Childhood Health and Educational Outcomes After Neonatal Abstinence Syndrome: A Systematic Review and Meta-analysis

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Objective To systematically review and meta-analyze the association between neonatal abstinence syndrome (NAS) and adverse health or educational childhood outcomes.

Study design An all-language search was conducted across 11 databases between January 1, 1975, and September 3, 2019; 5865 titles were identified. Observational studies of children between 28 days and 16 years of age, in whom a diagnosis of NAS was documented, were included. Outcomes included reasons for hospital admissions, childhood diagnoses, developmental outcomes, and academic attainment scores. All studies underwent independent review by 2 trained reviewers, who extracted study data and assessed risk of bias using the Newcastle Ottawa Tool.

Results Fifteen studies were identified that included 10 907 children with previous NAS and 1 730 213 children without previous NAS, aged 0-16 years. There was a strong association between NAS and subsequent child maltreatment (aOR, 6.49; 95% CI, 4.46-9.45; I^2 = 52%), injuries and poisoning (aOR, 1.34; 95% CI, 1.21-1.49; I^2 = 0%), and a variety of mental health conditions. Studies consistently demonstrated an increased incidence of strabismus and nystagmus among those with previous NAS. Children with NAS also had lower mean academic scores than the control group in every domain of testing across age groups.

Conclusions NAS is significantly associated with future child maltreatment, mental health diagnoses, visual problems, and poor school performance. Owing to the necessary inclusion of nonrandomized studies, incomplete reporting among studies, and likely unadjusted confounding, this review does not suggest causation. However, we highlight associations requiring further investigation and targeted intervention, to positively impact the life course trajectories of this growing population of children. *(J Pediatr 2020;226:149-56)*.

Neonatal abstinence syndrome (NAS) has become a global problem.[1-4] The syndrome describes the postnatal signs of physiologic distress after withdrawal of narcotics that a newborn infant has been exposed to in utero.[5] NAS has been declared a national crisis in the US as the incidence increased 6-fold: 8 in every 1000 infants were affected by NAS in 2014.[5,6] This surge is thought to be secondary to increased opioid prescribing in pregnancy, greater misuse of newer potent opioids, and improved provision of opioid substitution programs.[5,7]

NAS is a clinical diagnosis of a multisystem postnatal disorder affecting the gastrointestinal and central and autonomic nervous systems.[5,8] Affected newborn infants may experience physiologic stress, including allodynia, irritability, unstable body temperatures, electrolyte disturbances, hypertonia, and seizures.[4] Infants with NAS require close monitoring and often reintroduction and weaning of opioids.[7]

To date, research has largely focused on the management of NAS and effects of opioid exposure on neurodevelopment.[9,10] There is, however, a paucity of research into the long-term health and educational outcomes of these infants.[5,8,11] Longitudinal studies are particularly challenging because of confounding genetic and social factors, such as high levels of adversity in this population. This phenomenon is illustrated by the 147% increase in the number of children entering foster care owing to parental substance misuse in the US since 2000.[12-15]

Given the potential impact of NAS on the developing infant's physiology, the rapid increase in incidence and levels of adversity among this population, it is essential that we understand their life course trajectories.[3,5-8,16-18] The purpose of this study was to determine the frequency of adverse childhood health and educational outcomes after NAS compared with outcomes of unexposed children to inform and equip clinicians and policymakers tasked with the provision and planning of services to optimize the lifelong health and development of these children.

NAS	Neonatal abstinence syndrome

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Methods

This review is reported according to the PRISMA statement and MOOSE guidelines and follows an a priori protocol (CRD42019132659) (**Table I** and **Table II**; available at www.jpeds.com).[19-21] Observational studies published between 1975 and 2019 examining childhood outcomes after NAS were included. For the purposes of this review, NAS was defined as a clinical diagnosis of neonatal withdrawal after antenatal exposure to opioids. We excluded studies focusing on nonopioid NAS, studies with mixed populations of infants, where infants with NAS formed a nonrepresentative minority and could not be separated from those without NAS, studies focusing on NAS from postnatal opioid exposure, and studies focusing on neonatal outcomes or mortality. Excluded study designs were case reports, review articles, and expert opinions.[22]

A comprehensive search of published and grey literature was conducted across 11 databases from January 1, 1975, to September 3, 2019 (**Table III**; available at www.jpeds.com). The time frame was selected to capture studies published after the Finnegan Score was introduced in 1975, because this was the first clinically validated diagnostic tool for opioid-related NAS.[23] The search strategy, developed in Medline Ovid, consisted of 75 keywords and Mesh terms (**Figure 1**; available at www.jpeds.com). Synonyms, alternate spellings, abbreviations, and historical terms were incorporated into the search strategy. This strategy was subsequently adapted for other databases. Search sensitivity was augmented by using supplementary snowballing techniques, including searching the references of all full-text articles reviewed, hand searching of nonindexed journals, and contacting authors to clarify study details.

Children with a history of NAS as a result of antenatal opioid administration were the focus of this study. NAS cases were included if qualified providers using standardized scoring tools determined the diagnosis, or if NAS was stated as a diagnosis in the medical records (**Table IV**; available at www.jpeds.com). Infants experiencing withdrawal of any severity were included. Comparator cases included those who did not have a history of NAS and in whom antenatal opioid exposure was either excluded systematically by checking medical records, or it was stated as such in the study.

We included all health and educational outcomes assessed beyond the neonatal period, after 28 days of age until 16 years of age.

All references identified by searches were exported to Endnote X7.8 (Clarivate Analytics, Philadelphia, Pennsylvania) and duplicates were removed. Two reviewers screened titles and abstracts for relevance, independently; full-text articles of all abstracts deemed potentially relevant were assessed for inclusion. The initial quality assessment tool did not adequately discriminate between domains; we therefore deviated from our protocol and used the Newcastle Ottawa tool.[24] The methodologic quality of each full-text was assessed by 2 trained reviewers independently; a fourth reviewer arbitrated disagreements. No language restrictions were applied.

Data Extraction and Synthesis

Two reviewers independently extracted data from included studies to a piloted extraction tool. Study authors were contacted where data were unclear or additional clarification was needed.

All outcomes and comparisons were described in a narrative synthesis. Studies were grouped by clinical context, outcome, and study design. Where comparative studies addressing a particular outcome were deemed to be homogenous in terms of study design, population, definition of NAS and outcome assessment, dichotomous data were pooled in a random effects meta-analysis model using the Mantel-Haenszel method in RevMan (Cochrane, London, United Kingdom). In the absence of raw data, RRs were estimated as ORs, and pooled ORs were calculated using the generic inverse variance method, within random effects models.[25]

Meta-analysis data were presented as crude OR with their associated 95% CI, P values, and I^2 measures of heterogeneity. Where studies provided both crude and aOR—and adjusted for similar confounders—we performed separate meta-analyses. The degree of statistical heterogeneity was assessed using the I^2 statistic and owing to the nature of included non-randomized study designs, consistent with the Cochrane handbook, we only pooled studies where there was reasonable homogeneity of population, context, and definition.[26] We explored cases of severe heterogeneity ($I^2 > 85\%$) and offered caution in the interpretation of our findings.[27]

Where there were insufficient comparative studies addressing an outcome, but multiple case series providing incidence figures for that outcome, incidence data were presented and 95% CI were calculated using the Fisher exact test for binomial data.[28]

Results

Of the 5865 titles identified from searches, 581 full texts were assessed for eligibility, 15 eligible studies were identified, and 6 were amenable to meta-analysis (**Figure 2**).[11,29-42] This represented 10 907 children with a history of NAS and 1 730 213 unexposed children (**Table V**; available at www.jpeds.com).[11,29-42] Multiple publications from the same cohort were clarified, to avoid duplication of cases in the statistical analysis.

Studies were retrospective cohort studies (n = 8), prospective cohort studies (n = 1), and case series (n = 6).[11,29-42] Eight studies were deemed to be overall good quality, 4 were deemed fair, and 3 poor (**Table VI**; available at www.jpeds.com).[11,29-42] Included studies were published between 2003 and 2019 with infants born between 1998 and 2016.[11,29-42] The age range of included children was 0-16 years; ages for specific outcome assessments often were not provided (**Table V**).

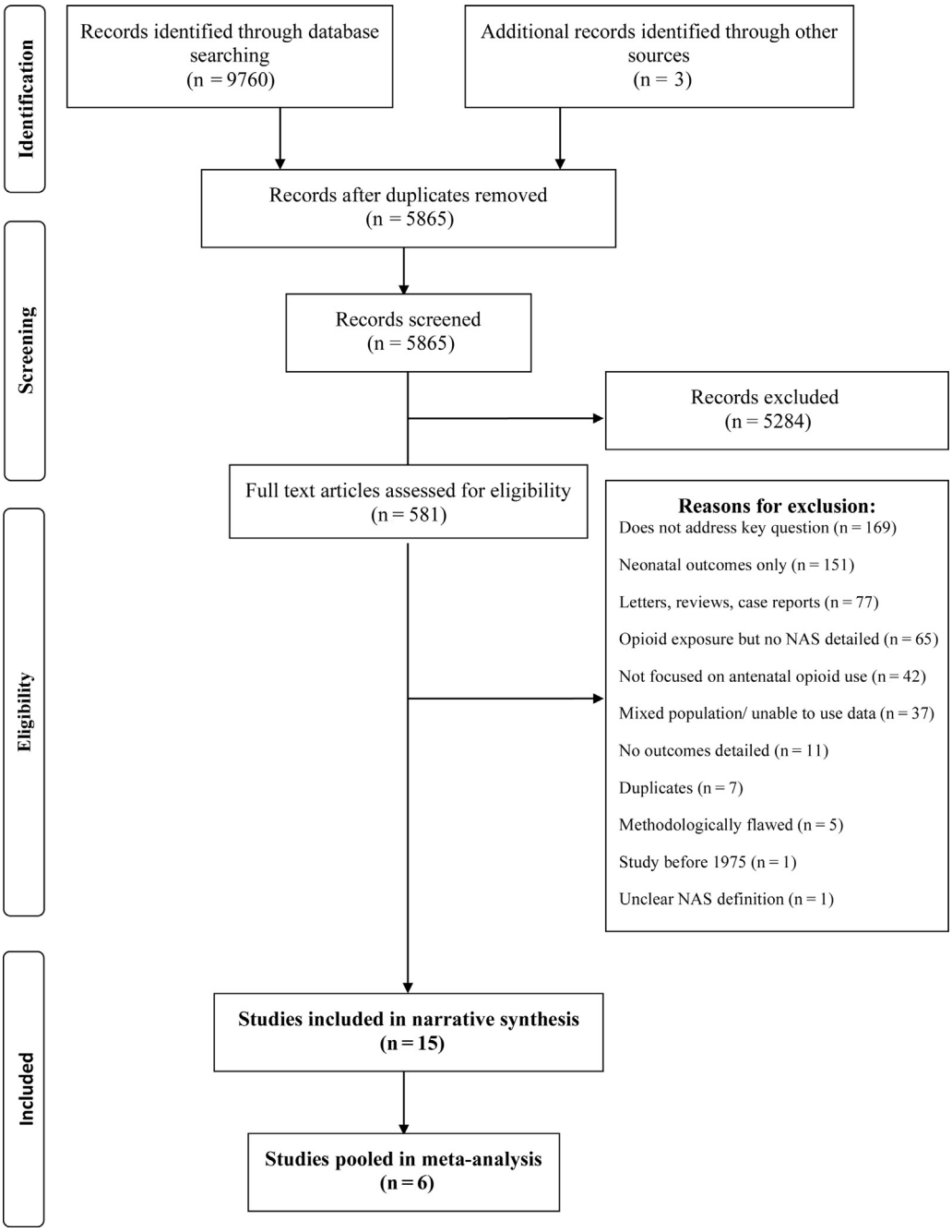

Figure 2. PRISMA flow diagram demonstrating included and excluded studies, and reasons for exclusion, in the systematic review of childhood outcomes after NAS.

Child Maltreatment and Injuries

A meta-analysis of 3 studies demonstrated higher odds of child maltreatment after NAS. The median ages were: Witt et al, 0-1 year; O-Donnell et al, 1 and 3 years for the exposed (NAS) and comparator (no NAS) groups respectively; and Uebel et al, 1-4 years.[11,35,37] The odds of child maltreatment were 13.96 higher in those with NAS compared with those without NAS (95% CI, 8.59-22.68; I^2 = 74%) (**Figure 3**; available at www.jpeds.com). Studies adjusted for similar confounders: gestation, indicators of deprivation, maternal ethnicity, smoking status, and age. The pooled aOR was 6.49 (95% CI, 4.46-9.45; I^2 = 52%) (**Figure 4**). The substantial heterogeneity of the crude pooled estimate was partially explained within the adjusted analysis. Neglect was the commonest type of maltreatment after NAS, accounting for 72% and 43% of cases presented by O'Donnell et al and Uebel et al, respectively.[11,35] O'Donnell et al also highlighted that maltreatment was experienced at a younger age (median, 1 year) after NAS compared with those without NAS (median, 3 years).[35]

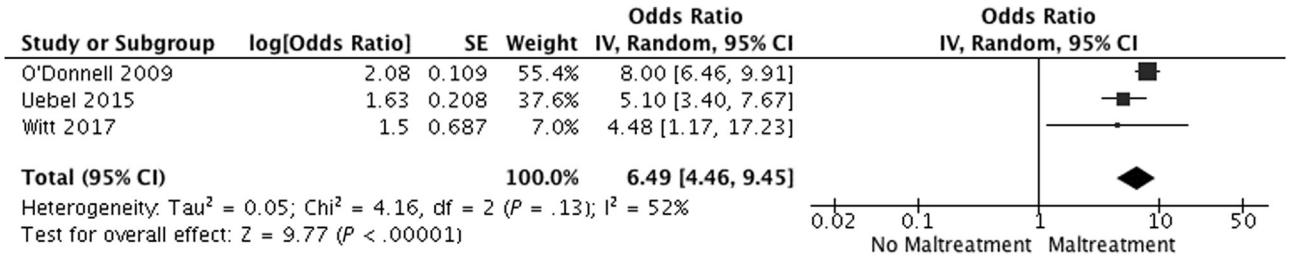

Figure 4. The odds of child maltreatment after NAS compared with those without previous NAS, by pooling adjusted data.

Two studies report frequency of hospital admissions for injuries and poisoning.[11,37] The pooled crude OR was 1.93 (95% CI, 1.75-2.12; I^2 = 0%; **Figure 5** [available at www.jpeds.com]) and the pooled aOR for injuries and poisoning after NAS was 1.34 (95% CI, 1.21-1.49; I^2 = 0%) (**Figure 6**).

Mental Health Diagnoses

Attention Deficit Hyperactivity Disorder. Three studies reported the probability of an *International Classification of Diseases* diagnosis of attention deficit hyperactivity disorder after NAS.[11,39,42] On pooling the crude data from these studies, a significant association with attention deficit hyperactivity disorder was found (OR, 3.21; 95% CI, 1.29-7.97; I^2 = 94%; **Figure 7** [available at www.jpeds.com]) Azuine et al and Uebel et al adjusted for similar confounders: maternal age, indicators of socioeconomic status, ethnicity, and birth outcomes. The pooled aOR for these 2 studies was 2.18 (95% CI, 0.78-6.14; I^2 = 86%; **Figure 8** [available at www.jpeds.com]). Substantial heterogeneity, although partially explained in the adjusted analysis, was thought to be due to age differences and differences in ascertainment; unfortunately, this factor could not be explored further and we therefore urge caution in interpreting these findings.

Autism. Two studies specifically assessed autism after NAS.[11,29] Uebel et al identified the diagnostic code for autism from medical records (≤13 years of age) and the aOR was 2.48 (95% CI, 1.47-4.18).[11] Fill et al identified autism in those aged 3-8 years referred for educational disability assessment and the OR was 0.82 (95% CI, 0.33-2.02); adjusted data were not provided.[29] These data were not pooled owing to contextual diversity.

Behavioral and Emotional Disorders. Four studies reported the probability of behavioral or emotional disorders (including conduct disorder) among children with previous NAS.[11,39,40,42] Owing to heterogeneity in outcome reporting, these studies were not pooled. Hall et al and Uebel et al both reported increased probability of behavioral or emotional disorders after NAS (OR, 5.31 [95% CI, 2.56-11.02] and OR 4.08 [95% CI, 2.88-5.8], respectively).[11,40] This finding was shown to persist by Uebel et al after adjusting for confounders (aOR, 2.3; 95% CI, 1.6-3.3). Within this group of disorders, Sherman et al and Uebel et al specifically highlight an increased risk of conduct disorder (OR, 2.88 [95% CI, 2.37-3.5] and OR, 3.42 [95% CI, 1.98-5.92], respectively).[11,42] Azuine et al, however, combined outcomes differently and did not report a significant increase in the risk of a conduct disorder or emotional disturbance after NAS (aRR, 1.48; 95% CI, 0.91-2.4).[39]

Speech and Language

Four studies reported data relating to speech and language development.[11,29,34,40] Two were deemed sufficiently clinically homogenous for meta-analysis.[11,40] The population age in these 2 studies was similar, median age 1-4 years and age range 2-4 years in Uebel et al and Hall et al, respectively. The pooled OR for speech and language impairment was 2.81 (95% CI, 1.82-4.33; I^2 = 26%; **Figure 9** [available at www.jpeds.com]). Hall et al did not provide adjusted data; however, Uebel et al presented an aOR of 2.42 (95% CI. 1.35-4.34).[11,40] Fill et al reported the probability of speech and language impairment among those aged 3-8 years with previous NAS referred for educational disability assessment.[29] After adjusting for sex, ethnicity, age,

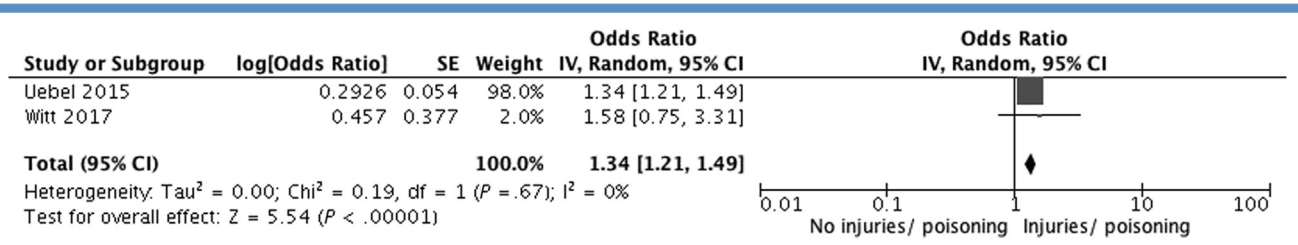

Figure 6. The odds of injuries and poisoning after NAS across studies, by pooling adjusted data.

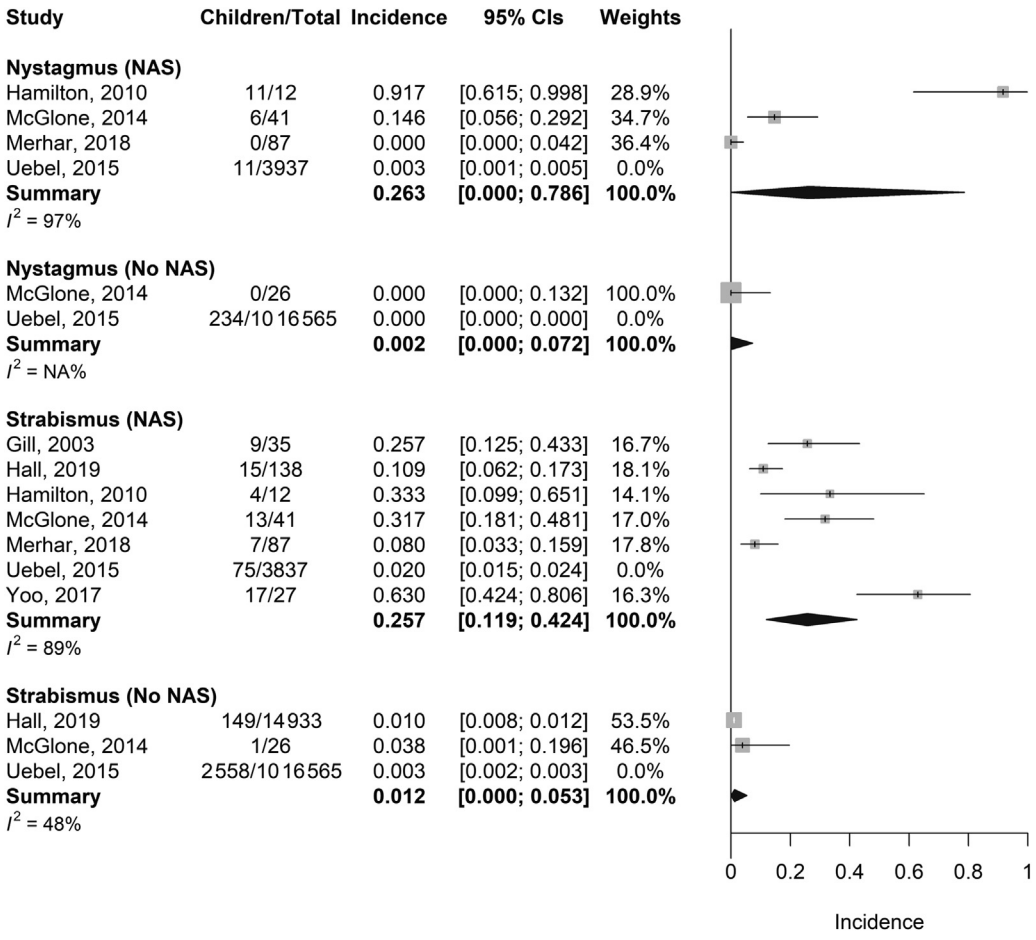

Figure 10. Forest plot of incidence of strabismus and nystagmus among those with and without previous NAS.

insurance status, postcode, maternal tobacco use, and maternal education status, the aOR of speech and language impairment was 1.26 (95% CI, 1.04-1.52).

Visual Problems

Seven studies explored visual outcomes after NAS.[11,30,31,33,34,38,40] The age range of included children was 0-13 years (**Table V**).[11,30,31,33,37,38,40] Studies consistently demonstrated a high incidence of strabismus and nystagmus after NAS compared with those without previous NAS (**Figure 10**). The pooled incidence of strabismus after NAS was 0.26 (95% CI, 0.12-0.42) compared with 0.01 (95% CI, 0-0.05) among those without previous NAS. The incidence of nystagmus after NAS was 0.26 (95% CI, 0.00-0.79) compared with 0 (95% CI, 0-0.13) among those without NAS.

Cognitive Outcomes

Uebel et al and Sherman et al highlight increased risk of intellectual disability after NAS with a pooled crude OR of 2.49 (95% CI, 1.88, 3.3; I^2 = 0%; **Figure 11** [available at www.jpeds.com]).[11,42] However, on adjusting for confounders, Uebel et al highlight an insignificant aOR of 1.68 (95% CI-0.96, 2.93). Fill et al explored a subset of the population, those referred for assessment of special educational needs. After adjusting for a range of factors including insurance status, maternal characteristics, and neonatal characteristics, those with previous NAS were more likely to be diagnosed with a learning disability than those without previous NAS aOR 1.26 (95% CI, 1.06-1.49).

Academic Attainment. Oei et al explored academic attainment: specifically reading, numeracy, writing grammar, and spelling ability among children with previous NAS.[36] Children with previous NAS had significantly lower mean scores than matched controls in every grade and at every domain of testing. Children were matched for gestation, socioeconomic status, year of birth, and sex. The proportion of children below national minimum standard at 3 distinct grades of school was compared when children were ages 8-9 years, 10-11 years, and 12-13 years. They found that across all 3 of these educational grades, children with previous NAS (n = 2234) were significantly more likely to be below national minimum standards compared with their matched controls (n = 4330): OR of 2.4 (95% CI, 2.1-2.7), 2.3 (95% CI, 2.1-2.6), and 2.1 (95% CI, 1.7-2.4) for grades 3, 5, and 7 respectively.[36]

Discussion

In this systematic review, we have explored the longer term childhood outcomes after NAS, using pooled data in meta-analyses where appropriate, to estimate the odds of a range of adverse health and educational outcomes. Our findings suggest that NAS is an early indicator of a wide variety of potential future childhood morbidities. NAS was associated with child maltreatment and injuries, in addition to varying mental health conditions, speech and language impairment, and visual problems. Although somewhat attenuated, findings remain detectable after adjustment for potential confounders. The OR of child maltreatment among children with previous NAS was between 4.46 and 9.45, after adjusting for confounders, posing considerable risk to this group of children. However, the quality of evidence for other outcomes was variable and often suboptimal, presenting an urgent need for further rigorous research in this area.

Key strengths of this review are its rigorous methodology, pragmatic approach, and inclusion of large recent studies. However, the nature of reviews such as this, which are focused on clinical associations, necessitates the inclusion of observational studies, because they are the only source of high-quality evidence capable of addressing our questions. The results of the review are, therefore, limited by the necessary synthesis of nonrandomized studies resulting in wide effect estimates. Many studies adjusted for confounders, however, there is likely unadjusted confounding and bias (such as increased surveillance of the NAS population) accounting for the significant associations between NAS and childhood morbidities. For example, we hypothesize that many of these associations are underpinned by inter-related adverse childhood experiences, such as parental separation, parental mental illness, or incarceration of a parent, in addition to parental substance abuse. These adverse childhood experiences have proven cumulative associations with deleterious outcomes such as abuse and mental health problems.[43-46] However, with NAS now a vast under-researched population problem, we believe that such difficulties studying the population in its purest and least confounded form should not prohibit pragmatic research into the longer term outcomes of these children.[47] This review does not suggest causation, but merely highlights the increased risk within this population, information that is invaluable to healthcare professionals, parents, and policymakers.

It is worth noting that the association with child maltreatment was largely underpinned by Australian studies; cultural and contextual differences may therefore affect the generalizability of these results. Our results are additionally limited by the quality of included studies and incomplete reporting. Many included studies identified cases and outcomes retrospectively, from different databases and electronic medical records using *International Classification of Diseases* codes, and did not provide sufficient information about outcome ascertainment such as age. Although this is suboptimal, encompassing a heterogeneous population with varying NAS severity and outcomes, it enables interrogation of population registries to provide meaningful insight into the potential risks facing this vulnerable population, which would otherwise go undetected.[12,47] We urge caution in the interpretation of crude data and pooled data demonstrating significant heterogeneity.

Although most studies were deemed to be of overall good quality, most did not provide details about antenatal drug exposure or polydrug use. Taking a pragmatic approach, we decided against excluding such studies because, although suboptimal, this is representative of the population seen in practice. Additionally, owing to the nature of cohort studies, the NAS population studied in this review was born several years ago, before improvements in the availability of opioid substitution therapy and indeed the opioid epidemic. The family profiles of today's children with NAS and their future trajectories may be different. Mindful of these limitations, we present a synthesis of the best available evidence.

Previous systematic reviews of neurodevelopmental outcomes after antenatal opioid exposure—although focused on different populations and addressing different questions—also highlight reduced cognitive scores, impaired neurodevelopment and visual problems.[48,49] Kaltenbach et al (in a randomized controlled trial follow-up) did not find any neurodevelopmental impairment among infants with NAS at 36 months; however, neurodevelopmental assessment at this young age may not be predictive of future childhood functioning.[50,51] This study was not included because it did not have an unexposed comparator group, and data for the NAS population could not be isolated.

The associations between NAS and adverse outcomes highlighted in our review are arguably unsurprising. These children are typically born to parents who themselves suffered childhood adversity.[52,53] Mothers who use opioids have higher rates of mental illness, poverty, incarceration, poor education, and poor physical health.[35,52-55] This factor may impede ability to provide a safe and nurturing environment for children.[35,38,55]

This review presents strong evidence for an association between NAS and later child maltreatment; however, the pathway for this association—including the hypothesized relationship with adverse childhood experiences—could not be explored. We suggest that further research explore adverse childhood experiences within the NAS population with a view to understanding the potential causative pathways underlying these associations. Such research should use propensity score matching to account for potential confounders.[11-13] Timely identification of children at risk for maltreatment—for prevention purposes—is notoriously difficult. The feasibility of using NAS as a surrogate early indicator (or flag) of abuse risk, to target supportive and preventative efforts, could be explored in further studies.

Limitations in the literature prevented us from addressing several questions: namely whether the associations highlighted in this review are influenced by the nature of antenatal opioid exposure, postnatal pharmacologic treatment, and placement in out-of-home care.[12] We agree with Wachman

et al that further prospective studies, adequately adjusting for antenatal exposure, sociodemographic factors, and neonatal treatment, are warranted to address these questions.[56] Ongoing work aiming to develop a core-outcome set for NAS research will help to shape the focus of future studies and enable more rigorous evidence synthesis.[57]

This review highlights that children with previous NAS are at considerable risk of child maltreatment and hospital admissions for injuries and poisoning. Regardless of whether this association is underpinned by uncaptured confounders, this is a real and sizeable risk faced by a growing population of children. Although tackling the opioid epidemic requires a thoughtful public health approach, so does the safeguarding of children born into the crisis.[52] Primary prevention of this problem would take the form of beneficial social and economic political policies to decrease poverty, address social disparities, and tackle health inequalities to prevent parental substance misuse, NAS, and child maltreatment.[6,35,58] However, until effective primary prevention is available, we recommend that secondary preventative strategies are tested in this at-risk population, including home visitation programs, parental training, and access to early intervention services to support the mother-infant dyad. In certain settings, such programs have had favorable effects on child development and decreasing child maltreatment.[35,58,59]

Children with NAS are often followed up during the neonatal period. However, long-term multidisciplinary surveillance and support for the varied associated issues pertaining to health, developmental, social, and educational issues that we identify here, are unlikely to be in place routinely. Such monitoring may be beneficial to permit early intervention, prevent harm, for example, from undetected visual impairment, and attempt to attenuate the effects of other negative outcomes.[11,29,35,48,49]

In this systematic review, we highlight that a diagnosis of NAS is a flag for future childhood risk of maltreatment, injuries and poisoning, mental health diagnoses, speech and language problems, and visual impairment. These are important issues for redress to prevent the worsening of population health disparities and to help improve the health trajectories of this growing population of children. ■

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1. exp Child/

2. exp Child, Preschool/ or exp Adolescent/

3. exp Infant/ or exp Infant, Newborn/

4. (child: or toddler: or baby or infant* or adolescent*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

5. 1 or 2 or 3 or 4

6. exp Neonatal Abstinence Syndrome/

7. Finnegan*.mp.

8. Neonatal withdrawal.mp.

9. substance addict*.mp.

10. drug abuse*.mp.

11. substance depend*.mp.

12. Substance abuse.mp.

13. Neonatal withdrawal.mp.

14. exp Substance Withdrawal Syndrome/

15. drug addict*.mp.

16. Neonatal abstinence.mp.

17. lipsitz.mp.

18. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19. exp Health Status/ or Health outcome.mp. or exp "Outcome Assessment (Health Care)"/

20. exp Child Development/

21. exp Educational Status/

22. exp Learning Disorders/ or exp Educational Measurement/

23. exp Schools/ or School performance.mp. or exp Cognition/

24. exp Social Learning/ or Learning/ or exp Spatial Learning/ or exp Verbal Learning/

25. exp Intelligence Tests/ or exp Intelligence/ or exp Intellectual Disability/

26. 19 or 20 or 21 or 22 or 23 or 24 or 25

27. cohort*.tw.

28. exp Epidemiologic Methods/

Figure 1. Medline Ovid search strategy to identify studies of childhood outcomes after NAS. *(Continues)*

29. exp Case-Control Studies/

30. (case$ and control$).tw.

31. exp Cohort Studies/

32. exp Retrospective Studies/

33. exp Cross-Sectional Studies/

34. 27 or 28 or 29 or 30 or 31 or 32 or 33

35. Animals/

36. animal stud*.mp.

37. exp "Review"/

38. exp Case Reports/

39. congenital malform*.mp.

40. growth retard*.mp.

41. head circumference.mp.

42. gastrointestinal dys*.mp.

43. gastrointestinal abnorm*.mp.

44. gastrointestinal dis*.mp.

45. seizure*.mp.

46. convulsi*.mp.

47. visual develop*.mp.

48. visual dis*.mp.

49. visual dys*.mp.

50. nystagmus.mp.

51. strabismus.mp.

52. visual acuity.mp.

53. refractive error*.mp.

54. nervous system dys*.mp.

55. CNS dys*.mp.

56. nervous system abnorm*.mp.

57. CNS abnorm*.mp.

58. nervous system malform*.mp.

59. CNS malform*.mp.

60. nervous system dis*.mp.

Figure 1. Continued.

61. CNS dis*.mp.

62. neurodevelop*.mp.

63. growth restric*.mp.

64. (hospital admis* or hospitali* or length of stay or hospital readmis*).ti.

65. adverse outcome.mp.

66. physical health.mp.

67. hospital stay.mp.

68. mental health condi*.mp.

69. mental health dis*.mp.

70. mental health outcome.mp.

71. behaviour* abnorm*.mp.

72. 26 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71

73. 5 and 18 and 34 and 72

74. 35 or 36 or 37 or 38

75. 73 not 74

76. limit 75 to (english language and yr="1975 -Current")

Figure 1. Continued

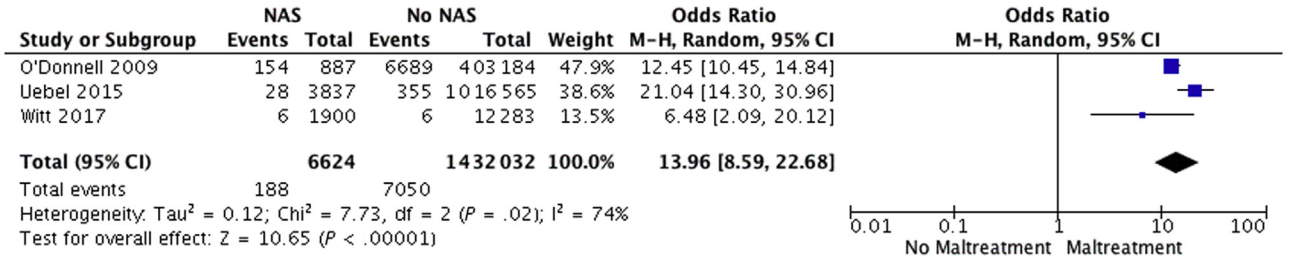

Figure 3. Odds of child maltreatment after NAS compared with those without previous NAS, by pooling crude data.

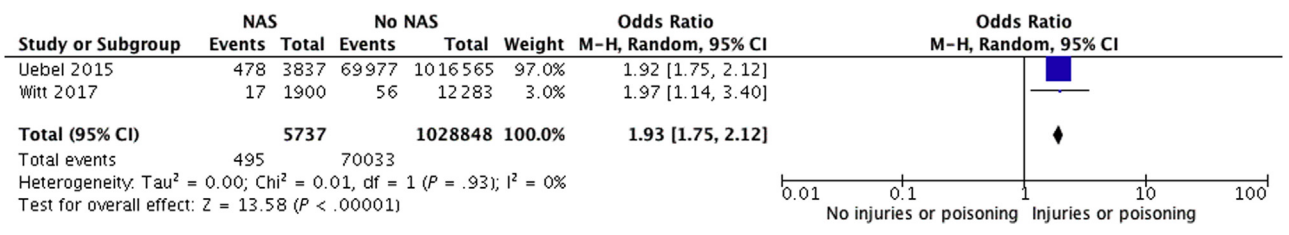

Figure 5. The odds of injuries and poisoning after NAS across studies, by pooling crude data.

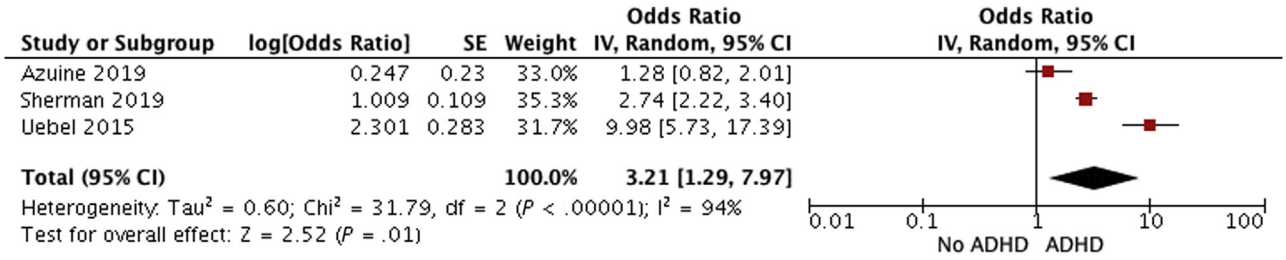

Figure 7. The pooled crude odds of attention deficit hyperactivity disorder (ADHD) after NAS.

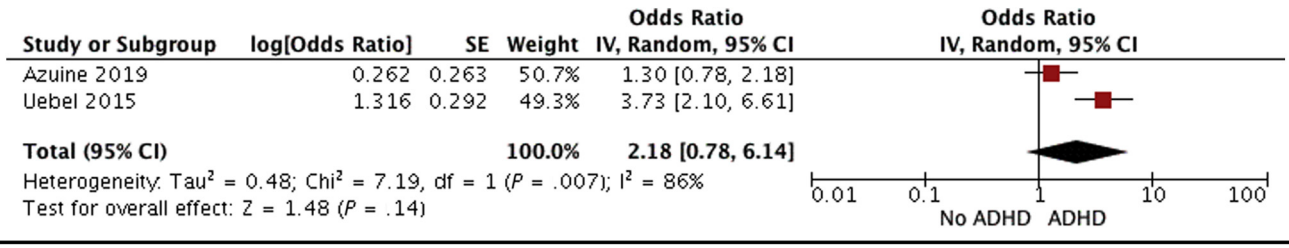

Figure 8. The pooled adjusted odds of attention deficit hyperactivity disorder (ADHD) after NAS.

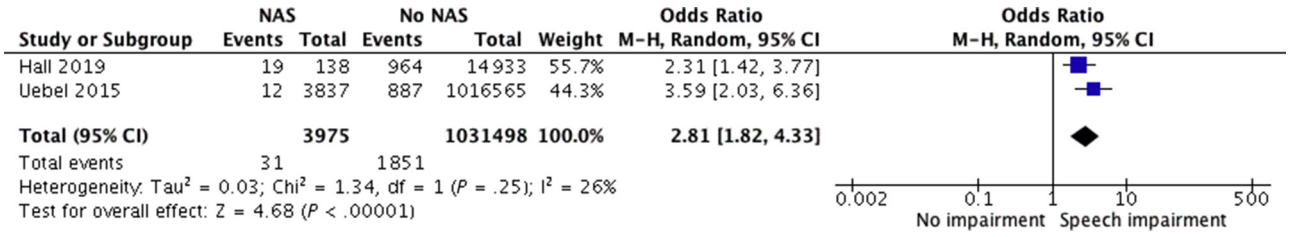

Figure 9. Pooled crude data for the probability of speech and language impairment after NAS; insufficient adjusted data were available for pooling.

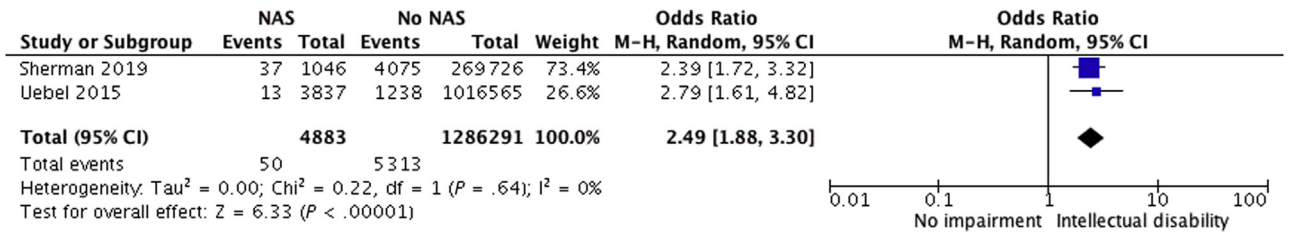

Figure 11. The pooled crude data for the probability of intellectual impairment after NAS; insufficient adjusted data were available for pooling.

Table I. PRISMA Checklist

Sections/topics	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1-3
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4, Fig 1, Table III
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Figure 1
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-6
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	5, e Table VI
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5-6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	6-7, Table II
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	e Table VI
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 3-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-9 Figures 3-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table VI
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	10-13
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).	10-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7):e1000097. https://doi.org/10.1371/journal.pmed1000097.
For more information, visit: www.prisma-statement.org.

Table II. MOOSE Checklist for Meta-analyses of Observational Studies of childhood outcomes after NAS

Item Nos.	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	3
2	Hypothesis statement	3
3	Description of study outcome(s)	5
4	Type of exposure or intervention used	4-5
5	Type of study designs used	4-5
6	Study population	4-5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	1, 5-6
8	Search strategy, including time period included in the synthesis and key words	5, Table III Figure 1
9	Effort to include all available studies, including contact with authors	4
10	Databases and registries searched	4-5, Table III
11	Search software used, name and version, including special features used (eg, explosion)	Table III, Figure 1
12	Use of hand searching (eg, reference lists of obtained articles)	4
13	List of citations located and those excluded, including justification	6, Figure 2
14	Method of addressing articles published in languages other than English	-
15	Method of handling abstracts and unpublished studies	4-5
16	Description of any contact with authors	5
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6-7
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	4-6
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	4-6
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	6-7
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	5, Table VI
22	Assessment of heterogeneity	6
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6 Figures 3-13
24	Provision of appropriate tables and graphics	Table I-VI, Figures 1-2
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figures 3-11
26	Table giving descriptive information for each study included	Table II
27	Results of sensitivity testing (eg, subgroup analysis)	-
28	Indication of statistical uncertainty of findings	6-10
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	-
30	Justification for exclusion (eg, exclusion of non-English language citations)	10-11
31	Assessment of quality of included studies	10-11 Table VI
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	10-13
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	10-13
34	Guidelines for future research	12-13
35	Disclosure of funding source	1

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. JAMA 2000;283(15):2008-2012. https://doi.org/10.1001/jama.283.15.2008.

Table III. Databases searched for systematic review of childhood outcomes after NAS

Databases searched	Search period
Cochrane Central Register of Controlled Trials	Inception-2019
EBSCO–CINAHL (Cumulative Index to Nursing and Allied Health Literature)	Inception-2019
Google Scholar	1975-2019
Ovid–EMBASE	1974-2019
Ovid–HMIC (Health Management Information Consortium)	1979-2019
Ovid–MEDLINE	1975-2019
Ovid–MEDLINE E-pub ahead of print	1975-2019
Ovid–MEDLINE In-Process and Other Non-Indexed Citations	1975-2019
PubMed	1975-2019
Scopus	Inception-2019
Web of Knowledge (science citation index expanded and conference proceedings citation index science)	1975-2019

Table IV. Ranking of confirmation of NAS or no NAS

Ranks	Descriptions
Ranking of confirmation of NAS among opioid exposed	
Rank 1*	NAS determined by the presence of signs consistent with NAS or the use of a standardized score by qualified providers
Rank 2*	NAS detailed in the medical records
Rank 3	NAS stated but no detail given
Rank 4	NAS suspected but no detail given
Ranking of NAS exclusion	
Rank a*	Antenatal opioid exposure excluded by toxicology screening
Rank b*	Antenatal opioid exposure excluded by multidisciplinary antenatal assessment
Rank c*	Antenatal opioid exposure and NAS excluded by checking of maternal and/or neonatal records
Rank d*	Exclusion of NAS stated but no detail given
Rank e	No attempt made to exclude antenatal opioid use or NAS

*Included in review.

Table V. Characteristics of included studies exploring childhood outcomes after NAS

Study (study design)	Year	Country	Age range (median)	NAS	No NAS	Exposure	Ascertainment	Outcomes	Main findings	Comments
Azuine et al[39] (Retrospective cohort)	2019	Massachusetts, US	0-16 years	281	8055	ICD-9 or ICD-10 code in medical records.	Electronic medical records 2013-2019	Diagnoses (ICD 9 and ICD 10)	**All age groups** **ADHD** OR, 1.28 (95% CI, 0.82-2.01) aOR, 1.3 (95% CI, 0.78-2.18) **Conduct disorder or emotional disturbance** OR, 1.37 (95% CI, 0.9-2.07) aOR, 1.48 (95% CI, 0.91-2.4) **Lack of expected normal physiologic development** OR, 2.18 (95% CI, 1.54-3.1) aOR, 2.06 (95% CI, 1.34-3.17) **Age <6 years** **ADHD** OR, 1.6 (95% CI, 0.82-3.11) aOR 1.01 (95% CI, 0.46-2.23) **Conduct disorder or emotional disturbance** OR, 2.17 (95% CI, 1.35-3.49) aOR 2.13 (95% CI, 1.2-3.77) **Lack of expected normal physiologic development** OR, 1.88 (95% CI, 1.33-2.66) aOR 1.8 (95% CI, 1.17-2.79) **Age ≥6 years** **ADHD** OR, 2.86 (95% CI, 1.67-4.91) aOR 2.55 (95% CI, 1.42-4.57) **Conduct disorder or emotional disturbance** OR, 2 (95% CI, 1.11-3.59) aOR 1.79 (95% CI, 0.95-3.35) **Lack of expected normal physiologic development** OR, 0.96 (95% CI, 0.43-2.12) aOR 0.62 (95% CI, 0.26-1.46)	Adjusted for pregnancy complications, birth outcomes, maternal age, household income, race, ethnicity, marital status, and maternal education.
Fill et al[29] (Retrospective cohort)	2018	Tennessee, US	3-8 years	1815	5441	ICD 10 code on Medicaid/ birth certificate	Medicaid/birth certificate data of infants born in Tennessee 2008-2011.	Those referred for assessment for an educational disability. - Learning disability - Developmental delay - Disorder of speech and language - Autism	**Eligibility for learning disability services** aOR 1.36 (95% CI, 1.15-1.6)* aOR 1.26 (95% CI, 1.06-1.49)† **Developmental delay** aOR 1.34 (95% CI, 1.03-1.76)* **Autism** OR, 0.82 (95% CI, 0.33-2.02) $P = .08$ **Speech and Language Impairment**: aOR 1.26 (95% CI, 1.04-1.52)*	*Adjusted for sex, race, ethnicity, age, public health region, insurance status, maternal smoking status in pregnancy, and maternal education status. †additional adjustment for gestation, birth weight and neonatal intensive care unit admission.
Gill et al[30] (Case series)	2003	Sydney, Australia	6-39 months (mean, 21 months)	35	n/a	NAS defined as those requiring pharmacologic treatment	Born May 1998 November 2000 and followed up in clinic, identified from medical record review.	Telephone survey Ophthalmologist (unblinded)	**Strabismus** n = 9 (5 on examination , 4 on telephone survey) **No strabismus** n = 26 (17 on examination 9 on telephone survey)	High attrition
Hamilton et al[31] (Case series)	2010	Scotland	Age at first assessment 3 months to 7 years (7 months)	12	n/a	Methadone exposure in utero, NAS defined as those requiring treatment.	Pediatric and neonatal case note review of children referred to a visual electrophysiology service who were exposed to methadone in utero.	Full ophthalmic examination Full orthoptic examination VEP testing (unblinded)	**Nystagmus** (n = 11) Those with severe NAS requiring treatment (n = 12) were more likely to have nystagmus than those exposed to methadone but without severe NAS; 11/12 (92%) vs 3/8 (38%), Fishers exact test $P = .018$ **Strabismus** (n = 4) Delayed visual maturation (n = 6) Refractive error (n = 2) Normal fundus (n = 11) Vessels over macula (n = 1)	Excluded those with gestation <32 weeks and those with other diagnosis to account for visual abnormalities. Polydrug exposure present. Varying ages of included children.

(*continued*)

Table V. Continued

Study (study design)	Year	Country	Age range (median)	NAS	No NAS	Exposure	Ascertainment	Outcomes	Main findings	Comments
Hall et al[40] (Retrospective cohort)	2019	Ohio, US	2-4 years	138	14 933	All infants requiring pharmacologic treatment for NAS.	Review of electronic medical records of all infants born 2014-2015. Hospital billing codes used to identify NAS.	Diagnoses (ICD-10): - Behavioral or emotional disorder - Developmental delay - Motor function developmental disorder - Otitis media - Plagiocephaly - Sensory disorder - Speech disorder - Strabismus - Torticollis	**Crude OR Behavioral or emotional disorder** OR, 5.31 (95% CI, 2.56-11.02) **Developmental delay** OR, 4.77 (95% CI, 3.28-6.95) **Motor function developmental disorder** OR, 3.65 (95% CI, 1.68-7.92) **Otitis media** OR, 1.14 (95% CI, 0.8-1.65) **Plagiocephaly** OR, 6.13 (95% CI, 3.48-10.79) **Sensory disorder** OR, 3.36 (95% CI, 2.22-5.09) **Speech disorder** OR, 2.31 (95% CI, 1.41-3.77) **Strabismus** OR, 12 (95% CI, 6.91-21.18) **Torticollis** OR, 4.32 (95% CI, 2.37-7.89)	Excluded those with gestation <34 weeks, complex clinical conditions, congenital anomalies. Baseline characteristics of gestation and gender similar between groups. Differences in ethnicity and insurance status between groups. No matching or adjustment for confounders. A sensitivity analysis was done for insurance status, which did not affect the significance of the results extracted for this review. Overlapping data with McAllister 2018.
McAllister et al[32] (Case series)	2018	Ohio, US	30-582 days (120.9 days)	783	n/a	All infants requiring pharmacologic treatment for NAS referred to a tristate clinic.	Retrospective review of clinic notes of children with NAS, born Jan 2012-Dec 2016. Hospital billing codes used to ascertain torticollis diagnosis.	Diagnosis of torticollis	**Torticollis** (n = 87) **Plagiocephaly and torticollis** (n = 58)	Excluded if gestation <35 weeks; major craniofacial abnormalities. Polydrug exposure present. High attrition. Overlapping data with Hall 2019.
McGlone et al[33] (Prospective cohort)	2014	Glasgow	26-30 months (27 weeks)	41	26	Infants exposed to methadone in utero. NAS defined as those requiring pharmacologic treatment.	Recruited within 3 days of life born October 2008 to April 2010.	Outcomes at 6 mo (VEP and clinical visual outcomes) pediatrician and 2 optometrists (blinded). Atkinson test battery of child development for functional vision.	Abnormal VEP (n = 24) Failed visual assessment (n = 20) including: Delayed visual maturation (n = 7) Abnormal pattern onset VEP (n = 7) Abnormal neonatal flash VEPs (n = 10) **Strabismus** (n = 13) **Nystagmus** (n = 6) Refractive error (n = 5)	Excluded those with gestation <36weeks, congenital abnormalities and neonatal illness. Polydrug exposure present.
Merhar et al[34] (Case series)	2018	Ohio, US	18-28 months (23 months)	87	n/a	Electronic medical record search to identify all those with a diagnosis of NAS	Electronic medical records of all patients seen in Cincinnati Neonatal Intensive Care Unit follow-up clinic 2011-2015.	Bayley III examination at 2 years (un-blinded)	Children with previous NAS scored significantly lower across all domains compared to normative Bayley data. **Cognitive** 96.5 ($P < .03$) **Language** 93.8 ($P < .03$) **Motor** 94 ($P < .03$)	Excluded those with other neonatal comorbidities, gestation <34 weeks, iatrogenic (postnatal) NAS. High attrition.
O'Donnell et al[35] (Retrospective cohort)	2009	Western Australia	0-15 years Exposed group (1 year) Comparator group (3 years)	887	403 184	ICD-9 and -10 codes for NAS on administrative data	Children born 1990-2005 with ICD 9 and ICD 10 codes for NAS using administrative data.	Substantiated child maltreatment allegation identified from probabilistic linkage to child protection data.	**Substantiated child maltreatment allegation:** OR, 12.45 (95% CI, 10.45-14.84) Adjusted OR, 8 (95% CI, 6.5-9.9) 73% of the substantiated child maltreatment after NAS was neglect	Adjusted for ethnicity, maternal age, maternal marital status, social disadvantage, and maternal occupation.

(*continued*)

Table V. Continued

Study (study design)	Year	Country	Age range (median)	NAS	No NAS	Exposure	Ascertainment	Outcomes	Main findings	Comments
Oei et al[36] (Retrospective cohort)	2017	New South Wales, Australia	Grade 3: 8-9 years Grade 5: 10-11 years Grade 7: 12-13 years	1688	3359	ICD 10 code for NAS	All children born 2000-2006 New South Wales; ICD 10 code for NAS present in administrative data linked to NAPLAN database.	NAPLAN database Below NMS at any point	**Below NMS on any occasion:** **Grade 3**: OR, 2.4 (95% CI, 2.1, 2.7) **Grade 5**: OR, 2.3 (95% CI, 2.1, 2.6) **Grade 7**: OR, 2.1 (95% CI, 1.7, 2.4) **Reading mean score (SD)** **Grade 3:** 360.8 ± 81.8 NAS; 410.3 ± 86.6 control Below NMS: OR, 3.1 (95% CI, 2.4-3.9) **Grade 5:** 449.2 ± 72.9 NAS; 490.3 ± 77.5 control Below NMS: OR, 2.6 (95% CI, 2.0-3.4) **Grade 7:** 493.5 ± 68.3 NAS; 533.8 ± 74.7 Below NMS: OR, 2.9 (95% CI, 2.0-4.3) **Numeracy mean score (SD)** **Grade 3:** 350.1 ± 65.5 vs 393.1 ± 75.2 Below NMS: OR, 2.2 (95% CI, 1.8-2.9) **Grade 5:** 440.3 ± 61.6 vs 485.2 ± 74.1 Below NMS: OR, 2.6 (95% CI, 1.9, 3.3) **Grade 7:** 489.8 ± 54.4 vs 536.6 ± 76.1 Below NMS: OR, 2.7 (95% CI, 1.8-4.1) **Writing mean score ± SD** **Grade 3:** 365.1 ± 78.2 vs 415.3 ± 69.4 Below NMS: OR, 3.2 (95% CI, 2.4-4.2) **Grade 5:** 428.7 ± 72.9 vs 474.8 ± 67.9 Below NMS: OR, 3.4 (95% CI, 2.7-4.3) **Grade 7:** 442.4 ± 100.8 vs 501.2 ± 81.3 Below NMS: OR, 3.4 (95% CI, 2.6-4.6) **Grammar mean score ± SD** **Grade 3:** 357.2 ± 96.8 vs 417.2 ± 96.8 Below NMS: OR, 3.1 (95% CI, 2.5-3.8) **Grade 5:** 446.9 ± 79.9 vs 496.5 ± 86.5 Below NMS: OR, 3.1 (95% CI, 2.5-3.8) **Grade 7:** 490.7 ± 77.5 vs 530.4 ± 83.7 Below NMS: OR, 2 (95% CI, 1.5, 2.8) **Spelling mean score ± SD** **Grade 3**: 356.5 ± 82.1 vs 412.3 ± 82.3 Below NMS: OR, 4.3 (95% CI, 3.4, 5.4) **Grade 5:** 447.3 ± 79.1 vs 496.4 ± 75.1 Below NMS: OR, 3.7 (95% CI, 2.8-4.8) **Grade 7:** 504.2 ± 81.9 vs 544.9 ± 72.6 Below NMS: OR, 3.1 (95% CI, 2.2-4.4)	Nonattendance was assigned as below NMS. Comparison with control group and general population. 75% of records linked. Overlap in population with Uebel 2015
Sandtorv et al[41] (Case series)	2018	Norway	Mean 10.4 years	18	n/a	Those scoring ≥8 on the modified Finnegan Score	Medical records and questionnaires completed by caregivers	Wechsler Preschool and Primary Scale of Intelligence test Wechsler Intelligence Scale for Children. The SNAP-IV The ASSQ	**Standardized regression coefficients for NAS as the independent variable.** **SNAP combined:** β 0.22 **SNAP inattention** β 0.29 **SNAP hyperactivity/impulsivity** β 0.12 **ASSQ total** β 0.09 **ASSQ social difficulties** β 0.09 **ASSQ motor/tics/OCD** β 0.22 **ASSQ autistic style** β –0.08	Comparator group (did not meet our inclusion criteria as no attempts made to exclude NAS) therefore the outcomes for those with NAS are not comparative. This is essentially a case series for this review's purpose.

(*continued*)

Table V. Continued

Study (study design)	Year	Country	Age range (median)	NAS	No NAS	Exposure	Ascertainment	Outcomes	Main findings	Comments
Sherman 2019 (42) (Retrospective cohort)		US	1-5 years	1046	269 726	ICD-9 code	Claims from the Truven Health Analytics' Multi-State Medicaid Database	Mental health diagnoses ICD 9 codes	**Any mental health disorder** 511 (48.9) vs 81 814 (30.3) **Specific delays in development (eg language, coordination)** 327 (31.3) vs 49 591 (18.4) **Disturbance of conduct** 113 (10.8) vs 10 879 (4) **Hyperkinetic syndrome (eg ADHD)** 94 (9) vs 9372 (3.5) **Adjustment reaction** 75 (7.2) vs 7799 (2.9) **Acute reaction to stress** 49 (4.7) vs 8123 (3) **Neurotic disorders** 43 (4.1) vs 7365 (2.7) **Special symptoms or syndromes** 41 (3.9) vs 9672 (3.6) **Disturbance of emotions** 39 (3.7) vs 5350 (2) **Intellectual disabilities** 37 (3.5) vs 4075 (1.5) **Psychoses with origin specific to childhood** 32 (3.1) vs 4752 (1.8)	No matching between comparator groups. Considerable differences between the populations compared. No adjustment for confounders. Only followed up those with 5 years of consecutive Medicaid enrolment: (33% of the initially identified population)

(*continued*)

Table V. Continued

Study (study design)	Year	Country	Age range (median)	NAS	No NAS	Exposure	Ascertainment	Outcomes	Main findings	Comments
Uebel et al[11] (Retrospective cohort)	2015	New South Wales, Australia	0-13 years (1-4 years)	3837	1 016 565	ICD 10 code for NAS	Administrative datasets: Perinatal data collection of NSW; admitted patient data collection; NICUs data collection	Hospitalization information including: 1. ICD-10 diagnoses 2. Hospitalization outcomes	**Child maltreatment** OR, 21.04 (95% CI, 14.3-30.96) aOR 5.08 (95% CI, 3.38-7.64) **Neglect** OR, 27.02 (95% CI, 14.91-48.98) aOR 4.81 (95% CI, 2.58-8.97) **Injury and poisoning** OR, 1.93 (95% CI, 1.75-2.12) aOR 1.34 (95% CI, 1.2-1.49) **Learning disability** OR, 2.79 (95% CI, 1.61-4.82) aOR 1.68 (95% CI, 0.96-2.93) **Behavioral and emotional disorders** OR, 4.08 (95% CI, 2.88-5.8) aOR 2.3 (95% CI, 1.6-3.3) **Conduct disorder** OR, 3.42 (95% CI, 1.98-5.92) aOR 2.11 (95% CI, 1.21-3.7) **ADHD** OR, 9.99 (95% CI, 5.73-17.39) aOR 3.73 (95% CI, 2.1-6.61) **Disorders of speech and language** OR, 3.59 (95% CI, 2.03-6.36) aOR 2.42 (95% CI, 1.35-4.34) **Autism** OR, 3.58 (95% CI, 2.15-6) aOR 2.48 (95% CI, 1.47-4.18) **Cerebral palsy** OR, 3.12 (95% CI, 2.01-4.86) aOR 1.9 (95% CI, 1.21-2.99) **Diseases of the eye** OR, 2.94 (95% CI, 2.49-3.47) aOR 1.93 (95% CI, 1.62-2.31) **Strabismus** OR, 7.9 (95% CI, 6.27-9.97) aOR 4.73 (95% CI, 3.69-6.05) **Nystagmus** OR, 12.49 (95% CI, 6.82-22.88) aOR, 7.99 (95% CI, 4.15-15.4) **Diseases of the digestive system** OR, 1.59 (95% CI, 1.33-1.89) aOR 1.15 (95% CI, 0.96-1.38) **Respiratory system diseases** OR, 1.47 (95% CI, 1.37-1.59) aOR 0.85 (95% CI, 0.79-0.93) **Asthma** OR, 1.8 (95% CI, 1.57-2.07) aOR 1.1 (95% CI, 0.95-1.27) **Respiratory infection** OR, 1.74 (95% CI, 1.55-1.95) aOR 1 (95% CI, 0.88-1.13) **Disease of the skin and subcutaneous tissue** OR, 1.98 (95% CI, 1.72-2.29) aOR 1.26 (95% CI, 1.08-1.46) **Diseases of the musculoskeletal system** OR, 1.40 (95% CI, 1.05-1.87) aOR 1.07 (95% CI, 0.79–1.43) **Infections and parasitic disease** OR, 1.54 (95% CI, 1.41-1.68) aOR 1.01 (95% CI, 0.92-1.11) **Diseases of the genitourinary system** OR, 1.06 (95% CI, 0.87-1.3) aOR 0.92 (95% CI, 0.75-1.13)	Adjusted for gender, young mother (<20 years) maternal smoking, prematurity, low socioeconomic indexes for area, rural residence, indigenous Australian. Excluded if gestational age at birth <23 weeks >45 weeks, and stillbirths.

(*continued*)

Table V. Continued

Study (study design)	Year	Country	Age range (median)	NAS	No NAS	Exposure	Ascertainment	Outcomes	Main findings	Comments
Witt et al[37] (Retrospective cohort)	2017	Washington, US	1-5 years (0-1 years)	1900	12 283	ICD-9 code on birth hospitalization discharge data	Singleton infants born in Washington State 1990-2008 identified using birth certificate data linked to hospitalization records	1. Hospital readmission in first 5 years of life 2. Infant mortality 3. Reason for hospital admission	**Child maltreatment** RR, 6.46 (95% CI, 2.09-20.02) aRR, 4.46 (95% CI, 1.16-17.15) **Injury and poisoning** RR, 1.96 (95% CI, 1.14-3.37) aRR, 1.58 (95% CI, 0.75-3.31) **Diseases of the nervous system** RR, 2.63 (95% CI, 1.64-4.22) aRR, 2.07 (95% CI, 1.12-3.82) **Diseases of the digestive system** RR, 2.18 (95% CI, 1.67-2.83) aRR, 2.07 (95% CI, 1.49-2.86) **Diseases of the respiratory system** RR, 2.09 (95% CI, 1.79-2.43) aRR, 1.59 (95% CI, 1.33-1.91) **Asthma** RR, 2.74 (95% CI, 2.08-3.61) aRR, 1.82 (95% CI, 1.29-2.57) **Respiratory Infections** RR, 1.80 (95% CI, 1.35-2.40) aRR, 1.28 (95% CI, 0.92-1.77) **Diseases of the skin and subcutaneous tissue** RR, 3.23 (95% CI, 2.33-4.48) aRR, 3.04 (95% CI, 2.12-4.36) **Infections and parasitic disease** RR, 1.87 (95% CI, 1.53-2.29) aRR, 1.72 (95% CI, 1.35-2.21) **Disease of the genitourinary system** RR, 2.29 (95% CI, 1.56-3.35) aRR, 2.28 (95% CI, 1.49-3.50)	Adjusted for maternal education, gestational age, race and intrapartum smoking.
Yoo et al[38] (Case series)	2017	Washington, US	1-18 months	27	n/a	NAS stated in medical records (including cases that did and did not require pharmacologic treatment)	Exposed children identified from addiction center clinic and medical charts used to extract data.	Strabismus (unblinded)	Strabismus n = 17	Limited detail as study was designed to follow-up neonates prenatally exposed to opioids not those specifically with NAS. Did not exclude premature neonates, or neonates with other morbidities. Polydrug exposure present.

ADHD, attention deficit hyperactivity disorder; *ASSQ*, Autism Spectrum Screening Questionnaire; *NMS*, National Minimum Standard; *SNAP-V*, Swanson, Nolan, and Pelham Questionnaire; *VEP*, visual evoked potential.

Table VI. Quality assessments scores for each study exploring childhood outcomes After NAS

		Selection (S)				Comparability (C)		Exposure/outcome (E/O)			Subtotal assessment			
Studies	Year	1	2	3	4	1a	1b	1	2	3	S	C	E/O	Conclusion
Cohort studies														
Azuine et al[39] 2019	2019	*	*	*	No	*	*	*	*	No	Good	Good	Good	Good
Fill et al[29]	2018	No	*	*	*	*	*	*	No	No	Fair	Good	Fair	Fair
Hall et al[30]	2019	*	*	*	No	No	No	*	No	*	Fair	Poor	Good	Poor
McGlone et al[33]	2014	*	No	*	*	*	*	*	*	No	Good	Good	Good	Good
O'Donnell et al[35]	2009	*	*	*	No	*	*	*	*	No	Good	Good	Good	Good
Oei et al[36]	2017	*	*	*	*	*	*	*	*	No	Good	Good	Good	Good
Uebel et al[11]	2015	*	*	*	No	*	*	*	*	No	Good	Good	Good	Good
Witt et al[37]	2017	*	*	*	No	*	*	*	No	*	Good	Good	Good	Good
Case series														
Gill et al[30]	2003	*	n/a	*	*	n/a	n/a	No	*	No	Fair	n/a	Fair	Fair
Hamilton et al[31]	2010	*	n/a	*	No	n/a	n/a	*	*	*	Fair	n/a	Good	Fair
Merhar et al[34]	2018	*	n/a	*	*	n/a	n/a	*	*	No	Good	n/a	Good	Good
McAllister et al[32]	2018	*	n/a	*	*	n/a	n/a	*	*	No	Good	n/a	Good	Good
Sandtorv et al[41]	2018	*	n/a	*	n/a	n/a	n/a	No	*	No	Good	n/a	Fair	Fair
Yoo et al[38]	2017	No	n/a	*	n/a	n/a	n/a	*	*	No	Poor	n/a	Good	Poor

n/a, not applicable.
Selection: 1 (representativeness) 2 (selection of comparators) 3 (exposure ascertainment) 4 (absence of outcome of interest at study start); comparability: 1a (controlled for gestation) 1b (controlled for other confounders); exposure/outcome: 1 (outcome assessment) 2 (follow-up duration) 3 (follow-up adequacy) subtotal assessment: S 0-1 (poor); 2 (fair); 3+ (good) C 0 (poor); 1 (fair); 2+ (good); E/O 0 (poor); 1(fair); 2+(good)
*Satisfactory.