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

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The authors declare no conflicts of interest. **Abbreviations:**

Adjusted Odds Ratio (aOR)

Attention Deficit Hyperactivity Disorder (ADHD)

Confidence Intervals (CI)

International Classification of Disease (ICD)

Neonatal Abstinence Syndrome (NAS)

Odds Ratio (OR)

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 1/1/75, and 9/3/19, and 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 two trained reviewers, who extracted study data and assessed risk of bias using the Newcastle Ottawa Tool.

Results: Fifteen studies were included comprising 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 (4.46, 9.45, I^2=52%)), injuries and poisoning (aOR 1.34 (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. Due to the necessary inclusion of non-randomized 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.

Neonatal Abstinence Syndrome (NAS) has become a global problem.(1-4) The syndrome describes the postnatal signs of physiological distress following withdrawal of narcotics that a newborn infant has been exposed to in utero.(5) NAS has been declared a national crisis in the United States 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, higher misuse of newer potent opioids, and improved provision of opioid substitution programs.(5, 7)

NAS is a clinical diagnosis of a multi-system postnatal disorder affecting the gastrointestinal, central and autonomic nervous systems.(5, 8) Affected newborn infants may experience physiological 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 is illustrated by the 147% increase in the number of children entering foster care due to parental substance in the USA since 2000.(12-15)

Given the potential impact of NAS on the developing infant's physiology, the rapid rise 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.

Methods

This review is reported according to the PRISMA statement and MOOSE guidelines and follows an *a-priori* protocol (CRD42019132659) (Table 1 and Table 2; 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 non-opioid NAS; studies with mixed populations of infants: where infants with NAS formed a non-representative 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 1/1/75 to 9/3/19 (Table 3; available at www.jpeds.com). The time frame was selected to capture studies published after the Finnegan Score was introduced in 1975,(23) as this was the first clinically validated diagnostic tool for opioid-related NAS. 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 non-indexed 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 4; 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 and duplicates 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 methodological quality of each full-text was assessed by two trained reviewers) independently; a forth 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. In the absence of raw data, risk ratios were estimated as odds ratios, and pooled odds ratios 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% confidence intervals (CI), p-values and I^2 measures of heterogeneity. Where studies provided both crude and adjusted odds ratios (aOR) – and adjusted for similar confounders – we performed separate meta-analyses. The degree of statistical heterogeneity was assessed using the I^2 statistic and due 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 six 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 5; 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),(11, 29, 35-37, 39, 40, 42) prospective cohort studies (n=1),(33) and case series (n=6).(30-32, 34, 38, 41) Eight studies were deemed to be overall good quality,(11, 32-37, 39) 4 were deemed fair,(29-31, 41) and three poor (Table 6; available at www.jpeds.com).(38, 40, 42) Included studies were published between 2003-2019 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 5).

Child maltreatment and injuries

Meta-analysis of three 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, and maternal ethnicity, smoking status and age. The pooled aOR was to 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)

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 ICD diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) after NAS.(11, 39, 42) On pooling the crude data from these studies, a significant association with ADHD 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 two 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 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 (up to 13 years of age) and the aOR was 2.48 (95% CI 1.47, 4.18).(11) Whereas Fill et al identified autism in those aged 3-8 years referred for assessment of educational disability and the OR was 0.82 (95% CI 0.33, 2.02): adjusted data were not provided.(29) These studies were not pooled due 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) Due 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 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 highlighted specifically increased risks 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 two 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 assessment for an education disability.(29) After adjusting for sex, ethnicity, age, 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 5).(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. Whereas 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 gender. The proportion of children below national minimum standard at three 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 three 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 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 following 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 sub-optimal, 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, as 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 non-randomized 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 policy makers.

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 ICD codes, and did not provide sufficient information about outcome ascertainment such as age. Although this is sub-optimal, 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, due 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 as 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) Opioid using mothers have higher rates of mental illness, poverty, incarceration, poor education and poor physical health.(35, 52-55) This 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 explores adverse childhood experiences within the NAS population with a view to understanding the potential causative pathways underlying these associations. Such research should employ propensity score matching to account for potential confounders.(11-13) Timely identification of children at-risk of 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 pharmacological treatment, and placement in out-of-home care.(12) We agree with Wachman et al that further prospective studies, adequately adjusting for antenatal exposure, socio-demographic factors, and neonatal treatment, are warranted to address these questions.(56) On-going work aiming to develop a core-outcome set for NAS research will help 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 reduce 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 reducing child maltreatment.(35, 58, 59)

Children with NAS are often followed up during the neonatal period. However long-term multi-disciplinary 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 e.g. 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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Figure 1 (online only): Medline Ovid search strategy to identify studies of childhood outcomes after NAS

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

Figure 3 (online only): Cdds of child maltreatment after NAS compared with those without previous NAS, by pooling crude data.

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

Figure 5 (online only): The odds of injuries and poisoning after NAS across studies, by pooling crude data.

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

Figure 7 (online only): The pooled crude odds of Attention Deficit Hyperactivity Disorder (ADHD) after NAS

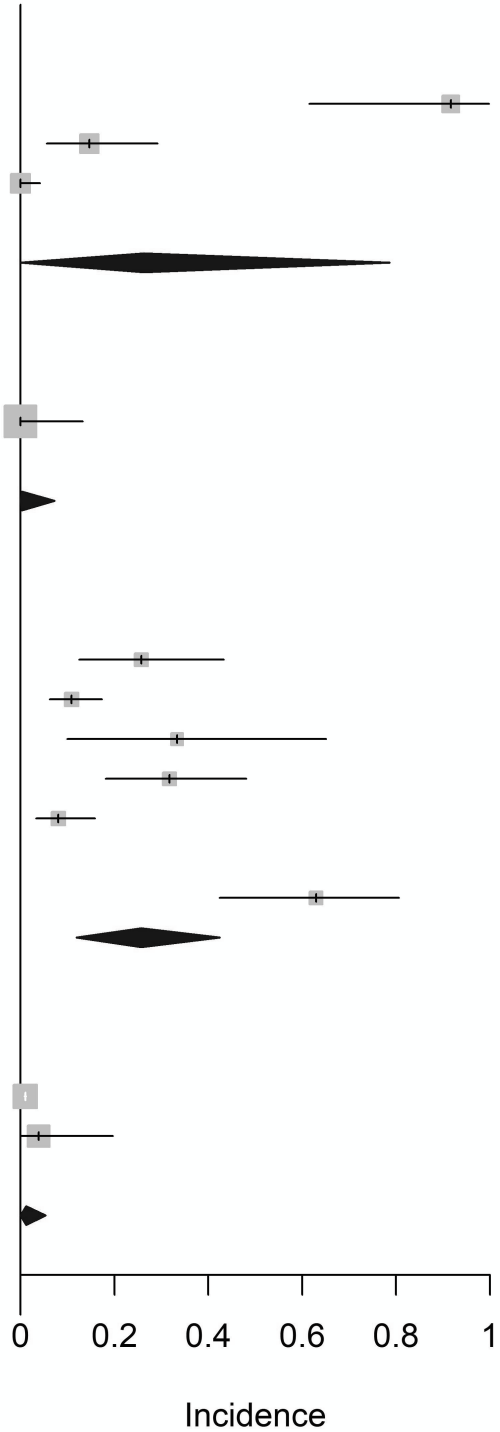
Figure 8 (online only): The pooled adjusted odds of Attention Deficit Hyperactivity Disorder (ADHD) after NAS

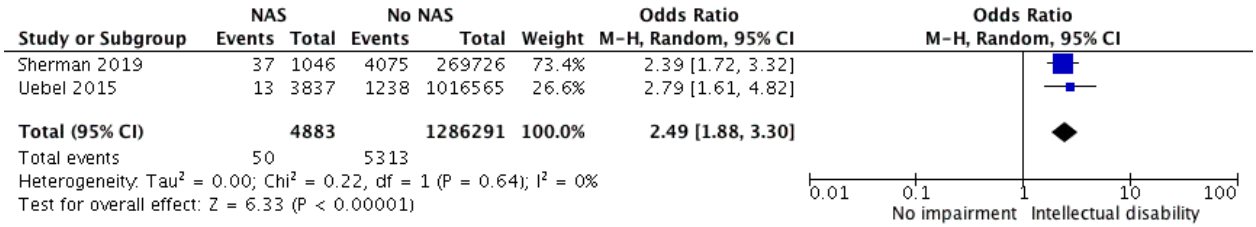
Figure 9 (online only): Pooled crude data for the probability of speech and language impairment after NAS; insufficient adjusted data were available for pooling.

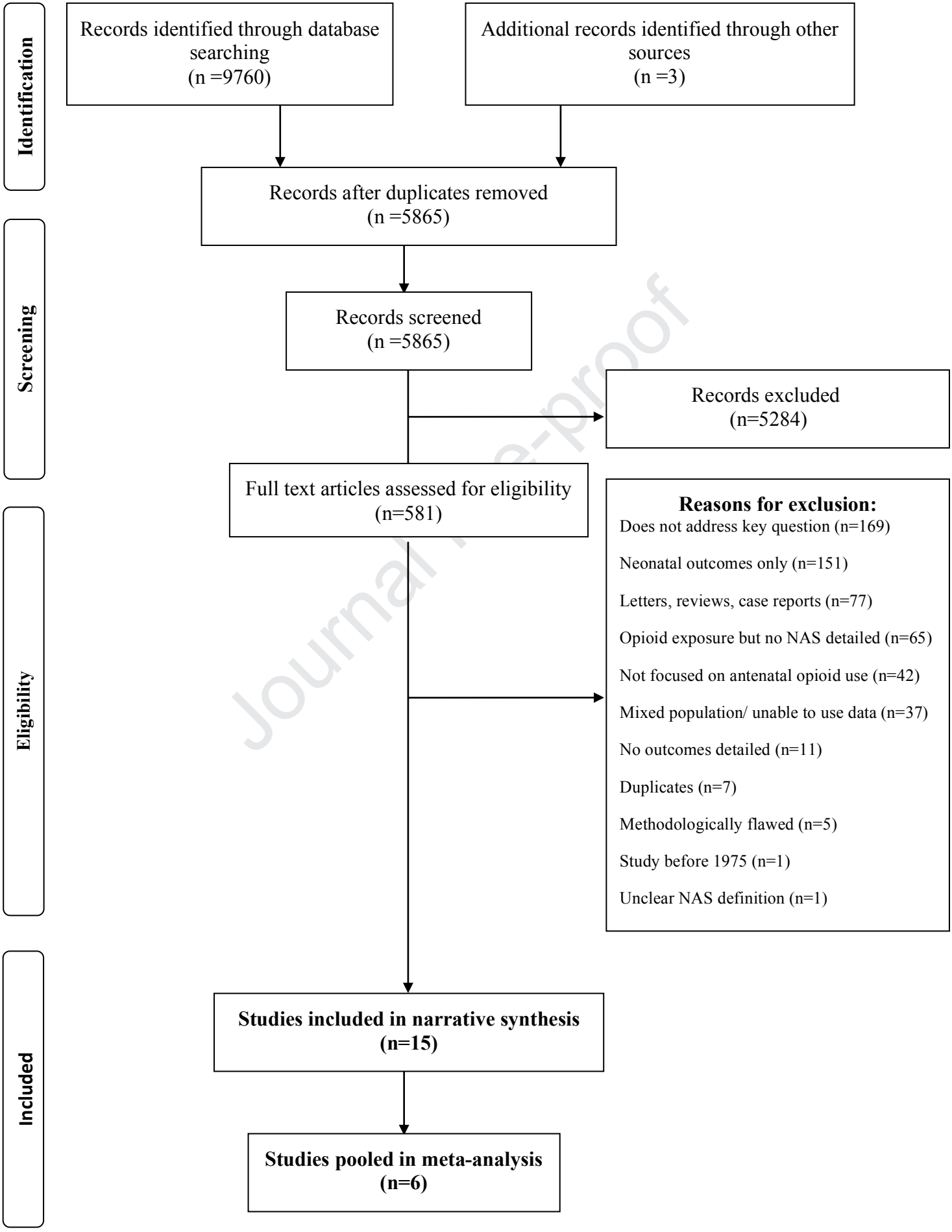
Figure 10: Forest plot of incidence of strabismus and nystagmus among those with and without previous NAS.

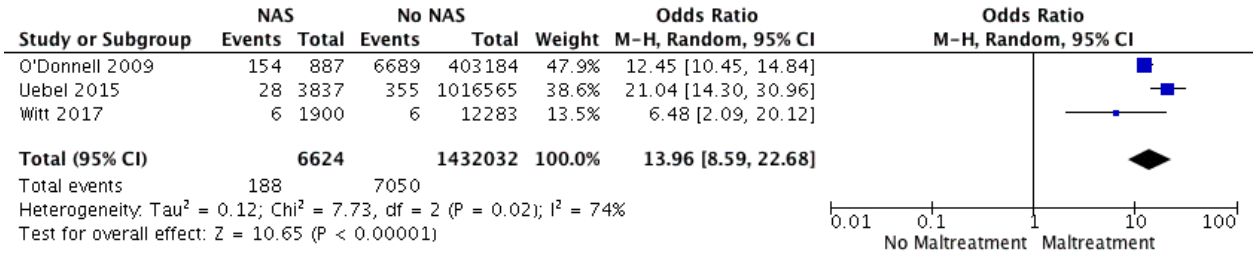
Figure 11 (online only): The pooled crude data for the probability of intellectual impairment after NAS; insufficient adjusted data were available for pooling

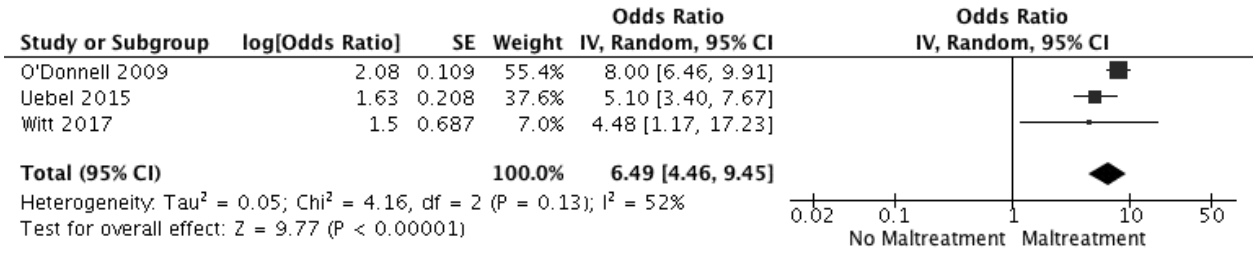
Study	Children/Total	Incidence	95% CIs	Weights
Nystagmus (NAS)				
Hamilton, 2010	11/12	0.917	[0.615; 0.998]	28.9%
McGlone, 2014	6/41	0.146	[0.056; 0.292]	34.7%
Merhar, 2018	0/87	0.000	[0.000; 0.042]	36.4%
Uebel, 2015	11/3937	0.003	[0.001; 0.005]	0.0%
Summary		**0.263**	**[0.000; 0.786]**	**100.0%**
I^2 = 97%				
Nystagmus (No NAS)				
McGlone, 2014	0/26	0.000	[0.000; 0.132]	100.0%
Uebel, 2015	234/1016565	0.000	[0.000; 0.000]	0.0%
Summary		**0.002**	**[0.000; 0.072]**	**100.0%**
I^2 = NA%				
Strabismus (NAS)				
Gill, 2003	9/35	0.257	[0.125; 0.433]	16.7%
Hall, 2019	15/138	0.109	[0.062; 0.173]	18.1%
Hamilton, 2010	4/12	0.333	[0.099; 0.651]	14.1%
McGlone, 2014	13/41	0.317	[0.181; 0.481]	17.0%
Merhar, 2018	7/87	0.080	[0.033; 0.159]	17.8%
Uebel, 2015	75/3837	0.020	[0.015; 0.024]	0.0%
Yoo, 2017	17/27	0.630	[0.424; 0.806]	16.3%
Summary		**0.257**	**[0.119; 0.424]**	**100.0%**
I^2 = 89%				
Strabismus (No NAS)				
Hall, 2019	149/14933	0.010	[0.008; 0.012]	53.5%
McGlone, 2014	1/26	0.038	[0.001; 0.196]	46.5%
Uebel, 2015	2558/1016565	0.003	[0.002; 0.003]	0.0%
Summary		**0.012**	**[0.000; 0.053]**	**100.0%**
I^2 = 48%				

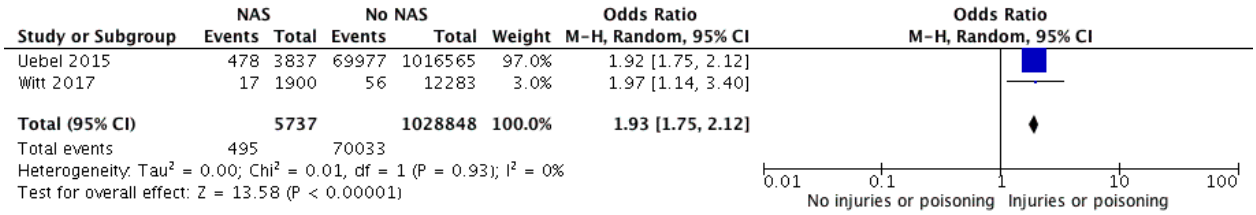


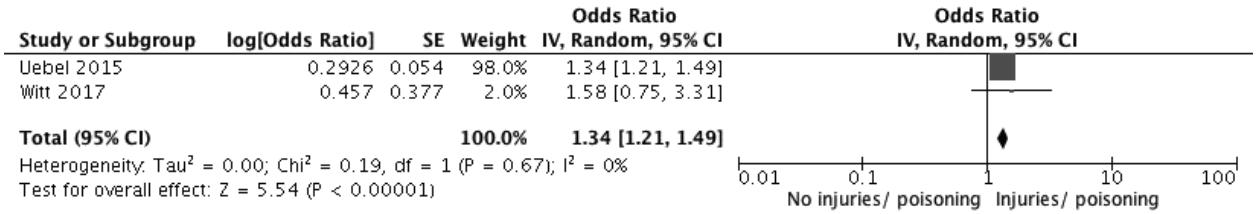


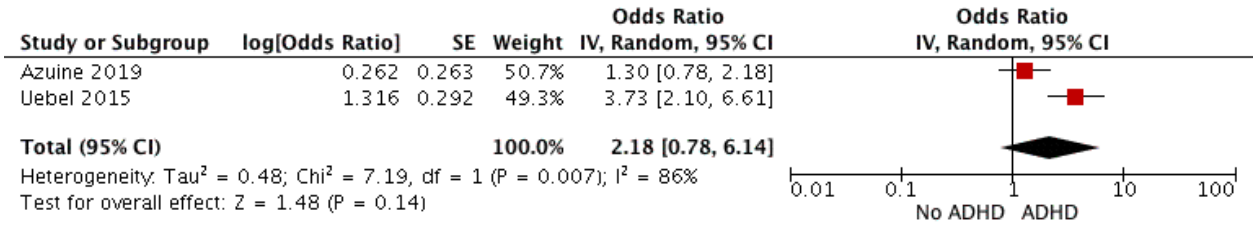


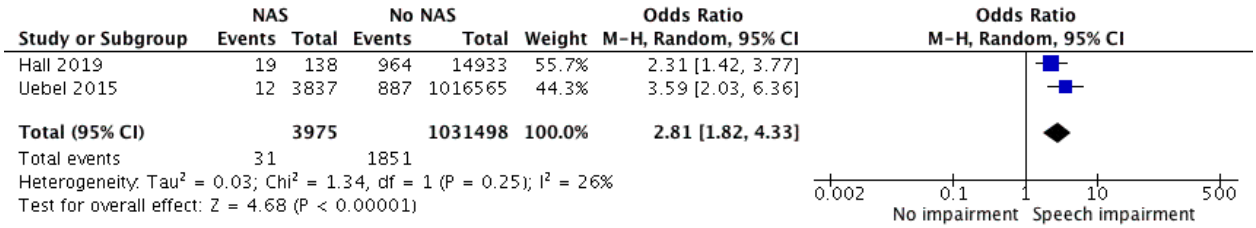












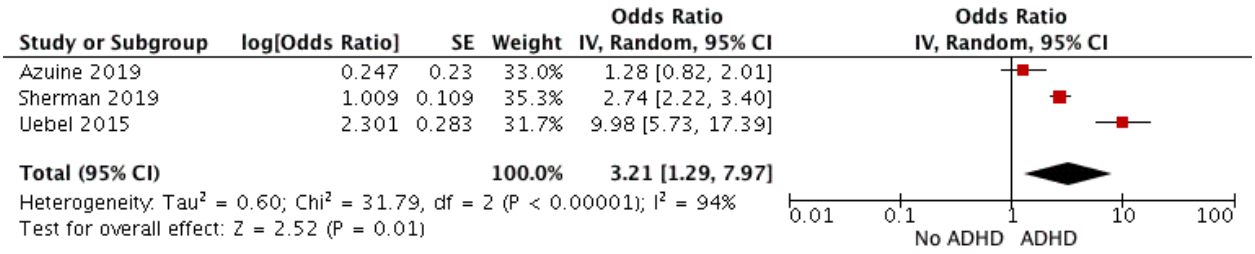


Table 1 (online only): PRISMA Checklist

Section/topic	#	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 (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4, Fig 1, Table 3
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 (i.e., 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 (e.g., 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 (e.g., 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 (e.g., 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 (e.g., I^2) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5, e Table 6
Additional analyses	16	Describe methods of additional analyses (e.g., 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 (e.g., study size, PICOS, follow-up period) and provide the citations.	6-7, Table 2
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 6
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).	eTable 6
Additional analysis	23	Give results of additional analyses, if done (e.g., 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 (e.g., healthcare providers, users, and policy makers).	10-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., 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 (e.g., 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. doi:10.1371/journal.pmed1000097

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

Table 2 (online only): MOOSE Checklist for Meta-analyses of Observational Studies of childhood outcomes after NAS

Item No	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 3 Figure 1
9	Effort to include all available studies, including contact with authors	4
10	Databases and registries searched	4-5, Table 3
11	Search software used, name and version, including special features used (eg, explosion)	Table 3, 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 6
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 1-4, 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 2
27	Results of sensitivity testing (eg, subgroup analysis)	-
28	Indication of statistical uncertainty of findings	6-10

Item No	**Recommendation**	**Reported on Page No**
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 6
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. doi: 10.1001/jama.283.15.2008.

Table 3 (online only): Databases searched for systematic review of childhood outcomes after NAS	
Database 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 4 (online only): Ranking of confirmation of NAS or no NAS (*included in review)

Ranking of confirmation of NAS amongst 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 multi-disciplinary 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

Table 5 (online only): Characteristics of included studies exploring childhood outcomes after NAS

Study Author and Year (Study design)	Country	Age range (Median)	NAS	No NAS	Exposure	Ascertainment	Outcomes	Main findings	Comments
Azuine 2019 (39) (Retrospective cohort)	Massachusetts, USA	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)	**<u>All age groups</u>** **ADHD** OR1.28 (0.82-2.01) Adj OR 1.3 (0.78-2.18) **Conduct disorder or emotional disturbance** OR 1.37 (0.9-2.07) aOR 1.48 (0.91-2.4) **Lack of expected normal physiological development** OR 2.18 (1.54-3.1) aOR 2.06 (1.34-3.17) **<u>Age <6 years</u>** **ADHD** OR 1.6 (0.82-3.11) aOR 1.01 (0.46-2.23) **Conduct disorder or emotional disturbance** OR 2.17 (1.35-3.49) aOR 2.13 (1.2-3.77) **Lack of expected normal physiological development** OR 1.88 (1.33-2.66) aOR 1.8 (1.17-2.79) **<u>Age 6 years and over</u>** **ADHD** OR 2.86 (1.67-4.91) aOR 2.55 (1.42-4.57) **Conduct disorder or emotional disturbance** OR 2 (1.11-3.59) aOR 1.79 (0.95-3.35) **Lack of expected normal physiological development** OR 0.96 (0.43-2.12) aOR 0.62 (0.26-1.46)	Adjusted for: pregnancy complications, birth outcomes, maternal age, household income, race, ethnicity, marital status, and maternal education.

Fill 2018 (29) (Retrospective cohort)	Tennessee, USA	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 (1.15-1.6) [T] aOR 1.26 (1.06-1.49) [T T] **Developmental delay** aOR 1.34 (1.03-1.76) [T] **Autism** OR 0.82 (0.33-2.02) P=0.08 **Speech and Language Impairment**: aOR 1.26 (1.04-1.52) [T]	[T] adjusted for sex, race, ethnicity, age, public health region, insurance status, maternal smoking status in pregnancy, and maternal education status. [T T] Additional adjustment for gestation, birth weight and neonatal intensive care unit admission.
Gill 2003 (30) (Case series)	Sydney, Australia	6-39 months (mean 21 months)	35	n/a	NAS defined as those requiring pharmacological treatment	Born May 1998 November 2000 and followed up in clinic, identified from medical record review.	Telephone survey Ophthalmologist (un-blinded)	**Strabismus** N= 9 (5 on exam, 4 on telephone survey) **No strabismus** N= 26 (17 on exam 9 on telephone survey)	High attrition
Hamilton 2010 (31) (Case series)	Scotland	Age at first assessment 3 months -7 years (7 months)	12	n/a	Methadone exposure in-utero, NAS defined as those requiring treatment.	Paediatric and neonatal case note review of children referred to a visual electrophysiology service who were exposed to methadone in-utero.	Full ophthalmic exam Full orthoptic exam VEP (visual evoked potential) testing (Un-blinded)	**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%) versus 3/8 (38%), Fishers exact test p=0.018 **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.
Hall 2019 (40) (Retrospective cohort)	Ohio, USA	2-4 years	138	14933	All infants requiring pharmacological 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 (2.56-11.02) **Developmental delay:** OR 4.77 (3.28-6.95) **Motor function developmental disorder:** OR 3.65 (1.68-7.92) **Otitis media:** OR 1.14 (0.8-1.65)	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

								Plagiocephaly OR 6.13 (3.48-10.79) **Sensory disorder** OR 3.36 (2.22-5.09) **Speech disorder** OR 2.31 (1.41-3.77) **Strabismus** OR 12 (6.91-21.18) **Torticollis** OR 4.32 (2.37-7.89)	insurance status, which did not affect the significance of the results extracted for this review. Overlapping data with McAllister 2018.
McAllister 2018 (32) (Case series)	Ohio, USA	30-582 days (120.9 days)	783	n/a	All infants requiring pharmacological treatment for NAS referred to a tri-state 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 2014 (33) (Prospective cohort)	Glasgow	26-30 months (27 weeks)	41	26	Infants exposed to methadone in-utero. NAS defined as those requiring pharmacological treatment.	Recruited within 3 days of life born October 2008 - April 2010.	Outcomes at 6m (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 2018 (34) (Case series)	Ohio, USA	18-28months (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 exam at 2 years (un-blinded)	Children with previous NAS scored significantly lower across all domains compared to normative Bayley data. **Cognitive** 96.5 (p<0.03) **Language** 93.8 (p<0.03) **Motor** 94 (p<0.03)	Excluded those with other neonatal comorbidities, gestation <34 weeks, iatrogenic (postnatal) NAS. High attrition.
O'Donnell 2009 (35) (Retrospective cohort)	Western Australia	0-15 years Exposed group (1 year) Comparator group (3 years)	887	403184	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 (10.45, 14.84) Adjusted OR: 8 (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.

Oei 2017 (35) (Retrospective cohort)	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 National Minimum Standard (NMS) at any point	**<u>Below NMS on any occasion:</u>** ***Grade 3***: OR 2.4 (2.1, 2.7) ***Grade 5***: OR 2.3 (2.1, 2.6) ***Grade 7***: OR 2.1 (1.7, 2.4) **<u>Reading mean score (SD)</u>** ***Grade 3:*** 360.8 (81.8) NAS; 410.3 (86.6) control Below NMS OR 3.1 (2.4, 3.9) ***Grade 5:*** 449.2 (72.9) NAS; 490.3 (77.5) control Below NMS OR 2.6 (2.0, 3.4) ***Grade 7:*** 493.5 (68.3) NAS; 533.8 (74.7) Below NMS OR 2.9 (2.0, 4.3) **<u>Numeracy mean score (SD)</u>** ***Grade 3:*** 350.1 (65.5) vs. 393.1 (75.2) Below NMS OR 2.2 (1.8, 2.9) ***Grade 5:*** 440.3 (61.6) vs. 485.2 (74.1) Below NMS OR 2.6 (1.9, 3.3) ***Grade 7:*** 489.8 (54.4) vs. 536.6 (76.1) Below NMS OR 2.7 (1.8, 4.1) **<u>Writing mean score (SD)</u>** ***Grade 3*:** 365.1 (78.2) vs. 415.3 (69.4) Below NMS OR 3.2 (2.4, 4.2) ***Grade 5:*** 428.7 (72.9) vs. 474.8 (67.9) Below NMS OR 3.4 (2.7, 4.3) ***Grade 7*:** 442.4 (100.8) vs. 501.2 (81.3) Below NMS OR 3.4 (2.6, 4.6) **<u>Grammar mean score (SD)</u>** ***Grade 3:*** 357.2 (96.8) vs. 417.2 (96.8) Below NMS OR 3.1 (2.5, 3.8) ***Grade 5:*** 446.9 (79.9) vs. 496.5 (86.5) Below NMS OR 3.1 (2.5, 3.8)	Non-attendance was assigned as below National Minimum Standard. Comparison with control group and general population. 75% of records linked. Overlap in population with Uebel 2015

								Grade 7: 490.7 (77.5) vs. 530.4 (83.7) Below NMS OR 2 (1.5, 2.8) **<u>Spelling mean score (SD)</u>** ***Grade 3***: 356.5 (82.1) vs. 412.3 (82.3) Below NMS OR 4.3 (3.4, 5.4) ***Grade 5:*** 447.3 (79.1) vs. 496.4 (75.1) Below NMS OR 3.7 (2.8, 4.8) ***Grade 7:*** 504.2 (81.9) vs. 544.9 (72.6) Below NMS OR 3.1 (2.2, 4.4)	
Sandtorv 2018 (41) (Case series)	Norway	Mean 10.4 years	18	n/a	Those scoring 8 or above on the modified Finnegan Score	Medical records and questionnaires completed by caregivers	Wechsler Preschool and Primary Scale of Intelligence (WPPSI) test Wechsler Intelligence Scale for Children (WISC-R). The Swanson, Nolan, and Pelham Questionnaire, r (SNAP-IV) The Autism Spectrum Screening Questionnaire (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.
Sherman 2019 (42) (Retrospective cohort)	USA	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 (e.g. language, coordination)** 327 (31.3) vs. 49,591 (18.4) **Disturbance of conduct** 113 (10.8) vs. 10,879 (4) **Hyperkinetic syndrome (e.g. ADHD)**	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

								94 (9) vs. 9,372 (3.5) **Adjustment reaction** 75 (7.2) vs. 7,799 (2.9) **Acute reaction to stress** 49 (4.7) vs. 8,123 (3) **Neurotic disorders** 43 (4.1) vs. 7,365 (2.7) **Special symptoms or syndromes** 41 (3.9) vs. 9,672 (3.6) **Disturbance of emotions** 39 (3.7) vs. 5,350 (2) **Intellectual disabilities** 37 (3.5) vs. 4,075 (1.5) **Psychoses with origin specific to childhood** 32 (3.1) vs. 4,752 (1.8)	enrolment: (33% of the initially identified population)
Uebel 2015 (11) (Retrospective cohort)	New South Wales, Australia	0-13 years (1-4 years)	3837	1, 016,565	ICD 10 code for NAS	Administrative data sets: Perinatal data collection (PDC) of NSW; admitted patient data collection (APDC); NICUs data collection	Hospitalization information including: 1.ICD 10 diagnoses 2. Hospitalization outcomes	**Child maltreatment** OR 21.04 (14.3-30.96) aOR 5.08 (3.38-7.64) **Neglect** OR 27.02 (14.91-48.98) aOR 4.81 (2.58-8.97) **Injury and poisoning** OR 1.93 (1.75, 2.12) aOR 1.34 (1.2, 1.49) **Learning disability** OR 2.79 (1.61-4.82) aOR 1.68 (0.96-2.93) **Behavioral and emotional disorders** OR 4.08 (2.88-5.8) aOR 2.3 (1.6-3.3) **Conduct Disorder** OR 3.42 (1.98-5.92) aOR 2.11 (1.21-3.7)	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.

								ADHD OR 9.99 (5.73-17.39) aOR 3.73 (2.1-6.61) **Disorders of speech and language** OR 3.59 (2.03-6.36) aOR 2.42 (1.35-4.34) **Autism** OR 3.58 (2.15-6) aOR 2.48 (1.47-4.18) **Cerebral palsy** OR 3.12 (2.01, 4.86) aOR 1.9 (1.21, 2.99) **Diseases of the eye:** OR: 2.94 (2.49, 3.47) aOR 1.93 (1.62, 2.31) **Strabismus** OR 7.9 (6.27, 9.97) aOR 4.73 (3.69, 6.05) **Nystagmus** OR: 12.49 (6.82, 22.88) aOR: 7.99 (4.15, 15.4) **Diseases of the digestive system** OR 1.59 (1.33-1.89) aOR 1.15 (0.96,1.38) **Respiratory system diseases** OR 1.47 (1.37, 1.59) aOR 0.85 (0.79, 0.93) **Asthma** OR 1.8 (1.57, 2.07) aOR 1.1 (0.95, 1.27) **Respiratory infection** OR 1.74 (1.55, 1.95) aOR 1 (0.88, 1.13) **Disease of the skin and subcutaneous tissue** OR 1.98 (1.72, 2.29)	

								aOR 1.26 (1.08, 1.46) **Diseases of the musculoskeletal system** OR 1.40 (1.05–1.87) aOR 1.07 (0.79–1.43) **Infections and parasitic disease** OR 1.54 (1.41, 1.68) aOR 1.01 (0.92, 1.11) **Diseases of the genitourinary system** OR 1.06 (0.87, 1.3) aOR 0.92 (0.75, 1.13)	
Witt 2017 (37) (Retrospective cohort)	Washington, USA	1-5 years (0- 1 years)	1900	12283	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 re-admission in first 5 years of life 2. Infant mortality 3. Reason for hospital admission	**Child maltreatment** RR 6.46 (2.09, 20.02) aRR 4.46 (1.16, 17.15) **Injury and poisoning** RR 1.96 (1.14, 3.37) aRR 1.58 (0.75, 3.31) **Diseases of the nervous system** RR 2.63 (1.64, 4.22) aRR 2.07 (1.12, 3.82) **Diseases of the digestive system** RR 2.18 (1.67, 2.83) aRR 2.07 (1.49, 2.86) **Diseases of the respiratory system** RR 2.09 (1.79, 2.43) aRR 1.59 (1.33, 1.91) **Asthma** RR 2.74 (2.08, 3.61) aRR 1.82 (1.29, 2.57) **Respiratory Infections** RR 1.80 (1.35, 2.40) aRR 1.28 (0.92, 1.77) **Diseases of the skin and subcutaneous tissue** RR 3.23 (2.33, 4.48) aRR 3.04 (2.12, 4.36)	Adjusted for maternal education, gestational age, race and intrapartum smoking.

								Infections and parasitic disease RR 1.87 (1.53, 2.29) aRR 1.72 (1.35, 2.21) **Disease of the genitourinary system** RR 2.29 (1.56, 3.35) aRR 2.28 (1.49, 3.50)	
Yoo 2017 (38) (Case series)	Washington, USA	1-18 months	27	n/a	NAS stated in medical records (including cases that did and did not require pharmacological treatment)	Exposed children identified from addiction center clinic and medical charts used to extract data.	Strabismus (Un-blinded)	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.

Table 6 (online only): Quality assessments scores for each study exploring childhood outcomes after NAS

	Selection (S)[1]				Comparability (C)		Exposure/ outcome (E/O)			Subtotal assessment			Conclusion
	1	2	3	4	1a	1b	1	2	3	S+	C&	E/O&	
Cohort studies													
Azuine 2019 (38)	*	*	*	No	*	*	*	*	No	Good	Good	Good	Good
Fill 2018 (28)	No	*	*	*	*	*	*	No	No	Fair	Good	Fair	Fair
Hall 2019 (29)	*	*	*	No	No	No	*	No	*	Fair	Poor	Good	Poor
McGlone 2014 (32)	*	No	*	*	*	*	*	*	No	Good	Good	Good	Good
O'Donnell 2009 (34)	*	*	*	No	*	*	*	*	No	Good	Good	Good	Good
Oei 2017 (35)	*	*	*	*	*	*	*	*	No	Good	Good	Good	Good
Uebel 2015 (11)	*	*	*	No	*	*	*	*	No	Good	Good	Good	Good
Witt 2017 (36)	*	*	*	No	*	*	*	No	*	Good	Good	Good	Good
Case series													
Gill 2003 (29)	*	n/a	*	*	n/a	n/a	No	*	No	Fair	n/a	Fair	Fair
Hamilton 2010 (30)	*	n/a	*	No	n/a	n/a	*	*	*	Fair	n/a	Good	Fair
Merhar 2018 (33)	*	n/a	*	*	n/a	n/a	*	*	No	Good	n/a	Good	Good
McAllister 2018 (31)	*	n/a	*	*	n/a	n/a	*	*	No	Good	n/a	Good	Good
Sandtorv 2018 (40)	*	n/a	*	n/a	n/a	n/a	No	*	No	Good	n/a	Fair	Fair
Yoo 2017 (37)	No	n/a	*	n/a	n/a	n/a	*	*	No	Poor	n/a	Good	Poor

[1] **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**: + 0-1 (Poor); 2 (Fair); 3+ (Good) & 0 (Poor); 1 (Fair); 2+ (Good)

* Satisfactory

Figure 1 (online only): Medline Ovid search strategy to identify studies of childhood outcomes after NAS

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/

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.

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")