (Cohen's  $d = .30$ ). However, as this study does not have a comparison group, these findings do not delineate differences in cortisol reactivity between children with PME and healthy controls. Therefore, the interpretation of these findings was limited.

***The Child Behaviour Checklist.*** Seven articles used the CBCL as their primary outcome measure of behaviour to detect emotional and/or behavioural problems in their samples. Five of the seven articles reported an effect of PME on child behavioural outcomes. van Dyk et al. (2014) assessed 36 South African children aged between two and four years. They reported that MA-exposed children exhibited elevated t-scores on the internalising behaviour (Cohen's  $d = .19$ ) and externalising behaviour (Cohen's  $d = .53$ ) problem scales. Although, these scores were not significantly different in comparison to the control group. The small effect size and insignificant  $p$  value suggests that there was no real effect of PME on internalising behaviours; however, for externalising behaviours, the medium effect size suggests that there was a difference between groups with and without PME. The study may not have been sufficiently powered to detect this effect given the small sample size.

In the U.S. sample of children with PME, Derauf and colleagues (2012) assessed a sample of 35 children at three years and reported no statistically significant differences in CBCL internalising (Cohen's  $d = .34$ ), externalising (Cohen's  $d = .12$ ) or total problem (Cohen's  $d = .10$ ) scores between groups. Once again, given the small sample size of this study, it is possible that a difference could not be detected due to a lack of power. Twomey et al. (2013) assessed 214 children aged 5 years and found significant associations between PME and externalising behaviours (Cohen's  $d = .48$ ), reporting MA-exposed children were more than twice as likely to exceed the clinical cut-off for externalising behaviour problems than comparison children. There were no statistically significant differences between

internalising (Cohen's  $d = .11$ ) and total behaviour problem scores (Cohen's  $d = .06$ ) between the exposed and non-exposed groups. LaGasse and colleagues (2012) assessed a sample of 330 children between three and five years old. They found that PME was associated with increased anxious/depressed problems (age 3: Cohen's  $d = .18$ ; age 5: Cohen's  $d = .15$ ) and increased emotional reactivity (age 3: Cohen's  $d = .18$ ; age 5: Cohen's  $d = .14$ ) across ages three and five. In addition, PME was associated with greater externalising problems (Cohen's  $d = .13$ ) and ADHD problems (Cohen's  $d = .12$ ) at age 5 but not age three (Cohen's  $d$ 's  $\leq .04$ ). They found no other significant differences between groups of children with and without PME across ages (Cohen's  $d$ 's  $\leq .14$ ).

In a sample of 320 children, Abar et al. (2013) reported increased emotional reactivity (Cohen's  $d = .26$ ), anxious/depressed problems (Cohen's  $d = .27$ ) and aggression (Cohen's  $d = .27$ ) in children with PME at 5 years of age. On the withdrawn, sleep problems and somatic complaints subscales, they did not report significant differences based on MA exposure (Cohen's  $d$ 's  $\leq .12$ ). However, the effects of PME on behavioural and emotional control problems and later executive function deficits were mediated by early adversity; therefore, PME was indirectly associated with these outcomes. In a sample of 290 children aged 7.5 years, Eze and colleagues (2016) found PME to be significantly associated with increased externalising (Cohen's  $d = .26$ ), rule-breaking (Cohen's  $d = .30$ ) and aggressive behaviour (Cohen's  $d = .30$ ). They did not report significant differences between children on internalising (Cohen's  $d = .16$ ) and total problems (Cohen's  $d = .15$ ) scales. Mediation analysis highlighted that the relation between PME and behavioural problems was significantly mediated by early adversity, therefore, demonstrating that early adversity was a greater predictor of behavioural problems in children at 7.5 years.

Himes and colleagues (2014) assessed the impacts of PME on children aged 6.5 and 7.5 years. They found that PME predicted child neurobehavioural disinhibition as measured

by their total scores on the Child Memory Scale, CBCL and CPRS-R combined. They also assessed whether postnatal MA-exposure would significantly predict behavioural problems in children. They found that postnatal MA-exposure alone did not significantly predict neurobehavioural disinhibition, therefore highlighting the particular contribution of PME on later behavioural difficulties. Individual scores relating to their measure of neurobehavioural disinhibition were not reported, which meant that effects sizes could not be calculated. Therefore, the interpretation of these results in relation to behavioural dysfunction, as defined by the current review, was limited.

***Connors Kiddie Continuous Performance Test.*** Derauf and colleagues (2012) also reported that children with PME had poorer scores on the K-CPT, indicating that they had greater difficulty with sustained attention (Cohen's  $d = .70$ ) and adjusting to changing task demands (Cohen's  $d = 1.21$ ). In a sample of 301 children aged 5.5 years, Kiblawi et al. (2013) found children with PME had an increased risk of developing ADHD than children without PME (Cohen's  $d = .60$ ). They also found that children with PME were more likely to exhibit difficulties with sustained attention and less consistent reaction times; however, effect sizes could not be calculated based on the data reported in the paper, thus, results were interpreted with caution. Piper and colleagues (2011) assessed a sample of 66 children between seven and nine years. They found no significant difference between groups based on MA exposure, therefore, indicating that that PME had no effect on vigilance, impulsivity or inattentiveness as measured by the K-CPT.

***Behaviour Rating Inventory of Executive Function.*** Furthermore, when comparing parental ratings of executive function between children with and without PME, there was a significant difference between ratings on the behavioural regulation scale (Piper et al., 2011). Results indicated that children with PME have difficulty with impulse control, therefore the ability to stop their behaviour at an appropriate time. There were no differences between

groups in their ability to regulate their emotional responses and shift between activities and places without difficulty. However, Cohen's  $d$  effect sizes were unable to be calculated based on the data reported in the Piper et al. (2011) paper, and so the results were interpreted with caution.

***Connors Parent Report Scale.*** In a sample of 298 children, Diaz and colleagues (2014) found that prenatal methamphetamine exposure was not associated with oppositional behaviours (Cohen's  $d = .19$ ), hyperactivity (Cohen's  $d = .26$ ) and ADHD problems (Cohen's  $d = .22$ ) in children aged 7.5 years.

### **Discussion**

The data suggest that PME has an impact on infant and child behavioural outcomes. More specifically, the results indicate that children with PME display more pronounced behavioural difficulties as they age, in comparison to children without PME. To place the current findings in context, it is valuable to compare the results to reviews investigating the effects of prenatal cocaine exposure on neurobehaviour in infants and children, which is thought to have a similar neurochemical action on brain development (Salisbury et al., 2009).

In neonates, neurobehavioural dysfunction five days after birth, in the form of under arousal, poor quality of movement and increased stress levels, was consistent with findings from cocaine-exposed neonates (Lester et al., 2002). However, in cocaine-exposed neonates, these neurobehavioural deficits persisted up to one month after birth, variable with our results. Findings from this review were also consistent with a review of 42 studies on prenatal cocaine exposure by Lester and LaGasse (2010) whereby adverse effects of PME were not observable until age five. These findings may be attributed to a latent or "sleeping" teratogenic effect (Mayes & Ward, 2003) given that the effects of PME were subtler in earlier years of infancy and became more pronounced later in the child's development (Lewis,

Galbally, Gannon, & Symeonides, 2014). Difficulties with internalising behaviours were inconsistently reported and with small effect sizes. As such, we cannot confidently propose that PME has an impact on internalising behaviours (e.g. anxiety, depression, social withdrawal).

It is possible that PME adversely impacted on behavioural outcomes in children under five years of age, however, this conclusion could not be drawn based on the current evidence. Both Derauf et al. (2012) and van Dyk et al. (2014) had small sample sizes ( $N$ 's  $\leq 35$ ) and possibly lacked power to detect differences between groups with and without PME. Overall, the majority of the effect sizes were within the small to medium range of Cohen's  $d$  cut off scores. While most of the effects were small, it is important to consider the clinical significance of these effects in the context of a child's life. For example, externalising behavioural problems are indicative of deficits in executive function, self-regulation and social relationships (Twomey et al., 2013), which can have serious implications for children and their families as they are exposed to school settings, where social, behavioural and academic demands increase (Shonkoff & Phillips, 2000).

The concept of fetal programming may provide an explanation for the effects of PME on child behavioural outcomes. Fetal programming refers to way in which a specific environmental factor modifies fetal developmental trajectories, resulting in persistent changes in the structure and function of biological systems. These changes create enduring effects which may elicit certain responses to environmental stimuli later in development (Gluckman & Hanson, 2006; Lewis et al., 2014). Preliminary evidence suggests that PME is associated with increased stress reactivity (Kirlic et al., 2013), which supports the hypothesis by Salisbury and colleagues (2009) that MA exposure relates to changes in hypothalamic-pituitary-adrenal (HPA) system programming. The HPA-axis is imperative not only for stress regulation, but also for emotions and emotion-regulation (Lupien, McEwen, Gunnar, &

Heim, 2009). Lewis and colleagues highlight that dysregulation in the stress response is a common feature of emotional and behavioural difficulties in childhood. As such, it is reasonable to suggest that MA exposure *in utero* may impact on HPA-axis programming, resulting in behavioural dysregulation in neonates and children. It is also important to note that early adversity and the postnatal environment impact of the expression of behavioural difficulties (Lester et al., 2009). A model proposed by Lester et al. (2009) outlines the cumulative effects of the prenatal and postnatal environment, and the subsequent implications for behavioural dysregulation in children prenatally exposed to MA.

### **Limitations and Directions for Future Research**

It is important to highlight some of the limitations of the articles examined in the current review. First, 13 of the 15 articles were a part of the IDEAL study. Therefore, these inferences may not be generalisable to the wider population of women who use MA during pregnancy, given that the majority of findings were derived from the same, select cohort. Second, the main outcome measures used to quantify methamphetamine use across pregnancy and assess behavioural outcomes in infants and children (e.g. the CBCL, the BRIEF and the CPRS) were based on self-report and are less reliable than structured interviews by trained professionals, which may introduce reporting bias (Althubaiti, 2016). Third, 11 of the 15 studies were of a case-control design. This design limits the ability to determine the temporal association between PME and behavioural outcomes, and the causal relationship between the two (Song & Chung, 2010). Therefore, future research would benefit from conducting more longitudinal studies to understand the behavioural trajectories of children with PME (Shonkoff & Phillips, 2000), and allow for more accurate assessment of causality between PME and behavioural outcomes.



Furthermore, limitations of this review must be noted, and the findings considered in the light of these limitations. This review was restricted by the bias introduced by having a single reviewer conduct the search protocol and data extraction. Another restriction was the scope of the study; it is possible that the narrow scope may have excluded potentially relevant papers to contribute a broader understanding of this area of research. Furthermore, this review did not delineate findings based on the timing of MA use across gestation and dose-related effects. This is an important outcome to understand and should be investigated in future research. Given these limitations, which were predominately based on the scope of the review, it is recommended that a meta-analysis is conducted to examine the neurodevelopmental implications of PME on fetal development as a whole. This would provide this area of research with a more in-depth interpretation of the overall effects of PME on fetal and child development.

### **Implications for Health Professionals, Policy Makers and Parents**

In conclusion, this review has found consistent reports of behavioural dysregulation in children prenatally exposed to MA *in utero*, in the form of externalising behaviours and ADHD type difficulties. These highlight the need for increased efforts to prevent maternal use of MA during pregnancy as well as the importance of early identification and prevention of behavioural dysregulation in children with PME. In light of these results, it may be possible to detect children at risk of later developing dysfunctional behavioural patterns as early as in the neonatal period (Lester et al., 2009). Further, if early markers are not identified in neonates, more perceptible behavioural problems (i.e. externalising and ADHD behaviours) may alert caregivers to the fact that their child is experiencing difficulties. It is crucial to implement policies and practices which provide postnatal service provision for

caregivers of children with PME, so they have to ability to support and promote a more adaptive developmental trajectory for their child.

## References

- Abar, B., LaGasse, L. L., Derauf, C., Newman, E., Shah, R., Smith, L. M., ... Lester, B. M. (2013). Examining the relationships between prenatal methamphetamine exposure, early adversity, and child neurobehavioral disinhibition. *Psychology of Addictive Behaviors, 27*(3), 662–673. doi: 10.1037/a0030157
- Althubaiti, A. (2016). Information bias in health research: Definition, pitfalls, and adjustment methods. *Journal of Multidisciplinary Healthcare, 9*, 211–217. doi: 10.2147/JMDH.S104807
- Barr, A. M., Panenka, W. J., MacEwan, G. W., Thornton, A. E., Lang, D. J., Honer, W. G., & Lecomte, T. (2006). The need for speed: An update on methamphetamine addiction. *Journal of Psychiatry and Neuroscience, 31*(5), 301–313. Retrieved from <https://psycnet.apa.org/record/2007-03390-002>
- Breslau, J., Lane, M., Sampson, N., & Kessler, R. C. (2008). Mental Disorders and Subsequent Educational Attainment in a US National Sample. *Journal of Psychiatric Research, 42*(9), 708–716. doi: 10.1016/j.jpsychires.2008.01.016
- Brown, J. A., & Hohman, M. (2006). The Impact of Methamphetamine Use on Parenting. *Journal of Social Work Practice in the Addictions, 6*(1–2), 63–88. doi: 10.1300/J160v06n01\_04
- Burchfield, D. J., Lucas, V. W., Abrams, R. M., Miller, R. L., & DeVane, C. L. (1991). Disposition and Pharmacodynamics of Methamphetamine in Pregnant Sheep. *JAMA, 265*(15), 1968–1973. doi: 10.1001/jama.1991.03460150072026
- Chang, L., Cloak, C., Patterson, K., Grob, C., Miller, E. N., & Ernst, T. (2005). Enlarged striatum in abstinent methamphetamine abusers: A possible compensatory response. *Biological Psychiatry, 57*(9), 967–974. doi: 10.1016/j.biopsych.2005.01.039

- Chang, L., Smith, L. M., LoPresti, C., Yonekura, M. L., Kuo, J., Walot, I., & Ernst, T. (2004). Smaller subcortical volumes and cognitive deficits in children with prenatal methamphetamine exposure. *Psychiatry Research, 132*(2), 95–106. doi: 10.1016/j.psychresns.2004.06.004
- Cho, A. K., & Melega, W. P. (2002). Patterns of methamphetamine abuse and their consequences. *Journal of Addictive Diseases, 21*(1), 21–34. doi: 10.1300/J069v21n01\_03
- Courtney, K. E., & Ray, L. A. (2014). Methamphetamine: An update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. *Drug and Alcohol Dependence, 143*, 11–21. doi: 10.1016/j.drugalcdep.2014.08.003
- Cruickshank, C. C., & Dyer, K. R. (2009). A review of the clinical pharmacology of methamphetamine. *Addiction, 104*(7), 1085–1099. doi: 10.1111/j.1360-0443.2009.02564.x
- Derauf, C., LaGasse, L. L., Smith, L. M., Newman, E., Shah, R., Neal, C., ... Lester, B. M. (2012). Prenatal Methamphetamine Exposure and Inhibitory Control among Young School-Age Children. *The Journal of Pediatrics, 161*(3), 452–459. doi: 10.1016/j.jpeds.2012.02.002
- Derauf, C., Lester, B. M., Neyzi, N., Kekatpure, M., Gracia, L., Davis, J., ... Kosofsky, B. (2012). Subcortical and Cortical Structural Central Nervous System Changes and Attention Processing Deficits in Preschool-Aged Children with Prenatal Methamphetamine and Tobacco Exposure. *Developmental Neuroscience, 34*(4), 327–341. doi: 10.1159/000341119
- Dowling, C., & Morgan, A. (2018). Is methamphetamine use associated with domestic violence? Retrieved from <https://aic.gov.au/publications/tandi/tandi563>

- Erinoff, L. (1995). General considerations in assessing neurotoxicity using neuroanatomical methods. *Neurochemistry International*, 26(2), 111–114. doi: 10.1016/0197-0186(94)00105-4
- Ernst, T., Chang, L., Leonido–Yee, M., & Speck, O. (2000). Evidence for long-term neurotoxicity associated with methamphetamine abuse: A 1H MRS study. *Neurology*, 54(6), 1344-1349. doi: 10.1212/wnl.54.6.1344
- Eze, N., Smith, L. M., LaGasse, L. L., Derauf, C., Newman, E., Arria, A., ... Lester, B. M. (2016). School-Aged Outcomes following Prenatal Methamphetamine Exposure: 7.5-Year Follow-Up from the Infant Development, Environment, and Lifestyle Study. *The Journal of Pediatrics*, 170, 34-38.e1. doi: 10.1016/j.jpeds.2015.11.070
- Frost, D. (2000). Effects of methamphetamine-induced neurotoxicity on the development of neural circuitry: A hypothesis. *Brain Research Reviews*, 34(3), 103–118. doi: 10.1016/S0165-0173(00)00042-4
- Galland, B. C., Mitchell, E. A., Thompson, J. M. D., & Woulides, T. (2013). Auditory evoked arousal responses of 3-month-old infants exposed to methamphetamine in utero: A nap study. *Acta Paediatrica, International Journal of Paediatrics*, 102(4), 424–430. doi: 10.1111/apa.12136
- Garcia-Bournissen, F., Rokach, B., Karaskov, T., & Koren, G. (2007). Cocaine detection in maternal and neonatal hair: Implications to fetal toxicology. *Therapeutic Drug Monitoring*, 29(1), 71–76. doi: 10.1097/ftd.0b013e3180310ddd
- Gluckman, P., & Hanson, M. A. (2006). *Developmental Origins of Health and Disease: The developmental origins of health and disease: an overview*. doi: 10.1017/cbo9780511544699.002

- Joya, X., Pacifici, R., Salat-Batlle, J., Garcíá-Algar, O., & Pichini, S. (2015). Maternal and neonatal hair and breast milk in the assessment of perinatal exposure to drugs of abuse. *Bioanalysis*, 7(10), 1273–1297. doi: 10.4155/bio.15.60
- Kiblawi, Zeina N., Smith, L. M., LaGasse, L. L., Derauf, C., Newman, E., Shah, R., ... Lester, B. (2013). The Effect of Prenatal Methamphetamine Exposure on Attention as Assessed by Continuous Performance Tests: Results from the Infant Development, Environment, and Lifestyle (IDEAL) Study. *Journal of Developmental and Behavioral Pediatrics*, 34(1), 31–37. doi: 10.1097/DBP.0b013e318277a1c5
- Kiblawi, Z.N., Smith, L. M., Diaz, S. D., LaGasse, L. L., Derauf, C., Newman, E., ... Lester, B. (2014). Prenatal methamphetamine exposure and neonatal and infant neurobehavioral outcome: Results from the IDEAL study. *Substance Abuse*, 35(1), 68–73. doi: 10.1080/08897077.2013.814614
- Kirlic, N., Newman, E., [Link to external site, this link will open in a new window](#), LaGasse, L. L., Derauf, C., Shah, R., ... Lester, B. M. (2013). Cortisol reactivity in two-year-old children prenatally exposed to methamphetamine. *Journal of Studies on Alcohol and Drugs*, 74(3), 447–451. doi: 10.15288/jsad.2013.74.447
- LaGasse, L. L., Derauf, C., Smith, L. M., Newman, E., Shah, R., Neal, C., ... Lester, B. M. (2012). Prenatal methamphetamine exposure and childhood behavior problems at 3 and 5 years of age. *Pediatrics*, 129(4), 681–688. doi: 10.1542/peds.2011-2209
- LaGasse, L. L., Woules, T., Newman, E., Smith, L. M., Shah, R. Z., Derauf, C., ... Lester, B. M. (2011). Prenatal methamphetamine exposure and neonatal neurobehavioral outcome in the USA and New Zealand. *Neurotoxicology and Teratology*, 33(1), 166–175. doi: 10.1016/j.ntt.2010.06.009
- Lester, B. M., & Lagasse, L. L. (2010). Children of addicted women. *Journal of Addictive Diseases*, 29(2), 259–276. doi: 10.1080/10550881003684921

- Lester, B. M., Tronick, E. Z., LaGasse, L., Seifer, R., Bauer, C. R., Shankaran, S., ... Maza, P. L. (2002). The maternal lifestyle study: Effects of substance exposure during pregnancy on neurodevelopmental outcome in 1-month-old infants. *Pediatrics*, *110*(6), 1182–1192. doi: 10.1542/peds.110.6.1182
- Lester, B. M., Bagner, D. M., Liu, J., LaGasse, L. L., Seifer, R., Bauer, C. R., ... Das, A. (2009). Infant neurobehavioral dysregulation: Behavior problems in children with prenatal substance exposure. *Pediatrics*, *124*(5), 1355–1362. doi: 10.1542/peds.2008-2898
- Lewis, A. J., Galbally, M., Gannon, T., & Symeonides, C. (2014). Early life programming as a target for prevention of child and adolescent mental disorders. *BMC Medicine*, *12*(1), 33. doi: 10.1186/1741-7015-12-33
- Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews. Neuroscience*, *10*(6), 434–445. doi: 10.1038/nrn2639
- Mayes, L. C., & Ward, A. (2003). *Principles of Neurobehavioral Teratology*. Cambridge University Press.
- Meredith, C. W., Jaffe, C., Ang-Lee, K., & Saxon, A. J. (2005). Implications of chronic methamphetamine use: A literature review. *Harvard Review of Psychiatry*, *13*(3), 141–154. doi: 10.1080/10673220591003605
- Miller, D. B., & O’Callaghan, J. P. (2003). Elevated environmental temperature and methamphetamine neurotoxicity. *Environmental Research*, *92*(1), 48–53. doi: 10.1016/s0013-9351(02)00051-8
- Murray, J. B. (1998). Psychophysiological Aspects of Amphetamine-Methamphetamine Abuse. *The Journal of Psychology*, *132*(2), 227–237. doi: 10.1080/00223989809599162

Neurodevelopment [Def. 1]. (n.d.). In *Merriam Webster Online*, Retrieved from

<https://www.merriam-webster.com/medical/neurodevelopment>.

Nguyen, D., Smith, L. M., Lagasse, L. L., Derauf, C., Grant, P., Shah, R., ... Lester, B. M.

(2010). Intrauterine growth of infants exposed to prenatal methamphetamine: Results from the infant development, environment, and lifestyle study. *The Journal of Pediatrics*, *157*(2), 337–339. doi: 10.1016/j.jpeds.2010.04.024

Piper, B. J., Acevedo, S. F., Kolchugina, G. K., Butler, R. W., Corbett, S. M., Honeycutt, E.

B., ... Raber, J. (2011). Abnormalities in parentally rated executive function in methamphetamine/polysubstance exposed children. *Pharmacology, Biochemistry and Behavior*, *98*(3), 432–439. doi: 10.1016/j.pbb.2011.02.013

Salisbury, A. L., Ponder, K. L., Padbury, J. F., & Lester, B. M. (2009). Fetal Effects of

Psychoactive Drugs. *Clinics in Perinatology*, *36*(3), 595–619. doi: 10.1016/j.clp.2009.06.002

Shonkoff, J., & Phillips, D. (2000). *From neurons to neighborhoods the science of early child development*. Retrieved from

<http://www.vlebooks.com/vleweb/product/openreader?id=none&isbn=9780309504881>

Smith, L. M., LaGasse, L. L., Derauf, C., Grant, P., Shah, R., Arria, A., ... Lester, B. M.

(2008). Prenatal Methamphetamine Use and Neonatal Neurobehavioral Outcome. *Neurotoxicology and Teratology*, *30*(1), 20–28. doi: 10.1016/j.ntt.2007.09.005

Smith, L. M., LaGasse, L. L., Derauf, C., Newman, E., Shah, R., Haning, W., ... Lester, B.

M. (2011). Motor and cognitive outcomes through three years of age in children exposed to prenatal methamphetamine. *Neurotoxicology and Teratology*, *33*(1), 176–184. doi: 10.1016/j.ntt.2010.10.004



- Song, J. W., & Chung, K. C. (2010). Observational Studies: Cohort and Case-Control Studies. *Plastic and Reconstructive Surgery*, *126*(6), 2234–2242. doi: 10.1097/PRS.0b013e3181f44abc
- Sowell, E. R., Leow, A. D., Bookheimer, S. Y., Smith, L. M., O'Connor, M. J., Kan, E., ... Thompson, P. M. (2010). Differentiating Prenatal Exposure to Methamphetamine and Alcohol versus Alcohol and Not Methamphetamine using Tensor-Based Brain Morphometry and Discriminant Analysis. *Journal of Neuroscience*, *30*(11), 3876–3885. doi: 10.1523/JNEUROSCI.4967-09.2010
- Stek, A. M., Baker, R. S., Fisher, B. K., Lang, U., & Clark, K. E. (1995). Fetal responses to maternal and fetal methamphetamine administration in sheep. *American Journal of Obstetrics and Gynecology*, *173*(5), 1592–1598. doi: 10.1016/0002-9378(95)90654-1
- Stek, A. M., Fisher, B. K., Baker, R. S., Lang, U., Tseng, C. Y., & Clark, K. E. (1993). Maternal and fetal cardiovascular responses to methamphetamine in the pregnant sheep. *American Journal of Obstetrics and Gynecology*, *169*(4), 888–897. doi: 10.1016/0002-9378(93)90022-b
- Tanabe, J., Tregellas, J. R., Thompson, L., Dalwani, M., Owens, E., Crowley, T., & Banich, M. (2009). Medial orbitofrontal cortex gray matter is reduced in abstinent substance dependent individuals. *Biological Psychiatry*, *65*(2), 160–164. doi: 10.1016/j.biopsych.2008.07.030
- Thompson, L. P., Crimmins, S., Telugu, B. P., & Turan, S. (2015, September 15). Intrauterine hypoxia: Clinical consequences and therapeutic perspectives. doi: 10.2147/RRN.S57990
- Thompson, P. M. (2004). Structural Abnormalities in the Brains of Human Subjects Who Use Methamphetamine. *Journal of Neuroscience*, *24*(26), 6028–6036. doi: 10.1523/JNEUROSCI.0713-04.2004

- Twomey, J., LaGasse, L., Derauf, C., Newman, E., Shah, R., Smith, L., ... Lester, B. (2013). Prenatal methamphetamine exposure, home environment, and primary caregiver risk factors predict child behavioral problems at 5 years. *American Journal of Orthopsychiatry*, 83(1), 64–72. doi: 10.1111/ajop.12007
- United Nations Office on Drugs and Crime. (2018). *World drug report 2018*.
- van Dyk, J., Ramanjam, V., Church, P., Koren, G., & Donald, K. (2014). Maternal methamphetamine use in pregnancy and long-term neurodevelopmental and behavioral deficits in children. *Journal of Population Therapeutics and Clinical Pharmacology*, 21(2). Retrieved from <https://jptcp.com/index.php/jptcp/article/view/329>
- Villemagne, V., Yuan, J., Wong, D. F., Dannals, R. F., Hatzidimitriou, G., Mathews, W. B., ... Ricaurte, G. A. (1998). Brain dopamine neurotoxicity in baboons treated with doses of methamphetamine comparable to those recreationally abused by humans: Evidence from [11C]WIN-35,428 positron emission tomography studies and direct in vitro determinations. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 18(1), 419–427. doi: 10.1523/JNEUROSCI.18-01-00419.1998
- Volkow, N. D., Chang, L., Wang, G. J., Fowler, J. S., Leonido-Yee, M., Franceschi, D., ... Miller, E. N. (2001). Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. *The American Journal of Psychiatry*, 158(3), 377–382. doi: 10.1176/appi.ajp.158.3.377
- Warton, F. L., Meintjes, E. M., Warton, C. M. R., Molteno, C. D., Lindinger, N. M., Carter, R. C., ... Jacobson, S. W. (2018). Prenatal methamphetamine exposure is associated with reduced subcortical volumes in neonates. *Neurotoxicology and Teratology*, 65, 51–59. doi: 10.1016/j.ntt.2017.10.005

- Warton, F. L., Taylor, P. A., Warton, C. M., Molteno, C. D., Wintermark, P., Lindinger, N. M., ... Meintjes, E. M. (2018). Prenatal methamphetamine exposure is associated with corticostriatal white matter changes in neonates. *Metabolic Brain Disease, 33*(2), 507–522. doi: 10.1007/s11011-017-0135-9
- Wells, G., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2009). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Retrieved from [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)
- Wilson, J. M., Kalasinsky, K. S., Levey, A. I., Bergeron, C., Reiber, G., Anthony, R. M., ... Kish, S. J. (1996). Striatal dopamine nerve terminal markers in human, chronic methamphetamine users. *Nature Medicine, 2*(6), 699–703. doi: 10.1038/nm0696-699

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