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NICU NETWORK NEUROBEHAVIORAL SCALE TO ASSESS NEURODEVELOPMENT IN INFANTS WITH PRENATAL TOXIC SUBSTANCE OR DRUG EXPOSURE: A SYSTEMATIC REVIEW

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Abstract

This systematic review examines the use of the NICU Network Neurobehavioral Scale (NNNS) in assessing neurodevelopment in infants prenatally exposed to toxic substances or drugs. Thirteen studies (2010-2024) were reviewed, focusing on exposures to air pollution, bisphenol A and phthalates, mercury, metal, pesticides, tobacco, methamphetamine, marijuana, methylenedioxymethamphetamine, and methadone. Sample sizes ranged from 28 to 658 infants, with assessments conducted from birth to 37 days postpartum. Data on exposure was collected via maternal samples, infant meconium and saliva, placenta tissue biopsy, and records such as self-reports during pregnancy, interviews, and medical records. Findings revealed that prenatal exposure to toxic substances showed both detrimental effects and, in some cases, unexpected positive outcomes. In contrast, drug exposure was primarily linked to adverse impacts, including impairments in self-regulation, attention, quality of movement, and stress responses. In conclusion, the NNNS is a valuable tool for assessing neurobehavioral outcomes in infants prenatally exposed to toxic substances and drugs. These findings highlight the importance of early neurodevelopmental assessments to inform timely interventions for at-risk infants.

Keywords: NICU Network Neurobehavioral Scale, Neurodevelopment, Infants, Prenatal Exposure, Drug Exposure

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Introduction

Assessing newborn development has become increasingly crucial as infants face more severe health challenges and require complex care. Neonatal assessments are crucial for detecting instability, providing developmental insights, and guiding interventions for at-risk infants (Sullivan et al., 2012). High-risk infants include those born prematurely, with special healthcare needs, or exposed to environmental or familial risks (DeMauro & Hintz, 2018). Additional risk factors are low birth weight (under 2,500 grams), severe asphyxia, and maternal complications during pregnancy (Blackmon et al., 2004).

Globally, more infants than ever are being exposed to drugs and environmental toxins before birth. The United Nations Office on Drugs and Crime reported a rise in global drug users aged 15 to 64, from 210 million in 2009 to 269 million in 2018. Environmental risk factors contribute to over 25% of the global disease burden among children under five (Neira & Prüss-Ustün, 2016). In 2000, more than 4.7 million children under five died from illnesses linked to unhealthy environments (World Health Organization, 2017). Prenatal exposure to substances such as tobacco, alcohol, and illicit drugs can impair children's neurological development, leading to cognitive and motor delays, poor attention regulation, and an increased risk of behavioral issues in later childhood (Bunney et al., 2017; Salisbury et al., 2007).

Despite these known risks, systematic reviews on the developmental outcomes of at-risk infants, particularly those exposed to prenatal substances, remain limited. While the general risks of prenatal substance exposure have been well-documented, less is understood about how specific substances—such as alcohol, tobacco, and illicit drugs—differ in their impact on neurodevelopmental outcomes. Furthermore, research based on the NICU Network Neurobehavioral Scale (NNNS), a reliable tool for assessing neurological integrity, self-regulation, and behavioral responses in infants, remains scarce. The NNNS has proven effective in identifying infants requiring early intervention (Haffner & Sankovic, 2022; Liu et al., 2010). However, its application in evaluating the impact of different prenatal substance exposures is still underexplored.

This study fills this gap by systematically reviewing the neurodevelopmental outcomes in at-risk infants prenatally exposed to various toxic substances and drugs, as assessed using the NNNS. By examining the developmental effects associated with exposure to different toxic substances and drugs, this study explores how specific substances contribute to developmental delays. The findings will enhance the understanding of substance-specific impacts and inform the development of targeted early intervention strategies for this vulnerable population.

Literature Review

Effects of Toxic Substance Exposure on Infant Neurodevelopment

Prenatal exposure to environmental toxicants plays a significant role in adverse neurodevelopmental outcomes. Historical incidents, such as the Minamata Bay mercury spill in 1950s Japan, have demonstrated the severe neurological consequences of such exposures, including cerebral palsy, intellectual disabilities, and congenital anomalies. Lead exposure at maternal blood concentrations exceeding 10 μg/dL has been associated with preterm birth, low birth weight, and elevated risks of gestational hypertension (Brenna, 2012). Concentrations above 30 μg/dL are linked to even more severe outcomes, including congenital anomalies and spontaneous abortion (Brenna, 2012).

Phthalates, commonly found in plastics and consumer products, are another significant risk factor for neurodevelopmental impairment. Research has shown that prenatal exposure to phthalates can impair executive functions in children, leading to attention problems, hyperactivity, and lower Intelligence Quotient scores (Engel et al., 2010; Zhang et al., 2019). Similarly, prenatal pesticide exposure, particularly organophosphates, is associated with lower cognitive scores, diminished working memory, and impaired verbal comprehension (Bouchard

et al., 2011). These findings underscore the lasting impacts of environmental toxicants on infant neurodevelopment.

Effects of Prenatal Drug Exposure on Infant Neurodevelopment

Prenatal drug exposure presents a considerable risk to infant neurodevelopment. Many substances can cross the placenta and affect the developing fetus, disproving earlier assumptions that the placenta serves as a protective barrier (Narkowicz et al., 2013). As a result, infants exposed to drugs in utero may face a range of adverse outcomes, from immediate withdrawal symptoms at birth to long-term developmental challenges.

For example, methadone exposure during pregnancy is linked to difficulties in attention and learning, while amphetamine exposure increases the risk of preterm birth, low birth weight, and trimmer head circumference (Ladhani et al., 2011; Levine & Woodward, 2018). Newborns exposed to drugs may exhibit withdrawal symptoms, including tremors, excessive crying, poor feeding, and rapid breathing within the first 24-48 hours after birth (Narkowicz et al., 2013).

Prenatal drug exposure can have lasting effects. Infants exposed to cocaine may exhibit attention deficits, impulsivity, and behavioral problems as they age (Bandstra et al., 2010; Noland et al., 2005). Even in the absence of immediate symptoms, the long-term effects of prenatal drug exposure emphasize the importance of early detection and intervention to prevent further developmental challenges.

The NICU Network Neurobehavioral Scale in Assessing At-Risk Infants

The NNNS is a critical assessment tool used to evaluate the neurodevelopment of healthy and at-risk infants, including those born prematurely or exposed to prenatal substances. It applies to infants aged 30-46 weeks corrected age or up to 48 weeks conceptual age (Lester & Tronick, 2004). Developed as an extension of the Neonatal Behavioral Assessment Scale, the NNNS incorporates a rigorous protocol to reduce examiner variability and minimize the influence of the infant's state, ensuring reliable and consistent assessments (Tronick & Lester, 2013).

The NNNS encompasses 13 dimensions that assess various neurological and behavioral domains: orientation, habituation, hypertonicity, hypotonicity, excitability, arousal, lethargy, non-optimal reflexes, asymmetric reflexes, stress, self-regulation, quality of movement, and handling (Lester & Tronick, 2004). These scores provide a comprehensive overview of an infant's neurobehavioral functioning, offering valuable data for clinical decision-making. The NNNS is especially beneficial in the neonatal intensive care unit (NICU) for infants at higher risk of neurodevelopmental challenges (Eeles et al., 2017), helping healthcare providers develop individualized care strategies to optimize developmental outcomes (Conradt et al., 2013; Eeles et al., 2017).

Studies have demonstrated that the NNNS accurately predicts developmental outcomes in key areas, including motor development, language abilities, and behavioral regulation (Spittle et al., 2014; 2017). Its high interrater reliability ensures consistent results across different examiners (Eeles et al., 2017), making it a reliable tool for clinical and research settings.

Research Methodology

Search Strategy and Inclusion Criteria

This systematic review analyzed the use of the NNNS to assess neurodevelopment in infants prenatally exposed to toxic substances or drugs. Using the keyword “NICU Network Neurobehavioral Scale,” a search of full-text articles published between 2010 and 2024 was conducted across Scopus, PubMed, ScienceDirect, Web of Science, Cochrane Library, and Wiley Online Library. The search identified 466 articles (Fig. 1). After removing duplicates, two reviewers independently screened 174 abstracts based on the following criteria.

Inclusion criteria: (1) use of the NNNS to assess neurodevelopment in infants; (2) focus on prenatal exposure to toxic substances or drugs; (3) original research articles; (4) full-text availability; (5) written in English; (6) published between 2010 and 2024.

Exclusion criteria: (1) studies of infants exposed to substances other than toxic substances or drugs; (2) studies reporting fewer than 4 of the 13 neurobehavioral dimensions of the NNNS; (3) studies of infants with maternal illness; (4) studies on the effects of pharmacologic treatment; (5) studies on postnatal exposure.

After screening the full-text articles, 170 were selected for evaluation. Of these, 157 were excluded for the following reasons: irrelevant topic (n = 47); exposure to other substances (n = 22); study of preterm infants (n = 23); NICU study programs (n = 12); study of infants with maternal illness (n = 8); healthy infants (n = 5); infant illness (n = 10); low-risk infants (n = 1); studies of pharmacological treatment effects (n = 13); review papers (n = 10); studies of fewer than 4 dimensions from 13 of the NNNS (n = 2); and postnatal/placental exposure (n = 4). Ultimately, 13 articles met the inclusion criteria. Of these, seven focused on prenatal drug exposure, and 6 examined prenatal toxic substance exposure.

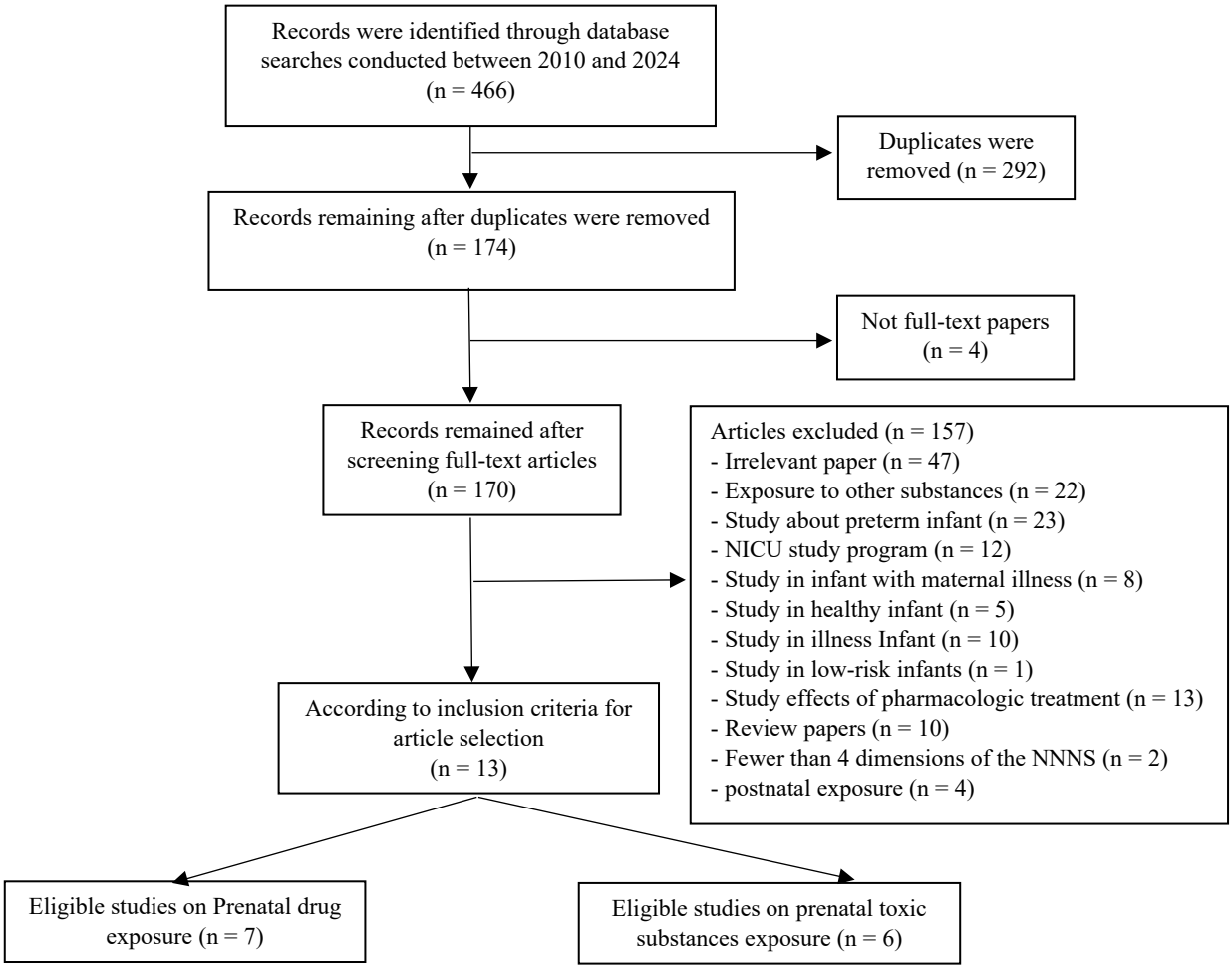

Figure 1 Flowchart of the study selection

Coding Procedure

The 13 selected studies were categorized into two groups based on using the NNNS to assess neurodevelopment in infants with prenatal exposure to different substances: prenatal toxic substances and prenatal drug exposure. Each group's studies were organized by exposure type, study site, subjects, dependent variables, sample size, and age at neurodevelopmental assessment using the NNNS, NNNS scores, and key findings.

Research Findings

Two key areas were identified across the final 13 studies, with the findings summarized below.

The NNNS on Neurodevelopment of Infants with Prenatal Toxic Substance Exposure

Six articles focused on the NNNS to assess the neurodevelopment of infants with prenatal toxic substance exposure, including exposure to intensive air pollution emitted from major roads (n = 1), bisphenol A and phthalates (n = 1), mercury (n = 1), metal mixtures (n = 1), and organophosphate pesticides (n = 2). Most studies were conducted in the United States (n = 5), and one was conducted in Thailand. (See Table 1.)

Table 1 The NNNS and Its Relation to the Neurodevelopment of Infants with Prenatal Toxic Substance Exposure

Author	Prenatal exposure/ Age of assessment	Independent variables	Sample size	Result
Sittiwang et al. (2022)	Prenatal exposure: Organophosphate pesticides/ Age of assessment: 5 weeks	Maternal urine during pregnancy	320	The NNNS Score: Latent profile analysis (profiles 1, 2, and 3) Main Findings: Higher prenatal maternal total dialkylphosphate concentrations were linked to infants with NNNS Profile 1, better self-regulation and attention but lower arousal and excitability scores (OR = 1.47; 95% CI = 1.05-2.06; P = .03).
Tung et al. (2022)	Prenatal exposure: Metal mixtures/ Age of assessment: at 24 hours-72 hours age	Placenta tissue biopsy	192	The NNNS Score: Latent profile analysis (profiles 1, 2, 3,4, and 5) Main Findings: High exposure to metal mixtures was linked to infants with NNNS Profile 5 (OR = 3.23; 95% CI = 0.92-11.36), marked by low self-regulation, high arousal, and hypertonicity, poor movement quality, increased non-optimal reflexes, and heightened stress signs.
Zhang et al. (2020)	Prenatal exposure: Intensive air pollution emitted from major roads/ Age of assessment: 34-37 wk.	Density of vehicle miles traveled	240	The NNNS Score: Summary scores and latent profile analysis (profiles 1, 2, and 3) Main Findings: Hypotonia showed a significant association with vehicle miles traveled (104 vehicle-mile/km^2) at distances of 150 m (β = .01, P < .05), 300 m (β = .01, P < .05), and 500 m (β = .01, P < .05).
Xu et al. (2016)	Prenatal exposure: Mercury/	Whole blood in maternal and cord blood	344	The NNNS Score: Summary scores Main Findings: Infants with higher prenatal mercury exposure

	Age of assessment: 5 weeks			exhibited increased asymmetric reflexes in girls (β = .16, P = .03), a decreased need for special handling during the assessment (β = -.04, P = .03), and a trend toward better attention (β = .17, P = .05).
Yolton et al. (2013)	Prenatal exposure: Organophosphate pesticides/ Age of assessment: 5 weeks	Maternal urine during pregnancy	350	The NNNS Score: Latent profile analysis (profiles 1, 2,3,4 and 5) Main Findings: High maternal urinary levels of diethyl phosphate metabolites were associated with improved attention (β = .07, P < .05), reduced lethargy (β = -.07, P = .04), and decreased hypotonia (β = -.10, P = .03). High maternal urinary levels of dialkylphosphates (DAPs) metabolites were associated with fewer signs of autonomic stress (β = -.01, P = .01).
Yolton et al. (2011)	Prenatal exposure: bisphenol A and phthalates/ Age of assessment: 5 weeks	Maternal urinary during pregnancy	350	The NNNS Score: Summary scores Main Findings: Prenatal exposure to bisphenol A showed no significant relationship with neurobehavioral outcomes. However, higher total di-butyl phthalate levels at 26 weeks of gestation were linked to decreased arousal (β = -.07, P = .04), improved self-regulation (β = .08, P = .05), reduced need for handling (β = -.04, P = .02) and increase in non-optimal reflexes in male infants (β = .22, P = .02).

Note: β = Standardized coefficient, P = Probability value, OR = Odds ratio, CI = Confidence interval

NNNS assessed neurobehavioral development in infants at 24-72 hours (n = 1), 34-37 weeks (n = 1), and 5 weeks after birth (n = 4). The sample sizes ranged from 192 to 350 participants, with an average of 299 participants per study. All six studies examined the effects of prenatal exposure on infants' neurobehavioral development.

Independent variables were collected from the density of vehicle miles traveled (n = 1), placenta tissue biopsy (n = 1), blood and cord blood (n = 1), and maternal urine (n = 3). The NNNS assessments were described using summary scores (n = 2), latent profile analysis (n = 3), and a combination of both approaches (n = 1).

The studies examined the relationships between prenatal exposure to toxic substances and the NNNS scores across the following domains: self-regulation (n = 3), arousal (n = 3), attention

(n = 3), handling (n = 2), hypotonia (n = 2), lethargy (n = 2), autonomic stress (n = 2), non-optimal reflexes (n = 2), excitability (n = 1), Hypertonicity (n = 1), asymmetric reflexes (n = 1), and quality of movement (n = 1). For infants exposed to high levels of automobile emission air pollution, among the 13-NNNS summary scores, hypotonia was significantly associated with vehicle miles traveled density (Zhang et al., 2020). After adjusting for covariates, higher cord whole blood total mercury was significantly associated with reduced need for special handling and higher asymmetry scores in female infants. Additionally, a non-significant trend suggested improved attention (Xu et al., 2016). Infants exposed to high levels of metal mixtures (cadmium, cobalt, copper, iron, manganese, molybdenum, selenium, zinc) exhibited a significant association with NNN Profile 5, characterized by extreme difficulties in regulation, heightened arousal and excitability, increased hypertonicity, a higher number of non-optimal reflexes, poor quality of movement, and marked signs of stress (Tung et al., 2022). In contrast, prenatal exposure to higher levels of organophosphates was associated with better attention, lower lethargy, reduced hypotonia, and fewer signs of autonomic stress (Yolton et al., 2013). According to Sittiwang et al. (2022), higher maternal total dialkylphosphate concentrations during pregnancy were linked to infants with NNNS Profile 1, characterized by better self-regulation and attention but lower arousal and excitability scores. Additionally, prenatal exposure to bisphenol A did not significantly affect neurobehavioral outcomes. However, higher concentrations of total di-butyl phthalate at 26 weeks of gestation were linked to reduced arousal, improved self-regulation, and less need for handling. Higher di-butyl phthalate exposure in male infants was associated with increased non-optimal reflexes (Yolton et al., 2011). Table 2 presents a comprehensive comparison of the effects of prenatal toxic substance exposure on neurodevelopmental outcomes across various studies. The table highlights key findings related to the impact of different substances on infant neurodevelopment, focusing on the domains of self-regulation, attention, arousal, and overall neurological integrity.

In summary, the studies consistently suggest that prenatal exposure to a range of toxic substances, including air pollution, mercury, metal mixtures, organophosphate pesticides, and endocrine-disrupting chemicals like bisphenol A and phthalates, can have detrimental effects on neurodevelopment. These exposures are closely linked to impairments in self-regulation, attention deficits, and challenges in arousal modulation, potentially leading to long-term developmental delays. Certain studies also noted unexpected positive outcomes. These findings underscore the need for early identification and targeted interventions to mitigate the adverse effects of prenatal toxic substance exposure.

Table 2 Comparison of Findings on Prenatal Toxic Substance Exposure and Neurodevelopmental Outcomes

Study	Toxic Substance	Neurodevelopmental Outcomes	Key Findings
Sittiwang et al. (2022)	Organophosphate Pesticides	Better self-regulation and attention but lower arousal and excitability	Improved attention, unexpected positive outcome
Tung et al. (2022)	Metal mixtures	Low self-regulation, high arousal, and hypertonicity, poor movement quality, increased non-optimal reflexes, and stress signs	Had adverse effects
Zhang et al. (2020)	Air pollution	Hypotonia	Had adverse effects

Study	Toxic Substance	Neurodevelopmental Outcomes	Key Findings
Xu et al. (2016)	Mercury	Increased asymmetric reflexes in girls, decreased handling, and a trend toward better attention	Improved attention, unexpected positive outcome
Yolton et al. (2013)	Organophosphate Pesticides	Improved attention, reduced hypotonia, and fewer stress signs	Improved attention, unexpected positive outcome
Yolton et al. (2011)	Bisphenol A and Phthalates	Bisphenol A had no significant effects, while higher di-butyl phthalate levels were associated with decreased arousal, improved self-regulation, reduced handling, and increased non-optimal reflexes	There is no effect for bisphenol A, but higher di-butyl phthalate is linked to improved self-regulation

The NNNS on Neurodevelopment of Infants with Prenatal Drug Exposure

Seven studies utilized the NNNS to evaluate the neurodevelopment of infants in response to prenatal drug exposure, including exposure to methamphetamine (n = 2), tobacco and marijuana (n = 1), smoking (n = 1), methylenedioxymethamphetamine (n = 1), methadone (n=1), and a combination of cocaine, opiates, tobacco, alcohol, and marijuana (n = 1). The most significant proportion of these studies were conducted in the United States (n = 3); others took place in the United Kingdom (n = 1), New Zealand (n = 1), and both the United States and New Zealand (n = 1). One study did not report the location (n = 1). (See Table 3.)

Table 3 The NNNS and Its Relation to the Neurodevelopment of Infants with Prenatal Drug Exposure

Author	Prenatal exposure/ Age of assessment	Independent variables	Sample size	Result
Wouldes & Woodward (2020)	Methadone/ Age of assessment: one week of birth or corrected gestational age for preterm	Methadone medical record	100	The NNNS Score: Summary score and Latent profile analysis (profiles 1, 2, 3, and 4) Main Findings: Methadone-exposed infants demonstrated significantly poorer attention (B = -.95, P < .01), regulation (B = -.86, P < .01), and quality of movement (B = -.16, P < .01). They were also significantly more excitable (B = .50, P < .01), more easily aroused (B = .40, P < .01), and exhibited more non-optimal reflexes (B = .88, P <

Author	Prenatal exposure/ Age of assessment	Independent variables	Sample size	Result
				.01), hypertonicity (B = .34, P < .01), and total stress (B = .05, P < .01).
Stroud et al. (2018a)	Tobacco and marijuana/ Age of assessment: postnatal days 0, 1, 2, 3, 5, 11, and 32. (7 times)	Maternal and infant saliva, Meconium	111	The NNNS Score: summary score Main Findings: Marijuana and tobacco-exposed, co-use infants demonstrated decreased self-regulation (β = -.38, P < .01) and attention (β = -.63, P = .05), an increased handling scores (β = .28, P < .01), and lethargy (β = .14, P < .05).
Stroud et al. (2018b)	Smoking/ Age of assessment: Days 0, 1, 2, 3-4, 5, 11, and 32	Saliva cotinine (Mother and infant), Meconium	52	The NNNS Score: summary scores Main Findings: Maternal smoking during pregnancy x fetal quality of movements was associated with decreased infant attention (B = - .10, P = .02), increased lethargy (B = 1.40, P < .01) and quality of movement (B = .37, P = .02). Infants with Maternal smoking group x fetal complex movements was linked to decrease self-regulation (B = -.97, P = .02). Infants with Maternal smoking group x fetal coupling index was showed more handling scores during the first postnatal month (B = .23, P = .03).
Kiblawi et al. (2014)	Methamphetamine/	Meconium	185	The NNNS Score: summary scores

Author	Prenatal exposure/ Age of assessment	Independent variables	Sample size	Result
	Age of assessment: 5 days of life and again at 1 month			Main Findings: Both exposed and comparison groups demonstrated high quality of movement (P = .03), decreased lethargy (P < .01), and fewer asymmetric reflexes (P = .01), with no significant differences in NNNS scores between the groups. At 1 month of life, arousal levels increased in exposed infants but declined in the comparison group (P = .03). Total stress was reduced in exposed infants (P = .03).
Singer et al. (2012)	3,4-methylenedioxymethamphetamine / Age of assessment: 1 month	Interviewed about substance-using	28	The NNNS Score: summary scores Main Findings: No differences were found between groups when comparing mean scores. However, examining score distributions revealed a nonsignificant trend for methylenedioxymethamphetamine -exposed infants to show more lethargic behaviors compared to non-methylenedioxymethamphetamine -exposed infants (91% vs. 73%, likelihood ratio χ^2 = 3.31, P = .07)
LaGasse et al. (2011)	Methamphetamine Age of assessment: 5 days	Self-report and meconium assay with alcohol, marijuana,	183	The NNNS Score: Summary Scores Main Findings: Methamphetamine exposure was associated with poorer quality of movement,

Author	Prenatal exposure/ Age of assessment	Independent variables	Sample size	Result
		and tobacco exposures		increased total, physiological, and central nervous system stress, and more non-optimal reflexes (P < .05). Heavy MA exposure was linked to lower arousal and excitability. First-trimester use predicted higher stress (β = .11, P = .03), physiological stress (β = .16, P < .01), and central nervous system stress (β = .21, P = .02). Third-trimester use predicted increased lethargy (β = .14, P < .01) and hypotonicity (β = .11, P = .03).
Liu et al. (2010)	Cocaine, opiate, tobacco, alcohol, and marijuana/ Age of assessment: 1 month	Report of drugs used and/or a positive meconium assay for cocaine	658	The NNNS Score: Latent profile analysis (profiles 1, 2, 3, 4 and 5) Main Findings: Infant Profile 5 (n = 72, 5.8%), representing the poorest performance, showed the most extreme negative scores. These infants had the lowest levels of attention and self-regulation, highest handling needs, and displayed increased arousal, excitability, and hypertonicity. They also exhibited the lowest quality of movement and the most severe signs of stress (P < .01).

Note: β = Standardized coefficient, B = Unstandardized coefficient, P = Probability value

The NNNS assessed neurobehavioral development within various timeframes, from birth to 37 days after birth. Specifically, assessments were conducted within five days after birth (n = 1),

within seven days after birth (n = 1), at 1 month of age (n = 2), and in multiple assessments (n = 3), such as at two-time points (birth and 30 days) or across seven-time points (0, 1, 2, 3, 5, 11, and 32 days). The sample sizes ranged from 28 to 658 participants, averaging 188 participants per study.

Independent variables were collected from maternal and infant saliva (n = 2), meconium (n = 4), interviews (n = 2), medical records (n = 2), and self-reports (n = 1). NNNS scores were reported through summary scores (n = 5), latent profile analysis (n = 1), and a combination of both approaches (n = 1).

The studies identified significant associations between prenatal drug exposure and NNNS scores across several domains, including quality of movement (n = 5), self-regulation (n = 4), attention (n = 4), lethargy (n = 4), arousal (n = 4), stress (n = 4), handling (n = 3), excitability (n = 3), hypertonicity (n = 2), non-optimal reflexes (n = 2), hypotonicity (n = 1) and asymmetric reflexes (n = 1). Prenatal methadone exposure was associated with significantly poorer attention, self-regulation, and quality of movement. Infants in this group also showed higher levels of excitability, increased arousal, and more non-optimal reflexes, hypertonicity, and overall signs of stress and abstinence compared to infants in the control group (Wouldes & Woodward, 2020). Infants prenatally exposed to marijuana and tobacco exhibited decreased self-regulation and attention, increased handling scores, and lethargy. Co-exposure compounded these effects, reducing self-soothing and increasing the need for handling (Stroud et al., 2018a). Maternal smoking was associated with fetal movement and decreased attention, self-regulation, and increased lethargy, quality of movement, and handling scores in infants during the first month (Stroud et al., 2018b). Methamphetamine-exposed infants exhibited a high quality of movement, reduced lethargy, and fewer asymmetric reflexes, comparable to the comparison group. During the first month of life, arousal levels increased in exposed infants but decreased in the comparison group. Additionally, total stress levels declined in exposed infants. However, both groups had a background of prenatal exposure to alcohol, tobacco, and marijuana (Kiblawi et al., 2014).

Another study linked methamphetamine exposure to poorer quality of movement, increased total stress, and to other non-optimal reflexes in infants. Heavy methamphetamine exposure was linked to lower arousal and excitability. First-trimester methamphetamine use predicted higher levels of stress, physiological stress, and central nervous system stress; third-trimester use was associated with increased lethargy and hypotonicity (LaGasse et al., 2011). No differences were found between the mean scores between the methylenedioxymethamphetamine-exposed and comparison groups. However, methylenedioxymethamphetamine-exposed infants showed increased lethargy and reduced motor, state, and physiological reactivity, though these differences were nonsignificant (Singer et al., 2012). For cocaine, opiate, tobacco, alcohol, and marijuana exposure, Infant Profile 5 showed the most severe deficits, including the lowest attention and self-regulation, highest handling needs, and elevated levels of arousal, excitability, and hypertonicity. These infants also exhibited the poorest movement quality and the most pronounced signs of stress (Liu et al., 2010). Table 4 offers a detailed comparison of the neurodevelopmental outcomes associated with prenatal drug exposure across various studies. It highlights the extent to which different substances, such as methamphetamine, cocaine, alcohol, and opioids, impact the developmental trajectory of infants. The table provides a comprehensive view of how prenatal exposure to these drugs affects key neurobehavioral domains, such as motor skills, attention, self-regulation, and stress responses. The comparative analysis facilitates a deeper understanding of the potential risks of different drugs. It emphasizes the need for targeted interventions to support at-risk infants in their early developmental stages.

In summary, the findings from these seven studies consistently show that prenatal drug exposure has a detrimental impact on neurodevelopmental outcomes in infants. The effects are

particularly evident in critical areas such as quality of movement, self-regulation, attention, and stress response. Infants exposed to substances like methamphetamine, cocaine, alcohol, and opioids demonstrate impairments in these key developmental domains, underscoring the importance of early intervention and support to mitigate long-term developmental challenges.

Table 4 Comparison of Findings on Prenatal Drug Exposure and Neurodevelopmental Outcomes

Study	Drugs	Neurodevelopmental Outcomes	Key Findings
Wouldes & Woodward (2020)	Methadone	Poor attention, self-regulation, and quality of movement; high excitability; increased non-optimal reflexes, hypertonicity, and stress	Deficits in multiple domains
Stroud et al. (2018a)	Tobacco, Marijuana	Decreased self-regulation and attention; increased handling and lethargy	Decreased self-regulation and attention
Stroud et al. (2018b)	Smoking	Decreased attention and self-regulation; increased lethargy and reduced quality of movement; increased need for handling	Decreased self-regulation and attention
Kiblawi et al. (2014)	Methamphetamine	Decreased lethargy; increased movement quality; low arousal	Had adverse effects
LaGasse et al. (2011)	Methamphetamine	Poor quality of movement; increased stress and non-optimal reflexes; low arousal and excitability	Had adverse effects
Liu et al. (2010)	Tobacco, Alcohol, Marijuana	Poor attention and self-regulation; increased handling, arousal, excitability, and hypertonicity; poor quality of movement; increased signs of stress	Decreased self-regulation and attention

Discussion

This study systematically reviewed the usefulness of the NNNS for assessing neurodevelopment in infants prenatally exposed to toxic substances or drugs. The findings show that the NNNS is effective in assessing neurobehavioral outcomes in these infants. The discussion focuses on two key areas:

1) Prenatal Toxic Substance Exposure and the NNNS Outcomes: Prenatal exposure to toxic substances, including air pollution, bisphenol A, phthalates, mercury, metal mixtures, and organophosphate pesticides, has been linked to neurodevelopmental effects, particularly in self-regulation, arousal, and attention. While certain substances (i.e., organophosphates and mercury) showed positive and negative effects, the overall trend suggests primarily adverse outcomes. Below are examples of toxic substance exposure and their impact on NNNS outcomes.

1.1) Air pollution: Prenatal exposure to high levels of traffic-related air pollution was linked to higher scores for hypotonia and lethargy, with a significant correlation between these outcomes and vehicle miles traveled (Zhang et al., 2020). These findings align with previous research,

which shows that prenatal exposure to environmental pollutants disrupts neuromotor development and self-regulation (Perera et al., 2006)

1.2) Phthalates: Exposure to phthalates, particularly di-butyl phthalate, was associated with reduced arousal, improved self-regulation, and a decreased need for handling (Yolton et al., 2011). These findings suggest that certain phthalates may have a protective effect on specific aspects of neurodevelopment, such as self-regulation.

1.3) Organophosphate pesticides: Contrary to the findings of studies reporting cognitive and behavioral deficits in older children exposed to organophosphate pesticides (Bouchard et al., 2011; Eskenazi et al., 2007), unexpected outcomes were observed in infants exposed to these pesticides, with improved attention noted (Sittiwang et al., 2022; Yolton et al., 2013). This discrepancy may be attributed to factors such as lower exposure levels in the studied cohort or protective influences like higher socioeconomic status and better nutrition (e.g., a diet rich in vegetables), which could have mitigated the potential adverse effects of exposure (Yolton et al., 2013).

1.4) Mercury: Prenatal mercury exposure presents a complex profile. While it was linked to increased asymmetry in reflexes in girls, it also showed a trend toward improved attention and reduced need for handling (Xu et al., 2016). These findings are partially consistent with studies suggesting that moderate mercury exposure, particularly through fish consumption, may have neurodevelopmental benefits due to omega-3 fatty acids (Chowdhury et al., 2022). Socioeconomic status, maternal behavior, and environmental context may further influence these neurodevelopmental outcomes.

The NNNS is widely recognized as effective in assessing the relationship between prenatal substance exposure and neurobehavioral development. This systematic review, which evaluated five categories of substances, highlighted that different types of substance exposure produce distinct effects on infant development.

While studies on specific exposures, such as phthalates, offer limited insight into neurobehavioral development, other toxic substances, including air pollution and metal, show significant adverse impacts on infant development. Notably, most studies on prenatal toxic substance exposure were conducted in the United States, with only one study based in Thailand. This geographical imbalance limits the generalizability of findings, as regional differences in healthcare systems, environmental exposures, and socioeconomic factors can influence outcomes. Nevertheless, environmental pollution is a global issue, with contaminants traveling through air, water, soil, and food, affecting children worldwide. Expanding the use of the NNNS to assess infants in diverse regions could offer a more comprehensive understanding of neurodevelopmental outcomes and inform intervention strategies that are globally relevant.

2) Prenatal Drug Exposure and the NNNS Outcomes: The neurodevelopmental effects of prenatal drug exposure were more consistently detrimental than those of exposure to toxic substances. In the seven studies included in the systematic review, infants exposed to methamphetamine, methadone, marijuana, and tobacco showed significant deficits in quality of movement, self-regulation, attention, and stress response. The following are examples of drug exposure and their associated effects on NNNS outcomes.

2.1) Methamphetamine: Prenatal exposure to methamphetamine was linked to poorer movement quality, heightened stress signs, and reduced arousal, particularly in infants with heavy exposure (Kiblawi et al., 2014; LaGasse et al., 2011). These findings align with previous research that underscores the neurotoxic effects of amphetamines on fetal brain development (Ross et al., 2015).

2.2) Methadone: Infants prenatally exposed to methadone exhibited widespread deficits across multiple NNNS domains, including attention, self-regulation, and movement quality, as well as increased excitability and stress (Wouldes & Woodward, 2020).

2.3) Cocaine, alcohol, tobacco, and marijuana: Exposure to substances such as cocaine, alcohol, tobacco, and marijuana resulted in some of the severest neurobehavioral impairments. Liu et al. (2010) found significant deficits in self-regulation and attention, along with elevated stress, excitability, and hypertonicity scores. These findings are consistent with studies highlighting the compounded effects of co-exposure to multiple substances, which further exacerbate neurodevelopmental disruptions in childhood (Fisher et al., 2011). In addition, marijuana and tobacco exposure were linked to increased lethargy and reduced motor activity, findings that align with Stroud et al. (2018a).

Despite some variation in the severity of outcomes, the studies reviewed here consistently reported adverse effects of prenatal drug exposure on neurodevelopmental domains assessed by the NNNS. This stands in contrast to the more variable outcomes observed with toxic substance exposure, highlighting the significant and widespread impact of prenatal drug exposure on early neurobehavioral development.

Conclusion

This systematic review highlights the value of the NNNS as a key tool for assessing neurodevelopment in infants with prenatal exposure to toxic substances and drugs. Exposure to environmental toxins, such as air pollution, phthalates, mercury, metal, and organophosphate pesticides, has mixed effects on neurodevelopment, often affecting attention and self-regulation. For example, exposure to air pollution led to hypotonia; phthalates improved self-regulation but reduced arousal. Organophosphate pesticides showed better attention, low arousal, and excitability. In contrast, prenatal drug exposure, including tobacco, methamphetamine, methadone, marijuana, and polydrug use, consistently resulted in deficits in self-regulation, attention, and increased stress. The combined effects of multiple drug exposures exacerbated these adverse outcomes. Variability in study methodologies, including differences in sample size, assessment timing, and exposure measurement, complicated the interpretation of NNNS outcomes. While the effects of toxic substance exposure were mixed, drug exposure predominantly resulted in adverse impacts.

The NNNS, with its multidimensional approach to evaluating attention, self-regulation, and stress responses, is an invaluable tool for understanding the neurodevelopmental outcomes of at-risk infants. Its sensitivity emphasizes the importance of early neurodevelopmental assessments to guide targeted interventions, improving outcomes for infants exposed to prenatal substances. We recommend utilizing the NNNS to identify neurodevelopmental risks early and inform intervention strategies. Future research should explore NNNS-based interventions, evaluate long-term outcomes, and investigate the influence of socioeconomic factors, maternal behavior, environmental context, and regional differences on neurodevelopment. Additional studies are needed to assess the feasibility and impact of NNNS-based interventions across diverse populations, particularly in low-resource settings. These efforts will enhance the equitable implementation of the NNNS in clinical practice, ensuring broader access to early neurodevelopmental assessments and interventions.

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