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Prenatal exposure to psychotropics and analgesics on cognitive, linguistic and educational outcomes – a scoping review with focus on validity and reliability of outcome measures

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Abstract

Objective To provide an overview of the observational studies on child's cognitive, linguistic, and educational outcomes following prenatal exposure to psychotropics and analgesics, including reporting of outcome measure validity and reliability.

Study design We searched four databases, MEDLINE, Embase, PsycINFO, and PubMed from inception to September 2023. We included all original studies involving participants less than 18 years old, who were prenatally exposed to psychotropics and/or analgesics with cognitive, linguistic, and/or educational outcomes and excluded those lacking comparison groups.

Results 80 studies were identified. Most studies (47%) focused on the effects of prenatal exposure to antiepileptics on child cognition. Valproate was consistently associated with an increased risk of neurodevelopmental disorders, whereas the results for other medications were sparse and conflicting. Neurodevelopmental outcomes were measured by psychometric assessments in 71 studies and by diagnostic codes in health care registries in nine studies. Only 33 of the 71 studies (46.5%) using psychometric measures mentioned the psychometric properties of the instruments used. In studies using diagnostic outcome measures, only one study reported positive predictive values and performed a sensitivity analysis to address outcome misclassification.

Conclusion Except for valproate, there is a concerning lack of studies on the impact of prenatal exposure to psychotropics and analgesics on cognitive, linguistic, and educational outcomes with existing studies yielding inconsistent findings. Regardless of whether psychometric measures or diagnostic codes were used, most studies

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lacked a robust assessment of outcome measures, which threatens their validity and interpretability. Future studies on long-term prenatal medication safety need to focus on the accuracy of neurodevelopmental outcome measures.

Keywords Pregnancy outcomes, Neurodevelopmental outcomes, Psychometric properties, Prenatal medication exposure

Background

Prenatal exposure to prescribed psychotropics and analgesics has become increasingly common, with recent studies estimating that approximately 2–8% of pregnant women use psychotropics, while up to 50–70% use analgesics during pregnancy [1–3]. These medications cross the placenta and the blood-brain barrier and have the potential to interfere with normal brain development [4, 5]. Findings from animal studies suggest that early exposure to antidepressant medications can disrupt the development of the serotonin system in the foetal and/neonatal brain. This disruption may lead to long-term neurobehavioral consequences [6, 7]. Consequently, there is a growing need to understand the potential long-term effects of prenatal medication exposure on a child's cognitive, linguistic, and educational outcomes [8, 9]. This need is motivated by the acknowledgment that the reproductive safety of medications cannot be assured without knowledge about the long-term neurodevelopmental effects on children [8, 10, 11].

The assessment of neurodevelopmental outcomes can be done using different measures, ranging from diagnostic tools to parental screening instruments and neuropsychological tests [12]. Moreover, school test results have been used to investigate educational achievements [13]. Two meta-analyses on cognitive outcomes after prenatal opioid exposure concluded that one of the key limitations is the heterogeneity in instruments used to evaluate neurodevelopmental outcomes [14, 15]. The diversity of measures used, along with their varying degrees of validity and reliability [16, 17], may impact the conclusions drawn about long-term effects. Measures of high validity and reliability play an important role in assuring high-quality results from observational data. Hence, it is crucial to conduct a precise evaluation of these outcomes to identify neurotoxic medications in epidemiologic studies.

Despite the increasing attention to long-term developmental outcomes in medication safety studies, the scientific literature is still limited regarding the validity and reliability of the neurodevelopmental outcome measures. This review expands on our previous systematic review including studies up to April 2019 [8] by including a broader range of cognitive, linguistic, and educational outcome measures. Hence, this study had a dual purpose: (1) to provide an overview of the characteristics and study findings in observational studies on child's cognitive, linguistic, and educational outcomes following prenatal exposure to psychotropics and analgesics and (2) to describe the reporting of validity and reliability of the outcome measures in the eligible studies.

Methods and materials

Search strategy

A systematic search was conducted from inception to September 10th, 2023 in MEDLINE, Embase, PsycINFO, and PubMed databases in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. Search strategies were developed by the authors (FF, MA), with support from a research librarian and other authors (JvKT, HN). An example of the search terms used can be found in the supplementary materials (Supplemental Table 4).

Inclusion and exclusion criteria

Inclusion criteria for participants, exposures, outcomes, study design, comparison group(s), and language were defined before the screening process. Participants were defined as children (< 18 years) born to mothers who used psychotropic and/or analgesic medication during pregnancy. All types of epidemiologic studies such as cohort and case-control studies were considered eligible for inclusion. Non-original studies (e.g., reviews, commentaries), studies without a comparison group, qualitative studies, and animal studies were excluded. Studies were restricted to publications in English, but no restriction on publication date was applied.

Exposures

Exposures were defined as prenatal exposure to antiepileptics (ATC-code N03), antidepressants (ATC-code N06A), antipsychotics (ATC-code N05A), anxiolytics (ATC-code N05B), hypnotics and sedatives (ATC-code N05C), and analgesics (Anatomical Therapeutic Chemical (ATC)-codes N02 and M01A).

Outcomes

The neurodevelopmental outcomes included both diagnostic codes and standardized psychometric instruments. The diagnostic codes eligible for this review are divided into three domains: language, education, and cognition. Included diagnoses were ICD-10 code F80, specific developmental disorders of speech and language (language), ICD-10 code F81, specific developmental disorder of scholastic skills (education), and ICD-10 codes

F70-79, intellectual disabilities (cognition). Diagnoses were typically given by a paediatrician specialized in child development, and often after a multidisciplinary clinical evaluation.

Language, education, and cognition outcomes were also examined using psychometric instruments and assessments including clinical tests, screening tests, and checklists. These instruments were typically administered by speech-language therapists, psychologists, physicians, nurses, researchers, teachers, and parents.

Most studies in this review focused on cognition, which was evaluated on different parameters including intelligence quotient (IQ) and general cognitive development. Thus, cognition was further differentiated into IQ and general cognitive development which were explored as two different outcomes in this study.

Screening of articles

Search results from the four databases (PubMed, Embase, MEDLINE, and PsycINFO) were saved in the reference management system EndNote, where duplicates were removed. The remaining search results were uploaded to the systematic review data management platform Covidence. Two reviewers (FF, MA) independently screened the titles and abstracts based on the inclusion criteria. After the initial screening full-text reports were obtained for all titles that appeared to meet the inclusion criteria. A third reviewer was asked to evaluate the title and abstract to resolve any disagreement (JvKT or HN). Reasons for excluding studies were recorded and listed in a PRISMA flowchart (Fig. 1). A meta- analysis was not performed given the heterogeneity in the included studies in terms of age of the child and different methods of assessments to ascertain the outcome.

AR extracted the data using a data extraction sheet (Supplemental Table 1). Data variables extracted from the eligible studies were qualitatively synthesised and were key study characteristics including design, type of data collection (primary and secondary), sample size, exposure, comparison group(s), outcome(s) measures, and type (diagnostic codes, psychometric instruments, age at assessment), reporting of confounders, statistical methods, and results (i.e., effect size after covariate adjustment).

For studies using psychometric outcome measures, we extracted information about the validity and reliability of the instruments, whereas for studies using diagnostic outcome measures, we extracted information about how validity was assessed. This included reporting on validity measures (e.g., positive predictive values of the clinical diagnosis), use of various (validated) algorithms to capture the clinical outcome, case validation, and/or performing bias analyses to address outcomes misclassification.

Psychometric outcome measures

We extracted all available qualitative and quantitative information reported about the psychometric properties (validity and reliability) of the instruments used in the eligible studies. This included validity and reliability measures reported from a normative sample (i.e., an external sample used to obtain test norms) or from the study sample.

Validity is the extent to which an instrument truly measures the construct(s) it is intended to measure. Content validity focuses on the degree to which the concept being evaluated is fully covered by the measurement. Criterion validity refers to how well the assessment aligns with a gold standard. Construct validity is the measurement's conformance to accepted theory and comprehension of the construct being assessed [18].

Reliability is the extent to which measurement is free from measurement error. It can be operationalized as the consistency of scores for the same person over repeated measurements under different conditions. Reliability can further be divided into internal and external reliability. Internal reliability is the uniformity of the assessment itself, i.e., whether multiple test components (items) meant to measure the same construct yield the same results. Cronbach's alpha is a commonly used measure of the internal reliability of an assessment or test. It ranges between 0 and 1, and values between 0.70 and 0.95 typically indicate acceptable internal consistency [17].

External reliability involves using the same assessor at different time points (test-retest reliability) or using different assessors on the same occasion (inter-rater reliability) to obtain a measure of agreement over time or across raters [19].

Data were stratified by medication exposure group and outcome of interest.

Results

The literature search yielded 7,984 references. After the removal of 2,452 duplicate references, 5,532 were left for the title and abstract screening. Of these, 232 references underwent full-text evaluation, resulting in 68 eligible studies. An updated literature search conducted from July 2022 to September 2023 identified an additional 12 eligible studies. In total, 80 studies were included. Figure 1 shows the PRISMA flowchart.

Overview of the studies

An overview of the 80 eligible studies is presented in Table 1. The majority of perinatal pharmacoepidemiologic studies on cognition, language, and education outcomes were conducted in one or several of the Scandinavian countries ($n = 27$ studies), followed by the USA and the UK with 17 and 14 studies, respectively. The most common study design was a cohort design

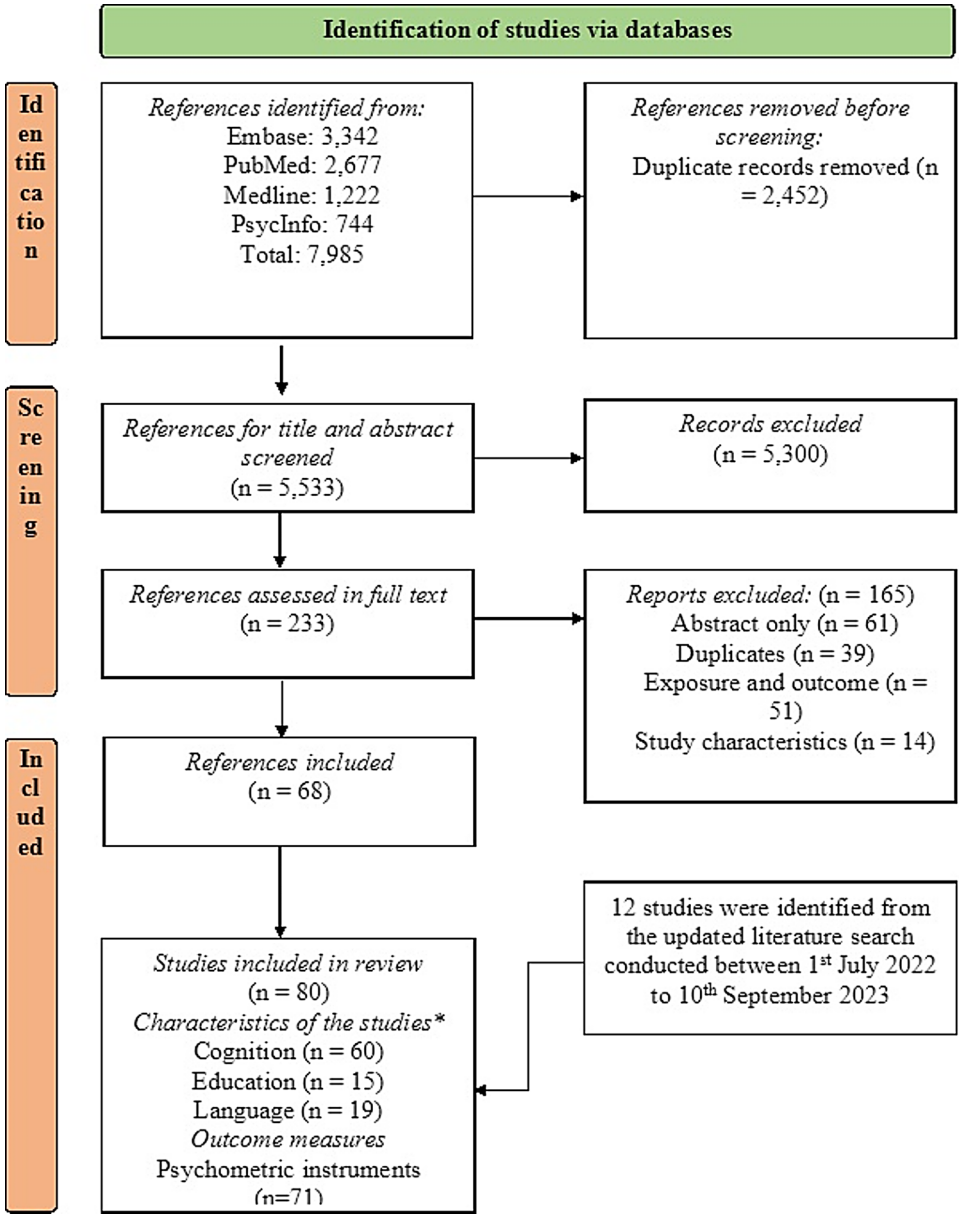


Fig. 1 PRISMA flowchart (*Outcomes are not mutually exclusive)

(*n* = 69 studies), followed by case-control (*n* = 7 studies) and cross-sectional study design (*n* = 4 studies). Eligible studies ranged considerably in study size (10 to 24,825 exposed children). Of the eligible studies, 69 focused on psychotropic medications. Among these, antiepileptics were by far the most studied psychotropic medications with 45 out of 69 studies examining this medication group; 25 studies focused on other psychotropic medications including antidepressants (*n* = 21 studies), anxiolytics (*n* = 3 studies), antipsychotics (*n* = 3 study), hypnotics (*n* = 3 studies), and sedatives (*n* = 1 study); and 11 focused on analgesics. One study included both antiepileptics and other psychotropics. Due to the substantial number of studies focused on antiepileptics, this medication group is described separately from other psychotropics. In total, 60 studies assessed cognitive outcomes such as IQ and cognitive development, 19 evaluated language and language development, and 15 examined educational outcomes (Fig. 2). Most papers assessed several outcomes within the same study. In 49 studies, neurodevelopmental outcomes were assessed by healthcare professionals such as psychologists, and nurses or by trained researchers (Table 1; Supplemental Tables 2, and Fig. 1). Psychologists were the most common administrators of the instruments (*n* = 23 studies). Confounders were accounted for in 73 studies, either by adjustment or by matching. Typical covariates were maternal age, ethnicity, education, socioeconomic status, maternal cognitive

Table 1 Study characteristics of the 80 studies included in the scoping review

Study characteristics	Number of studies (%)	Outcome measure	
		Psychometric instruments/tests	Diagnostic codes
Total	80 (100%)	71 (88.7%)	9 (11.3%)
Country[a]			
Scandinavian	27 (33.7%)	21 (29.6%)	6 (66.7%)
USA	17 (21.3%)	15 (21.1%)	2 (22.2%)
UK	14 (17.5%)	14 (19.7%)	-
Others	29 (36.2%)	28 (39.4%)	1 (11.1%) (France)
Study design			
Cohort	69 (86.2%)	60 (84.5%)	9 (100%)
Case-control	7 (8.7%)	7 (9.8%)	-
Cross-sectional	4 (5.0%)	3 (4.2%)	-
Type of data collection			
Primary	60 (75%)	60 (84.5%)	-
Secondary	20 (25.0%)	11 (15.5%)	9 (100%)
Exposure[b]			
Antiepileptics	45 (56.2%)	40 (56.3%)	5 (55.5%)
Other psychotropics	25 (31.2%)	22 (31.0%)	3 (33.3%)
Analgesics	11 (13.7%)	10 (14.1%)	1 (11.1)
Outcome of interest[c]			
Cognition			
IQ	34 (42.5%)	30 (42.2%)	4 (44.4%)
Cognitive	23 (28.7%)	16 (22.5%)	4 (44.4%)
development	21 (26.2%)	20 (28.1%)	1 (11.1%)
Language	15 (18.7%)	13 (18.3%)	2 (22.2%)
Education			
Source of outcome measure			
Psychologist	23 (28.7%)	23 (32.4%)	-
Researchers	24 (30.0%)	18 (25.3%)	-
Diagnostic codes	9 (11.2%)	-	9 (100%)
Teachers	7 (8.7%)	7 (9.8%)	-
Parents	6 (7.5%)	6 (8.4%)	-
Computerized test	3 (3.7%)	3 (4.2%)	-
Nurse	1 (1.2%)	1 (1.4%)	-
Paediatrician	1 (1.2%)	1 (1.4%)	-
Not specified	6 (7.5%)	6 (8.4%)	-
Psychometric properties[d]			
Validity	30 (37.5%)	27 (38.0%)	3 (33.3%)
Reliability	15 (18.7%)	15 (21.1%)	-
Not mentioned	43 (53.7%)	37 (52.1)	6 (66.6%)
Confounder control			
Adjustment	62 (77.5%)	53 (74.6%)	9 (100%)
Matching	11 (13.7%)	11 (15.5%)	
Not specified	7 (8.7%)	7 (9.8%)	

[a] Some studies were multinational; thus, the numbers add up to more than 100%. 6 studies in the UK and the USA and 1 study in the USA and Brazil. [b] one study includes antiepileptics and psychotropics. [c] Outcomes are not mutually exclusive. [d] Nine studies reported both the validity and reliability of psychometric instruments

ability, maternal prenatal depressive symptoms, maternal smoking, and alcohol intake during pregnancy.

Detailed characteristics and results for the included studies are presented in the Supplemental Table 1. An overview of the confounders assessed can be found in the supplemental text. Below, the main results are presented.

Antiepileptics

Study characteristics

Antiepileptics were the most studied medication group ($n = 45$ studies, median sample size of 176 (interquartile range (IQR): 96–538)) exposed children [9, 13, 20–56]. Of the studies on antiepileptics, 25 papers assessed IQ as a measure of child cognition, and 13 studies assessed general cognitive development. Language development and educational attainment were assessed in eight papers each. In these studies, developmental outcomes were assessed from the age of one to 19 years. Psychometric instruments were administered in 39 studies, whereas the remaining six studies employed diagnostic outcome measures. In 27 studies, the assessments were performed by psychologists or researchers using psychometric instruments.

Study findings

IQ and cognitive development Studies assessing exposure to antiepileptics and IQ ($n = 25$ studies) as a measure for cognition were unanimous in their conclusion on negative effects after valproate and antiepileptic polytherapy exposure on IQ ($n = 17$ studies) [9, 20, 25–27, 29, 31, 33, 34, 36, 37, 39–41, 46, 50, 52]. Findings regarding effects on IQ following exposure to other antiepileptics such as carbamazepine, lamotrigine, and topiramate were inconsistent [9, 20, 25–27, 29, 31, 33, 35–37, 39–41, 46, 50–55]. Thirteen studies assessed antiepileptic exposure and general cognitive development outcomes. Seven studies reported that valproate was associated with negative developmental outcomes when compared to other antiepileptics or the unexposed population [38, 43, 44, 47, 48, 56, 57]. While other study reported no significant differences [58]. Three studies reported no association between lamotrigine and levetiracetam exposure and general cognitive development [21, 28, 59]. Another study didn't find any difference between the verbal index scores of children of women with and without epilepsy [60]. Please refer to Supplemental Table 1 for effect estimates.

Language Eight studies investigated exposure to antiepileptics and language outcomes. Five studies found valproate to be associated with a greater risk of language delays when compared to other antiepileptic drugs (AED) and to the unexposed population [23, 24, 38, 42, 44]. One study showed an association between exposure to lamotrigine and speech delay [28]. Another study found no difference between children of women with and without epilepsy [58].

Education Educational outcomes were assessed in eight studies on different parameters such as learning disabilities (LD), school performance, and special educational support. Prenatal exposure to valproate was associated

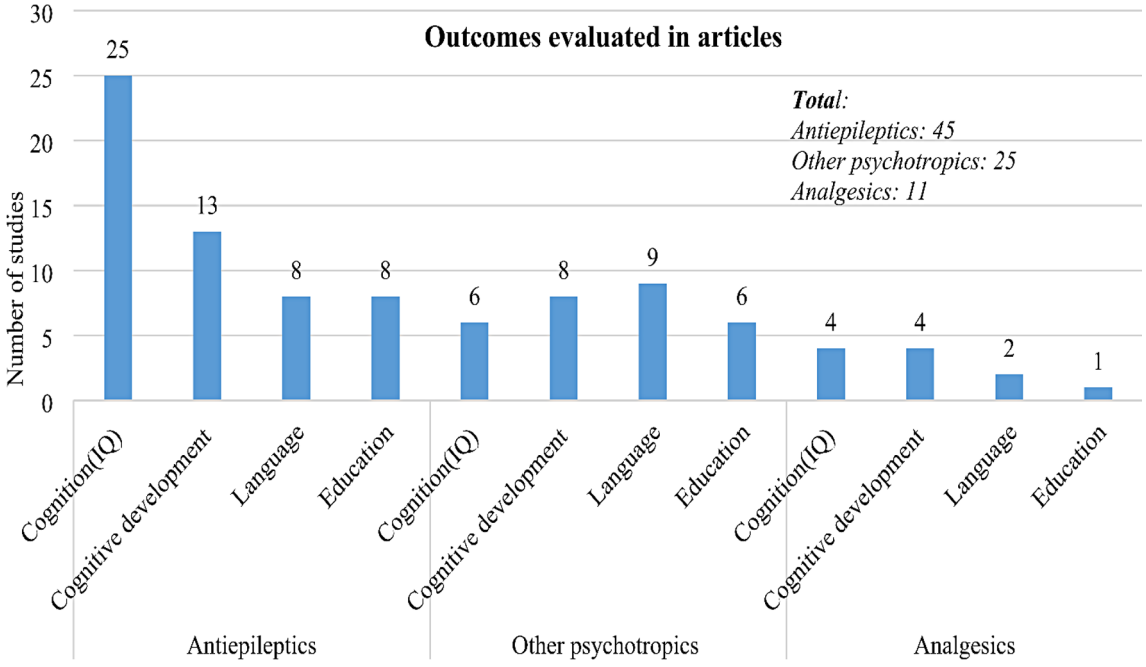


Fig. 2 Neurodevelopmental outcomes evaluated in eligible studies. Some studies evaluated more than one outcome

with the risk of LD, poorer school performance, and provision of special educational support ($n=4$ studies) [13, 29, 30, 49]. One study found that children prenatally exposed to antiepileptic polytherapy had an increased risk of not receiving a final grade in the last year of compulsory school [45]. Two studies found no association between prenatal antiepileptic exposure and receiving a grade point average less than 2 above 9th grade [32, 61]. One study found that compared to state-wide averages exposed children had delayed initiation of education, increased dropout rates and usage of special assistance [57].

Other psychotropics

Study characteristics

There were 25 studies that reported neurodevelopmental outcomes after exposure to psychotropics other than antiepileptics (median sample size 130 (IQR: 35-3982) exposed children) [32, 62–82]. Of these, antidepressants were the most frequently investigated psychotropic medication group ($n=21$ studies). The most studied developmental outcome was cognition including IQ and general cognitive development ($n=13$ studies). Language outcomes were assessed in nine studies, and educational attainment in six studies. Neurodevelopmental outcomes after other psychotropic exposure were assessed in children from the age of 6 months to 19 years.

Study findings

IQ and cognitive development 14 studies assessed the effects of exposure to other psychotropics on cognition. Nine studies found no association between antidepressant exposure and cognitive abilities in children [67, 69, 72, 73, 76, 79–83]. However, three studies on antidepressant exposure [63, 68, 77] and one on benzodiazepines (BZD) and z-hypnotics [64] found the exposed group to have lower cognitive abilities than the control group. One study on antipsychotics found no difference between exposed and unexposed children's IQ [84].

Language Among the nine studies that assessed the association between other psychotropics exposure and language outcomes, six studies reported an association between antidepressant and anxiolytic exposure and lower language skills [65, 69–71, 74, 75, 78]. Two studies did not find any association [81, 82].

Education Among the six studies on educational outcomes after prenatal exposure to other psychotropics, three studies found an association between antidepressant exposure and special education support [62, 66, 85], while the other three studies found no association [32, 71, 83].

Analgesics

Study characteristics

Neurodevelopmental outcomes following analgesic exposure were assessed in 11 studies, with a median sample size of 446 (IQR: 1034–3727) exposed children [86–94]. Eight studies assessed prenatal exposure to acetaminophen/paracetamol, while the remaining studies investigated exposure to opioid analgesics ($n=2$ studies) and aspirin ($n=1$ study). Cognition ($n=6$ studies) was the

predominant outcome in this category, with four studies on IQ and two on general cognitive development. Outcomes were assessed in children from the age of two to 11 years. Only one study employed the diagnostic codes. Six studies used psychometric instruments administered by psychologists and researchers, three studies used parental, nurse, and teacher questionnaires, and one study did not specify the test administrator.

Study findings

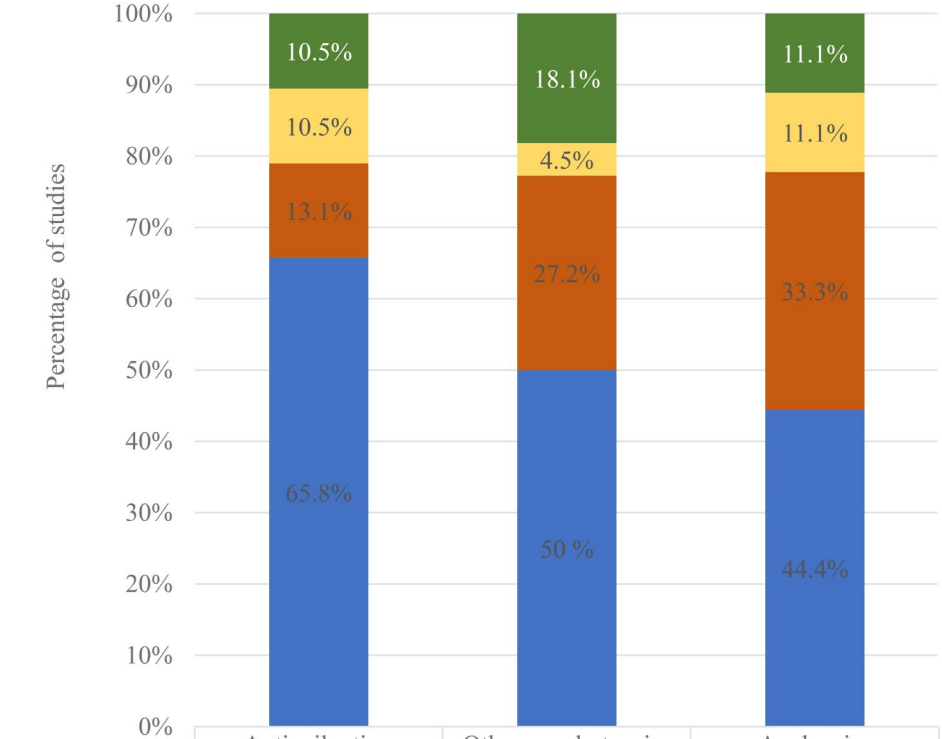
IQ and cognitive development Seven studies found no association between analgesic exposure and cognitive outcomes [88–90, 92–95]. While one study found association between analgesic use in pregnancy and intellectual disabilities in children [96].

Language Two studies examined the association between prenatal analgesic exposure and child linguistic outcomes. One study found an association between exposure to acetaminophen and language delay in girls but not in boys [91]. Another study found no differences between opioid analgesics exposed and unexposed children [87].

Education One study on analgesic exposure and educational outcomes found the exposed children to score lower on literacy and numeracy tests [86].

Psychometric properties of the developmental outcome measures

Only 33 of the 71 eligible studies (46.5%) commented on the validity and/or reliability of the instruments. Of these, validity was mentioned in 27 studies, reliability was mentioned in 15 studies, and nine studies reported both validity and reliability (Fig. 3). Further, out of the 33 papers that discussed psychometric properties, only two papers explicitly mentioned all the subclassifications of validity and reliability [27, 47]. Studies generally reported psychometric properties from normative samples originally used to validate the instrument (22 out of 33 studies) rather than the actual study sample. Only 11 studies out of 33 reported on validity ($n=6$ studies) and reliability ($n=9$ studies) for the study sample (Supplemental Fig. 2). An overview of reporting of the psychometric properties in the eligible studies is provided in Supplemental Table 2.



	Antiepileptics	Other psychotropics	Analgesics
Reported both	4	4	1
Only reliability	4	1	1
Only validity	5	6	3
Not mentioned	25	11	4

Fig. 3 Psychometric properties reported by the eligible studies ($n=71$)

Of the 27 studies that provided information on validity, 16 studies did not specify the type of validity but instead mentioned that the instrument used was considered a gold standard, valid, or had undergone external validation. Regarding reliability, seven studies commented on external reliability, six studies discussed internal reliability, and two studies did not specify the type of reported reliability. An overview of these psychometric instruments, classified by outcomes, is given below.

IQ and cognitive development

Out of 60 studies examining child's cognitive outcomes, both IQ and cognitive development, 18 studies addressed the validity of the psychometric instruments used, while 11 commented on their reliability. Only eight studies reported on both the properties. It was more common for studies to report the psychometric properties of the normative sample, with 15 studies doing so, compared to eight studies that reported on the psychometric properties for the study sample. Most of studies, eleven in total, discussed either external or internal reliability [27, 31, 34, 36, 47, 52, 64, 67, 76, 92], while six studies specified the type of validity being reported [27, 47, 67, 89, 93, 95].

Language

Out of 19 studies examining child language outcomes, nine studies reported on the validity of the outcome measures used, while only two reported on reliability. Only two studies addressed both validity and reliability. Reporting on the psychometric properties of the normative sample was more common, with eight studies doing so, compared to just one study that reported the properties of study sample. Only three studies specified the type of validity being addressed [65, 70, 87], while the others noted that the instrument used was considered the gold standard. Furthermore, only one study commented on external reliability [65].

Education

Of the 15 studies that evaluated child educational outcomes, only two mentioned the validity of the outcome measures used, and just one addressed reliability. Two studies reported the psychometric properties for the study sample, while only one reported these for the normative sample. None of the studies specified the type of validity, while only one study reported on external reliability [62].

Assessment of outcomes in studies using diagnostic codes

Nine studies used diagnostic outcome measures to evaluate neurodevelopmental outcomes in children. Only three of these studies addressed to some extent the validity of the diagnostic outcome measure (Table 2). Bjørk et al. referred to positive predictive values of ASD diagnostic codes [20] and performed a sensitivity analysis that required two diagnostic codes to address outcome misclassification. Blotiere et al. acknowledged that the diagnostic codes used were not externally validated [25]. Suarez et al. used validated algorithms to identify neurodevelopmental disorders in children [83]. The remaining six studies did not acknowledge or report on the validity of the diagnostic codes.

Discussion

This study examined the impact of prenatal exposure to psychotropic and analgesic medications on children's neurodevelopmental outcomes. A total of 80 eligible studies were analysed, covering cognitive function, language development, and educational attainment. Antiepileptics were the most studied medication ($n = 45$ studies), followed by antidepressants, BZD, and z-hypnotics ($n = 25$ studies). Reporting on the validity and reliability of outcome measures was limited, with only 46.5% (33/71 studies) of the studies using psychometric instruments and 33.3% (3/9 studies) of the studies using diagnostic codes providing any such information. The findings emphasize the need for standardized reporting and assessment practices in this area of research.

Summary of findings

Antiepileptics have been extensively studied for their potential adverse effect on neurodevelopmental outcomes. Of the 45 studies on antiepileptics, prenatal valproate exposure was consistently associated with poorer child cognitive and linguistic abilities. However, the results for other antiepileptics were somewhat conflicting. A recent study reported an association between prenatal topiramate exposure and increased risk of neurodevelopmental disorders [20]. This study also identified a time-dependent effect, indicating that children exposed to topiramate in the first trimester exhibited a higher rate of adverse neurodevelopmental outcomes compared to unexposed children. This signal raised concern among health authorities such as the Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medicines Agency (EMA). While awaiting further research, caution should be exercised when prescribing this medication to women of child-bearing age.

This review identified an significant knowledge gap concerning educational and language outcomes after prenatal exposure to BZD, hypnotics, sedatives, and analgesics. Despite the prevalence of these medications in the pregnant population, there have been relatively few studies investigating the effects on exposed children's educational and linguistic outcomes. It is well established that BZD can cross both placental and blood-brain barrier and bind to γ-amino butyric acid receptors in the developing foetal brain, potentially impacting brain growth

Table 2 Overview of methods used to address the validity of outcome measures in studies using diagnostic codes ($n=9$ studies)

Reference	Exposure	Outcomes[a]	Data source	Method					
				Validity of outcome discussed	Restriction to x2 Dx codes	Validated algorithm used	Reporting PPVs	Case validation	Quantitative bias analysis
Dudukina et al. (2023) [97]	AED	ASD; ADHD; ID	Nordic registries	---	---	---	---	---	---
Chowdhury et al. (2023) [96]	Analgesic	ASD; ID	USA	---	---	---	---	---	---
Suarez et al. (2022) [83]	SSRI	ASD; ADHD; SLD; LD; ID; BD; DCD	USA	Yes	---	---	---	---	---
Bjørk et al. (2022) [20]	AED	ASD; ID; NDD	Nordic registries	---	Yes	---	ASD: PPVs 86–90%	---	---
Daugaard et al. (2020) [22]	AED	ID; ID/DD	Danish registries	---	---	---	---	---	---
Blotiere et al. (2020) [25]	AED	NDD; MD; DD; CRD	French registries	Acknowledged no validation	---	---	---	---	---
Bech et al. (2018) [29]	AED	MD; DD; ASD; BD	Danish registries	---	---	---	---	---	---
Viktorin et al. (2017) [68]	SSRI	ID	Swedish registries	---	---	---	---	---	---
Brown et al. (2016) [71]	SSRI	Language; education	Finnish registries	---	---	---	---	---	---

[a] For the specific ICD-10 diagnostic codes, please refer to Supplemental Table 3

Abbreviations: AED: antiepileptic drugs, ASD: autism spectrum disorder, ADHD: Attention deficit hyperactivity disorder, BD: behavioural disorder, SLD: speech/language disorder, LD: learning disorder CRD: communication-related disorder, DD: delayed childhood outcomes, Dx: diagnosis, ID: intellectual disability, MD: mental retardation, NDD: Neurodevelopmental disorders, PPV: positive predictive value, PV: predictive value, x2: restricted to two diagnostic codes (main or sensitivity analysis)

and development [98, 99]. Prescription use of BZD are becoming increasingly common in pregnancy [100], and potential long-term effects of *in-utero* exposure to these medications should be established. Additionally, the use of analgesics in pregnancy has increased over the past decade [101]. However, only nine studies of this medication group were identified in this study.

There were 34 papers that focused on IQ as a measure of child cognition. However, the use of IQ tests alone is not an optimal method for measuring broader cognitive abilities. For example, McVerry et al. [47] have demonstrated that the susceptible phases of neocortical development are heterochronic and rely on the regional formation of cortical structures and functions. Indeed, evidence suggests that IQ tests do not adequately assess the functional integrity of neocortical areas that mediate the full range of higher-order cognition [102]. Consequently, IQ tests may not fully capture the effects of prenatal exposure to teratogens in the context of child development [103]. This highlights the need for more comprehensive tools to understand the complex brain-behaviour interactions involved in cognitive development. Therefore, studies investigating the effect of potential teratogens on cognition should consider examining other areas of cognitive functioning, such as socioemotional, linguistic, educational, and behavioural outcomes, which all are critical for child development [104, 105]. Furthermore, long-term follow-up is essential to monitor outcomes with varying developmental progressions. For instance, language skills are difficult to assess accurately using standardized tests before the ages of 3–5, while literacy and educational outcomes can only be reliably evaluated once a child has had sufficient learning opportunities in primary education. This emphasizes the importance of selecting appropriate age of evaluation for these outcomes.

This review identified that important confounders like maternal IQ were not accounted for in many (61.7%) eligible studies assessing child IQ. The influences of maternal cognitive competencies and maternal education on children's IQ have been a topic of discussion [106]. It is crucial to account for important confounders to obtain robust results.

Reporting on validity and reliability

The reproducibility of findings is pivotal for research on prenatal medication exposure and neurodevelopmental outcomes to support informed decisions about

medication use in pregnancy. Among the 33 studies that discussed the validity and/or reliability of the outcome measure, there was a lesser focus on assessing reliability. The reason for this remains uncertain. However, there are several factors that may contribute to the discrepancy. Firstly, it is possible that reporting validity is easier and less time-consuming, given the availability of literature on validated instruments. In contrast, assessing reliability requires repeated evaluations by the authors or test administrators, as it can vary substantially between study samples. Secondly, when researchers collect test scores from medical journals or reports, the necessary item-level data required for calculating internal reliability is often unavailable. Lastly, the lack of awareness regarding the importance of validity and reliability may result in these properties not being adequately evaluated.

This review highlights the need for increased emphasis on evaluating the validity and reliability of psychometric outcome measures. To provide robust evidence about possible associations between prenatal medication exposure and neurodevelopmental outcomes, studies must carefully consider and report the psychometric properties of the instruments used. One reason why reliability information for outcome measures is crucial is that low reliability reduces statistical power. Thus, the use of less reliable measures may obscure true relationships between medication exposure and child outcomes. While presenting a tool's psychometric characteristics based on previous research is a good starting point, it is rarely considered sufficient. Researchers should adhere to established standards in determining the validity, reliability, and interpretation of psychometric test results for their specific study samples.

Studies that use outcome measures based on diagnostic codes often lack descriptions of code validity or measures to address outcome misclassification. Therefore, researchers are encouraged to utilize validated algorithms, whenever feasible, to identify neurodevelopmental outcomes in health care registries. It is important to note that even data derived from such registries is not free of coding errors and misdiagnosis, as evidenced by previous studies [107]. To reduce invalid causal inference and outcome misclassification, the use of sensitivity analysis or well-validated outcome algorithms is necessary [107]. Very few studies using diagnostic outcome measures from health care registries attempt to quantitatively evaluate bias due to outcome misclassification [108]. Quantitative bias analyses, such as probabilistic bias analysis, enable the assessment of the direction, uncertainty, and magnitude of the bias by simulating the bias parameters [108, 109]. Probabilistic bias analysis allows researchers to assess how the association of risk factors and the exposure estimates changes with bias parameters [110]. Despite the concern regarding the impact of systematic error on associations and study results in pharmacoepidemiologic studies [111, 112], only one study included in this review attempted to address outcome misclassification in the analysis.

Strengths and limitations

The strength of this scoping review includes a comprehensive article search in four databases, adherence to the PRISMA guidelines, data extraction performed by three different authors, and evaluation by a multidisciplinary team with expertise in pharmacoepidemiology and children's cognitive development. Some limitations should be acknowledged. The present study did not include all neurodevelopmental outcomes, such as socio-emotional, and behavioural disorders. Thus, future studies should consider including other neurodevelopmental outcomes as well.

Conclusion

This review highlights several knowledge gaps and challenges in prenatal studies of medication use with cognitive, linguistic, and educational outcomes. Among the 80 eligible studies, the majority focused on prenatal exposure to antiepileptics, with consistent associations found between valproate use and neurodevelopmental outcomes. In contrast, relatively few studies assessed the effects of prenatal exposure to antidepressants, antipsychotics, benzodiazepines, and analgesics, and these studies presented inconsistent findings. Twenty-nine studies assessed offspring IQ, whereas other cognitive, linguistic, and educational outcomes were assessed in a minority of studies. Consequently, future studies should widen the scope both with regard to medications and neurodevelopmental outcomes studied.

More than half of the studies using psychometric measures did not report on the validity and reliability of the outcome measures. Using validated and reliable psychometric instruments and reporting on their properties is essential in future studies. Moreover, further studies using diagnostic outcome measures should use validated outcome algorithms, sensitivity analysis and modelling methods to address outcome misclassification. Taking such measures are critical to the generation of robust results, and to enable well-founded conclusions about medication safety in pregnancy.

Supplementary Information

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Supplementary Material 1

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Author contributions
AR has contributed to methodology, interpretation of the data and analysis, writing the original draft and revising and editing the final draft. FF and ML have contributed to methodology and writing the original draft. EO has contributed to interpretation of the data, writing the original draft, and revising and editing the final draft. AL and RB have contributed to analysis and revising and editing the final draft. KG, CK, GS have made contributions on analysis and writing and revising the final draft. JvKT and HN have contributed to conception, design of the work, interpretation of the work, writing the original draft and revising and editing the final draft. All authors read and approved the final draft of the manuscript.

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The data supporting this study was derived from publicly available sources, including electronic databases (MEDLINE, Embase, PsycINFO, and PubMed). All included studies are cited in the reference list and are also available in supplementary information files.

Declarations

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The authors declare no competing interests.

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References

1. Lupattelli A, Spigset O, Twigg MJ, Zagorodnikova K, Mårdby AC, Moretti ME, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. BMJ Open. 2014;4(2):e004365–e.
2. Werler MM, Mitchell AA, Hernandez-Diaz S, Honein MA, the National Birth Defects Prevention S. Use of over-the-counter medications during pregnancy. Am J Obstet Gynecol. 2005;193(3):771–7.
3. Molenaar NM, Bais B, Lambregtse-van den Berg MP, Mulder CL, Howell EA, Fox NS, et al. The international prevalence of antidepressant use before, during, and after pregnancy: a systematic review and meta-analysis of timing, type of prescriptions and geographical variability. J Affect Disord. 2020;264:82–9.
4. Akamine Y, China K, Uno T. The role of drug transporters on psychotropic penetration of the blood–brain barrier. CNPT. 2012;3:8–14.
5. Courade JP, Besse D, Delchambre C, Hanoun N, Hamon M, Eschalier A, et al. Acetaminophen distribution in the rat central nervous system. Life Sci. 2001;69(12):1455–64.
6. Maciag D, Simpson KL, Coppinger D, Yuefeng LU, Yue W, Lin RCS, Paul IA. Neonatal antidepressant exposure has lasting effects on behavior and serotonin circuitry. Neuropsychopharmacology. 2006;31(1):47–57.
7. Bourke CH, Stowe ZN, Owens MJ, Sibley DR. Prenatal antidepressant exposure: clinical and preclinical findings. Pharmacol Rev. 2014;66(2):435–65.
8. Hjorth S, Bromley R, Ystrom E, Lupattelli A, Spigset O, Nordeng H. Use and validity of child neurodevelopment outcome measures in studies on prenatal exposure to psychotropic and analgesic medications - a systematic review. PLoS ONE. 2019;14(7):e0219778–e.
9. Adab N, Kini U, Vinten J, Ayres J, Baker G, Clayton-Smith J, et al. The longer term outcome of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry. 2004;75(11):1575–83.
10. Hanson JW, Myrianthopoulos NC, Harvey MAS, Smith DW. Risks to the offspring of women treated with hydantoin anticonvulsants, with emphasis on the fetal hydantoin syndrome. J Pediatr. 1976;89(4):662–8.
11. Dean JCS, Hailey H, Moore SJ, Lloyd DJ, Turnpenny PD, Little J. Long term health and neurodevelopment in children exposed to antiepileptic drugs before birth. J Med Genet. 2002;39(4):251–9.
12. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med. 2013;11(1):126.
13. Elkjær LS, Bech BH, Sun Y, Laursen TM, Christensen J. Association between Prenatal Valproate Exposure and performance on standardized Language and Mathematics tests in School-aged children. JAMA Neurol. 2018;75(6):663–71.
14. Nelson LF, Yocum VK, Patel KD, Qeadan F, Hsi A, Weitzen S. Cognitive outcomes of young children after prenatal exposure to medications for opioid use disorder: a systematic review and Meta-analysis. JAMA Netw Open. 2020;3(3):e201195–e.
15. Yeoh SL, Eastwood J, Wright IM, Morton R, Melhuish E, Ward M, Oei JL. Cognitive and motor outcomes of children with prenatal opioid exposure: a systematic review and Meta-analysis. JAMA Netw Open. 2019;2(7):e197025–e.
16. Sheldrick RC, Marakovitz S, Garfinkel D, Carter AS, Perrin EC. Comparative accuracy of Developmental Screening questionnaires. JAMA Pediatr. 2020;174(4):366–74.
17. Spitzer RL, Fleiss JL. A re-analysis of the reliability of Psychiatric diagnosis. Br J Psychiatry. 1974;125(587):341–7.
18. Validity. In: Terwee CB, Knol DL, de Vet HCW, Mokkink LB, editors. Measurement in Medicine: a practical guide. Practical guides to Biostatistics and Epidemiology. Cambridge: Cambridge University Press; 2011. pp. 150–201.
19. Reliability. In: Terwee CB, Knol DL, de Vet HCW, Mokkink LB, editors. Measurement in Medicine: a practical guide. Practical guides to Biostatistics and Epidemiology. Cambridge: Cambridge University Press; 2011. pp. 96–149.
20. Bjørk M-H, Zoega H, Leinonen MK, Cohen JM, Dreier JW, Furu K, et al. Association of Prenatal Exposure to antiseizure medication with risk of Autism and Intellectual Disability. JAMA Neurol. 2022;79(7):672–81.
21. Meador KJ, Cohen MJ, Loring DW, May RC, Brown C, Robalino CP, et al. Two-year-old cognitive outcomes in children of pregnant women with Epilepsy in the maternal outcomes and Neurodevelopmental effects of antiepileptic drugs study. JAMA Neurol. 2021;78(8):927–36.
22. Daugaard CA, Pedersen L, Sun Y, Dreier JW, Christensen J. Association of Prenatal Exposure to Valproate and other antiepileptic drugs with intellectual disability and delayed childhood milestones. JAMA Netw Open. 2020;3(11):e2025570–e.
23. Unnikrishnan G, Jacob NS, Salim S, Jose M, Salini RA, Pavithran V, et al. Enduring language deficits in children of women with epilepsy and the potential role of intrauterine exposure to antiepileptic drugs. Epilepsia. 2020;61(11):2442–51.
24. Huber-Mollema Y, van Iterson L, Oort FJ, Lindhout D, Rodenburg R. Neurocognition after prenatal levetiracetam, lamotrigine, carbamazepine or valproate exposure. J Neurol. 2020;267(6):1724–36.
25. Blotière P-O, Miranda S, Weill A, Mikaeloff Y, Peyre H, Ramus F, et al. Risk of early neurodevelopmental outcomes associated with prenatal exposure to the antiepileptic drugs most commonly used during pregnancy: a French nationwide population-based cohort study. BMJ Open. 2020;10(6):e034829.
26. Kishk N, Hassan A, Madbouly N, Nawito A, Maher E, Heneidy S. Assessment of School-aged children of Mothers with Idiopathic Generalized Epilepsy. J Nerv Ment Dis. 2019;207(10):863–8.
27. Cohen MJ, Meador KJ, May R, Loblein H, Conrad T, Baker GA, et al. Fetal antiepileptic drug exposure and learning and memory functioning at 6 years of age: the NEAD prospective observational study. Epilepsy Behav. 2019;92:154–64.

28. Cohen-Israel M, Berger I, Martonovich EY, Klinger G, Stahl B, Linder N. Short- and long-term complications of in utero exposure to lamotrigine. Br J Clin Pharmacol. 2018;84(1):189–94.
29. Bech LF, Polcwiartek C, Kragholm K, Andersen MP, Rohde C, Torp-Pedersen C, et al. In utero exposure to antiepileptic drugs is associated with learning disabilities among offspring. J Neurol Neurosurg Psychiatry. 2018;89(12):1324–31.
30. Lacey AS, Pickrell WO, Thomas RH, Kerr MP, White CP, Rees MI. Educational attainment of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry. 2018;89(7):736–40.
31. Bromley RL, Baker GA, Clayton-Smith J, Wood AG. Intellectual functioning in clinically confirmed fetal valproate syndrome. Neurotoxicol Teratol. 2019;71:16–21.
32. Wibroe MA, Mathiasen R, Pagsberg AK, Uldall P. Risk of impaired cognition after prenatal exposure to psychotropic drugs. Acta Psychiatr Scand. 2017;136(2):177–87.
33. Kasradze S, Gogatishvili N, Lomidze G, Ediberidze T, Lazariashvili M, Khomeriki K, et al. Cognitive functions in children exposed to antiepileptic drugs in utero - study in Georgia. Epilepsy Behav. 2017;66:105–12.
34. Bromley RL, Calderbank R, Cheyne CP, Rooney C, Trayner P, Clayton-Smith J, et al. Cognition in school-age children exposed to levetiracetam, topiramate, or sodium valproate. Neurology. 2016;87(18):1943–53.
35. Gopinath N, Muneer AK, Unnikrishnan S, Varma RP, Thomas SV. Children (10–12 years age) of women with epilepsy have lower intelligence, attention and memory: observations from a prospective cohort case control study. Epilepsy Res. 2015;117:58–62.
36. Baker GA, Bromley RL, Briggs M, Cheyne CP, Cohen MJ, García-Fiñana M, et al. IQ at 6 years after in utero exposure to antiepileptic drugs: a controlled cohort study. Neurology. 2015;84(4):382–90.
37. Güveli T, Gürses B, Ataklı C, Akça Kalem D, Dirican Ş, Bebek A. Behavioral characteristics and cognitive development among school age children born to women with epilepsy. Neurol Res. 2015;37(4):295–300.
38. Shallcross R, Bromley RL, Cheyne CP, García-Fiñana M, Irwin B, Morrow J, Baker GA. In utero exposure to levetiracetam vs valproate: development and language at 3 years of age. Neurology. 2014;82(3):213–21.
39. Meador KJP, Baker GAP, Browning NP, Cohen MJE, Bromley RLP, Clayton-Smith JMD, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013;12(3):244–52.
40. Rihtman T, Parush S, Ornoy A. Developmental outcomes at preschool age after fetal exposure to valproic acid and lamotrigine: cognitive, motor, sensory and behavioral function. Reprod Toxicol. 2013;41:115–25.
41. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Effects of fetal antiepileptic drug exposure: outcomes at age 4.5 years. Neurology. 2012;78(16):1207–14.
42. Nadebaum C, Anderson VA, Vajda F, Reutens DC, Barton S, Wood AG. Language skills of school-aged children prenatally exposed to antiepileptic drugs. Neurology. 2011;76(8):719–26.
43. Shallcross R, Bromley RL, Irwin B, Bonnett LJ, Morrow J, Baker GA. Child development following in utero exposure: Levetiracetam vs sodium valproate. Neurology. 2011;76(4):383–9.
44. Meador KJ, Baker GA, Browning N, Cohen MJ, Clayton-Smith J, Kalayjian LA, et al. Foetal antiepileptic drug exposure and verbal versus non-verbal abilities at three years of age. Brain. 2011;134(2):396–404.
45. Forsberg L, Wide K, Källén B. School performance at age 16 in children exposed to antiepileptic drugs in utero—A population-based study. Epilepsia. 2011;52(2):364–9.
46. Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med. 2009;360(16):1597–605.
47. McVearry KM, Gaillard WD, VanMeter J, Meador KJ. A prospective study of cognitive fluency and originality in children exposed in utero to carbamazepine, lamotrigine, or valproate monotherapy. Epilepsy Behav. 2009;16(4):609–16.
48. Thomas SV, Ajaykumar B, Sindhu K, Nair MKC, George B, Sarma PS. Motor and mental development of infants exposed to antiepileptic drugs in utero. Epilepsy Behav. 2008;13(1):229–36.
49. Viinikainen K, Eriksson K, Mönkkönen A, Äikiä M, Nieminen P, Heinonen S, Kälviäinen R. The effects of valproate exposure in utero on behavior and the need for educational support in school-aged children. Epilepsy Behav. 2006;9(4):636–40.
50. Eriksson K, Viinikainen K, Mönkkönen A, Äikiä M, Nieminen P, Heinonen S, Kälviäinen R. Children exposed to valproate in utero—Population based evaluation of risks and confounding factors for long-term neurocognitive development. Epilepsy Res. 2005;65(3):189–200.
51. Holmes LB, Coull BA, Dorfman J, Rosenberger PB. The correlation of deficits in IQ with midface and digit hypoplasia in children exposed in utero to anticonvulsant drugs. J Pediatr. 2005;146(1):118–22.
52. Gaily E, Kantola-Sorsa E, Hiilesmaa V, Isoaho M, Matila R, Kotila M, et al. Normal intelligence in children with prenatal exposure to carbamazepine. Neurology. 2004;62(1):28–32.
53. Koch S, Titze K, Zimmermann RB, Schröder M, Lehmkuhl U, Rauh H. Long-term neuropsychological consequences of maternal Epilepsy and Anticonvulsant Treatment during pregnancy for School-Age Children and adolescents. Epilepsia. 1999;40(9):1237–43.
54. Vanoverloop D, Schnell RR, Harvey EA, Holmes LB. The effects of prenatal exposure to phenytoin and other anticonvulsants on intellectual function at 4 to 8 years of age. Neurotoxicol Teratol. 1992;14(5):329–35.
55. Gally E, Kantola-Sorsa E, Granström M-L. Intelligence of children of epileptic mothers. J Pediatr. 1988;113(4):677–84.
56. Thomas SV, Jeemon P, Jose M, Amrithum LM, Bhaskar D, Nair MKC, George B. Differential impact of antenatal exposure to antiseizure medications on motor and mental development in infants of women with epilepsy. Epileptic Disord. 2022;24(3):531–40.
57. Thomas SV, Salim S, Jacob NS, Jose M, Salini RA, Selvaraj S, et al. Language, intelligence, and educational outcomes of adolescents with antenatal exposure to antiseizure medications: prospective data from the Kerala Registry of Epilepsy and pregnancy. Seizure. 2022;100:76–81.
58. Developmental and behavioral consequences of intrauterine anti-seizure medication exposure. Istanbul; 2023. p. 37.
59. Bromley RL, Bullen P, Campbell E, Craig J, Ingham A, Irwin B, et al. Neurodevelopment of babies born to mothers with epilepsy: a prospective observational cohort study. Epilepsia. 2023;64(9):2454–71.
60. Meador KJ, Cohen MJ, Loring DW, Matthews AG, Brown C, Robalino CP, et al. Cognitive outcomes at age 3 years in children with fetal exposure to antiseizure medications (MONEAD study) in the USA: a prospective, observational cohort study. Lancet Neurol. 2023;22(8):712–22.
61. Ren T, Lee PMY, Li F, Li J. Prenatal Carbamazepine exposure and academic performance in adolescents: a Population-based Cohort Study. Neurology. 2023;100(7):e728–38.
62. Christensen J, Trabjerg BB, Sun Y, Dreier JW. Association of maternal antidepressant prescription during pregnancy with standardized test scores of Danish school-aged children. JAMA. 2021;326(17):1725–35.
63. Singal D, Chateau D, Struck S, Lee JB, Dahl M, Derksen S, et al. In utero antidepressants and neurodevelopmental outcomes in kindergarteners. Pediatrics. 2020;145(5):1.
64. Lupattelli A, Chambers CD, Bandoli G, Handal M, Skurtveit S, Nordeng H. Association of maternal use of benzodiazepines and Z-Hypnotics during pregnancy with motor and communication skills and Attention-Deficit/Hyperactivity disorder symptoms in preschoolers. JAMA Netw Open. 2019;2(4):e191435–e.
65. Smearman EL, Hendrix CL, Winiarski DA, Johnson KC, Smith AK, Ousley OY, et al. School-Age social behavior and pragmatic language ability in children with prenatal serotonin reuptake inhibitor exposure. Dev Psychopathol. 2020;32(1):21–30.
66. Kragholm K, Andersen MP, Mortensen RN, Bech LF, Polcwiartek C, Rohde C, et al. Exposure to selective serotonin reuptake inhibitors in utero and early elementary school outcomes. Acta Psychiatr Scand. 2018;137(6):481–90.
67. Marroun HE, White TJ, Fernandez GSE, Jaddoe VW, Verhulst FC, Stricker BH, Tiemeier H. Prenatal exposure to selective serotonin reuptake inhibitors and non-verbal cognitive functioning in childhood. J Psychopharmacol. 2017;31(3):346–55.
68. Viktorin A, Uher R, Kolevzon A, Reichenberg A, Levine SZ, Sandin S. Association of antidepressant medication use during pregnancy with intellectual disability in offspring. JAMA Psychiatry. 2017;74(10):1031–8.
69. Johnson KCKC, Smith AKAK, Stowe ZNZN, Newport DJDJ, Brennan PAPA. Preschool outcomes following prenatal antidepressant exposure: differences in language and behavior, but not cognitive function. J Clin Psychiatry. 2016;77(2):e176–82.
70. Handal M, Skurtveit S, Roth C, Hernandez-Diaz S, Selmer R. Prenatal exposure to Folic Acid and antidepressants and Language Development A Population-based Cohort Study. J Clin Psychopharmacol. 2016;36(4):333–9.

71. Brown AS, Gyllenberg D, Malm H, McKeague IW, Hinkka-Yli-Salomäki S, Artama M, et al. Association of selective serotonin reuptake inhibitor exposure during pregnancy with Speech, Scholastic, and Motor disorders in offspring. JAMA Psychiatry. 2016;73(11):1163–70.
72. Galbally M, Lewis AJ, Buist A. Child developmental outcomes in preschool children following antidepressant exposure in pregnancy. Aust N Z J Psychiatry. 2015;49(7):642–50.
73. Eriksen H-LF, Kesmodel US, Pedersen LH, Mortensen EL. No association between prenatal exposure to psychotropics and intelligence at age five. Acta Obstet Gynecol Scand. 2015;94(5):501–7.
74. Skurtveit S, Selmer R, Roth C, Hernandez-Diaz S, Handal M. Prenatal exposure to antidepressants and language competence at age three: results from a large population-based pregnancy cohort in Norway. BJOG. 2014;121(13):1621–31.
75. Odsbu I, Skurtveit S, Selmer R, Roth C, Hernandez-Diaz S, Handal M. Prenatal exposure to anxiolytics and hypnotics and language competence at 3 years of age. Eur J Clin Pharmacol. 2015;71(3):283–91.
76. Austin M-P, Karatas JC, Mishra P, Christl B, Kennedy D, Oei J. Infant neurodevelopment following in utero exposure to antidepressant medication. Acta Paediatr. 2013;102(11):1054–9.
77. Nulman I, Koren G, Rovet J, Barrera M, Pulver A, Streiner D, Feldman B. Neurodevelopment of children following prenatal exposure to Venlafaxine, selective serotonin reuptake inhibitors, or untreated maternal depression. Am J Psychiatry. 2012;169(11):1165–74.
78. Weikum WM, Oberlander TF, Hensch TK, Werker JF. Prenatal exposure to antidepressants and depressed maternal mood alter trajectory of infant speech perception. Proc Natl Acad Sci U S A. 2012;109(Supplement 2):17221–7.
79. Gidai J, Ács N, Bánhidy F, Czeizel AE. A study of the effects of large doses of medazepam used for self-poisoning in 10 pregnant women on fetal development. Toxicol Ind Health. 2008;24(1–2):61–8.
80. Gidai J, Ács N, Bánhidy F, Czeizel AE. An evaluation of data for 10 children born to mothers who attempted suicide by taking large doses of alprazolam during pregnancy. Toxicol Ind Health. 2008;24(1–2):53–60.
81. Nulman I, Rovet J, Stewart DE, Wolpin J, Pace-Asciak P, Shuhaiber S, Koren G. Child Development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. Am J Psychiatry. 2002;159(11):1889–95.
82. Nulman I, Rovet J, Stewart DE, Wolpin J, Gardner HA, Theis JGW, et al. Neurodevelopment of children exposed in Utero to antidepressant drugs. N Engl J Med. 1997;336(4):258–62.
83. Suarez EA, Bateman BT, Hernández-Díaz S, Straub L, Wisner KL, Gray KJ, et al. Association of antidepressant use during pregnancy with risk of Neurodevelopmental disorders in Children. JAMA Intern Med. 2022;182(11):1149–60.
84. Schrijver L, Robakis TK, Kamperman AM, Bijma H, Honig A, van Kamp IL, et al. Neurodevelopment in school-aged children after intrauterine exposure to antipsychotics. Acta Psychiatr Scand. 2023;147(1):43–53.
85. Liu X, Trabjerg BB, Munk-Olsen T, Christensen J, Dreier JW. Association of maternal antipsychotic prescription during pregnancy with standardized test scores of Schoolchildren in Denmark. JAMA Intern Med. 2022;182(10):1035–43.
86. Tronnes JN, Lupattelli A, Ystrom E, Nordeng H. Analysis of prenatal exposure to opioid analgesics and Scholastic skills in Children in Fifth Grade in Norway. JAMA Netw open. 2022;5(7):e2222425–e.
87. Skovlund E, Selmer R, Skurtveit S, Brandlistuen RE, Handal M. In utero exposure to analgesic opioids and language development in 5-year old children. Pharmacoepidemiol Drug Saf. 2020;29(6):736–44.
88. Tovo-Rodrigues L, Carpena MX, Martins-Silva T, Santos IS, Anselmi L, Barros AJD, et al. Low neurodevelopmental performance and behavioural/emotional problems at 24 and 48 months in Brazilian children exposed to acetaminophen during foetal development. Paediatr Perinat Epidemiol. 2020;34(3):278–86.
89. Bertoldi AD, Rifas-Shiman SL, Boing AC, Silva Dal Pizzol T, Miranda VIA, Silveira MPT, et al. Associations of acetaminophen use during pregnancy and the first year of life with neurodevelopment in early childhood. Paediatr Perinat Epidemiol. 2020;34(3):267–77.
90. Laue HE, Cassoulet R, Abdelouahab N, Serme-Gbedo YK, Desautels A-S, Brennan KJM, et al. Association between Meconium Acetaminophen and Childhood Neurocognitive Development in GESTE, a Canadian cohort study. Toxicol Sci. 2019;167(1):138–44.
91. Bornehag CG, Reichenberg A, Hallerback MU, Wikstrom S, Koch HM, Jonsson BA, Swan SH. Prenatal exposure to acetaminophen and children's language development at 30 months. Eur Psychiatry. 2018;51:98–103.
92. Liew Z, Ritz B, Virk J, Arah OA, Olsen J. Prenatal use of Acetaminophen and Child IQ: a Danish cohort study. Epidemiology. 2016;27(6):912–8.
93. Klebanoff MA, Berendes HW. Aspirin exposure during the first 20 weeks of gestation and IQ at four years of age. Teratology. 1988;37(3):249–55.
94. Streissguth AP, Treder RP, Barr HM, Shepard TH, Bleyer WA, Sampson PD, Martin DC. Aspirin and acetaminophen use by pregnant women and subsequent child IQ and attention decrements. Teratology. 1987;35(2):211–9.
95. Lye JM, Knight JA, Arneja J, Seeto RA, Wong J, Adel Khani N, et al. Maternal acetaminophen use and cognitive development at 4 years: the Ontario Birth Study. Pediatr Res. 2023;93(4):959–63.
96. Chowdhury MAK, Hardin JW, Love BL, Merchant AT, McDermott S. Relationship of nonsteroidal anti-inflammatory drug use during pregnancy with Autism Spectrum disorder and intellectual disability among offspring. J Womens Health (Larchmt). 2023;32(3):356–65.
97. Dudukina E, Szépligeti SK, Karlsson P, Asomaning K, Daltveit AK, Hakkarainen K, Hoti F, Kieler H, Lunde A, Odsbu I, Rantanen M, Reutfors J, Saarelainen L, Ehrenstein V, Toft G. Prenatal exposure to pregabalin, birth outcomes and neurodevelopment - a population-based cohort study in four Nordic countries. Drug Saf. 2023;46(7):661–75.
98. Mandelli M, Morselli PL, Nordio S, Pardi G, Principi N, Sereni F, Tognoni G. Placental transfer of diazepam and its disposition in the newborn. Clin Pharmacol Ther. 1975;17(5):564–72.
99. Guerre-Millo M, Rey E, Challier JC, Turquais JM, d'Athis P, Olive G. Transfer in vitro of three benzodiazepines across the human placenta. Eur J Clin Pharmacol. 1979;15(3):171–3.
100. Bais B, Molenaar NM, Bijma HH, Hoogendijk WJG, Mulder CL, Luik AI, et al. Prevalence of benzodiazepines and benzodiazepine-related drugs exposure before, during and after pregnancy: a systematic review and meta-analysis. J Affect Disord. 2020;269:18–27.
101. Zafeiri A, Raja EA, Mitchell RT, Hay DC, Bhattacharya S, Fowler PA. Maternal over-the-counter analgesics use during pregnancy and adverse perinatal outcomes: cohort study of 151 141 singleton pregnancies. BMJ Open. 2022;12(5):e048092–e.
102. Duncan J, Burgess P, Emslie H. Fluid intelligence after frontal lobe lesions. Neuropsychologia. 1995;33(3):261–8.
103. Rice D, Barone S. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ Health Perspect. 2000;108(3):511–33.
104. Cormier DC, Bulut O, McGrew KS, Kennedy K. Linguistic influences on cognitive test performance: Examinee characteristics are more important than test characteristics. J Intell. 2022;10(1):8.
105. Ritchie SJ, Bates TC, Deary IJ. Is Education Associated with improvements in General Cognitive ability, or in specific skills? Dev Psychol. 2015;51(5):573–82.
106. Meador K. Cognitive deficits from in Utero AED exposure. Epilepsy Curr. 2004;4(5):196–7.
107. Straub L, Bateman BT, Hernandez-Diaz S, York C, Zhu Y, Suarez EA, et al. Validity of claims-based algorithms to identify neurodevelopmental disorders in children. Pharmacoepidemiol Drug Saf. 2021;30(12):1635–42.
108. Hunnicutt JN, Ulbricht CM, Chrysanthopoulou SA, Lapane KL. Probabilistic bias analysis in pharmacoepidemiology and comparative effectiveness research: a systematic review: Probabilistic Bias Analysis in Pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2016;25(12):1343–53.
109. Phillips CV. Quantifying and reporting uncertainty from systematic errors. Epidemiology. 2003;14(4):459–66.
110. Zhang N, Cheng S, Ambroggio L, Florin TA, Macaluso M. Accounting for misclassification bias of binary outcomes due to underscreening: a sensitivity analysis. BMC Med Res Methodol. 2017;17(1):168.
111. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. United States: United States. Wolters Kluwer; 2008.
112. Grimes DA, Schulz KF. Bias and causal associations in observational research. Lancet. 2002;359(9302):248–52.

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