Title:

Advances in epidemiological methods and utilisation of large databases: A methodological review of observational studies on central nervous system drugs use in pregnancy and central nervous system outcomes in children

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Running heading:

Methodological review of CNS drug use in pregnancy and outcomes in children

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Abstract (279 words)

Introduction: Studies have used various epidemiological approaches to study the association between central nervous system (CNS) drugs use in pregnancy and CNS outcomes in children. Clinical adverse effects were generally focused on, while, variations in methodologies were not given sufficient attention.

Objective: To review the methodological characteristics of existing studies in order to identify any limitations and recommend further research.

Methods: A systematic literature search was conducted on observational studies listed in PubMed from 1 January 1946 to 21 September 2017. Following independent screening and data extraction, a review addressing the trends of relevant studies, differences between various data sources, methods used to address bias and confounders, and conduct statistical analyses was undertaken.

Results: 111 observational studies, 25 case-control studies, and 86 cohort studies were included in the review. Publications dating from 1978 to 2006 mainly focussed on antiepileptic drugs, but research on antidepressants has increased from 2007 onwards. Only one study focussed on antipsychotic use during pregnancy was identified. 46 studies obtained data from an administrative database/registry, 20 from ad hoc disease registries, and 41 from ad hoc clinical samples. Most studies (58%) adjusted the confounding factors using general adjustment, while only a few studies used advanced methods such as sibling-matched models and the propensity score methods. 42 articles used univariate analyses and 69 conducted multivariable regression analyses.

Conclusion: Multiple factors, such as different study designs and data sources have led to inconsistent findings in the association between use of CNS drug use in pregnancy and CNS outcomes. Researchers should allow for study designs with clearly defined exposure periods, at the very least in trimesters, and use advanced confounding adjustment methodology to increase the accuracy of the findings.

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Key points:

- Pregnancies as identified in administrative databases/registries with large sample sizes are highly likely to be representative of the general population.
- Explicit linkage records, between mothers and their children, should be used to study infant outcomes and drug exposure in pregnancy.
- Advanced methods such as sibling-matched models and propensity score methods can minimise potential bias and improve the accuracy of findings.
- A pre-specified time of drug exposure and an adequate follow-up period are essential in pregnancy safety studies.
- Adequate and validated outcome instruments/scales (also chosen based upon infant age) should be used.

1. Introduction

There has been an ongoing debate about whether pregnant women should take central nervous system (CNS) medications such as antidepressants (ADs), antipsychotics (APs) and/or antiepileptic drugs (AEDs) given the potential adverse outcome for the foetus. This must be weighed up against the risk of untreated depression, schizophrenia or epilepsy. Studies into the teratogenicity of the older generations of AEDs have shown that intrauterine exposure to anticonvulsants like valproate acid and phenytoin are associated with congenital malformations such as congenital heart anomalies, neural tube defects, cleft lip/plate and developmental delays (1-5). Findings on the potential adverse outcomes of ADs like selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) or tricyclic antidepressants (TCAs), however, remain conflicting with some studies showing a statistically significant increase in the risk of congenital heart defects, neurodevelopmental disorders including autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and neonatal convulsions (6-8). Pharmacologically, all CNS drugs can cross not only the blood-brain barrier for their intended action in the pregnant woman, but also the placenta, which could have unintended effects on the development of the foetus (9-11). Previous studies have shown that antipsychotic use in pregnancy (in particular some second generation APs such as olanzapine and clozapine) may lead to the development of gestational diabetes (12), and thus an increased risk of CNS-related birth defects. However, there is a lack of concrete evidence for a causal association between gestational APs use and adverse CNS outcome in offspring (13-16). The possible link between in-utero exposure to CNS medication and adverse CNS effects in children creates a dilemma in the pharmacological management of women with severe neurological or psychiatric disorders both when they are trying to conceive, and during pregnancy. The safety of CNS drugs use in pregnancy has become an important clinical issue and has been extensively studied over the past few decades.

Randomised controlled trials (RCTs) are usually regarded as the gold standard for evaluating medication efficacy and safety in the general population. However, it is not feasible to conduct RCTs in pregnant women due to ethical concerns (14, 17). Observational studies, including case-control and cohort studies, have some advantages over RCTs. One such advantage is the representativeness of the general population due to the large sample size available for analysis (18). Moreover, long-term effects and rare outcomes on the CNS of the offspring can be evaluated in observational studies. Any potential risk of neurodevelopmental disorders such as ASD and ADHD require a longer period of observation for reliable detection, since the diagnosis of these conditions is generally not made until some considerable time after the neonatal period. Observational studies of medication safety in pregnancy are therefore essential to complement information from RCTs (17, 19).

Systematic reviews and meta-analyses of observational studies are often undertaken to evaluate the clinical effects of medication in pregnant women. However, these analyses often focus on the extent

of the clinical adverse effects and may not give sufficient attention to the variations in methodologies used in the studies. Therefore, this methodological review was conducted to assess the methodological characteristics of existing case-control and cohort studies, which investigate the association between CNS drugs use in pregnancy and adverse CNS outcomes in neonates and children.

2. Methods

2.1 Systematic literature search

A systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist using PubMed to search for observational studies that investigated the association between the use of CNS drugs during pregnancy and adverse CNS outcomes in neonates and children between 1 January 1946 and 21 September 2017. The following combination of search terms was used: (Pregnancy) AND (CNS outcomes) AND [(Antidepressants) OR (Antipsychotics) OR (Antiepileptics)]. These search terms were chosen based on recommendations by Medical Subject Headings (MeSH) terms in PubMed as well as the Cochrane Pregnancy and Childbirth Group Search Strategy (20). The complete list of search terms can be found in Electronic Supplementary Material 1.

2.2 Inclusion and exclusion criteria

Observational studies that used either case-control or cohort design and which reported the association between gestational AEDs/ADs/APs use and infant CNS outcomes (neurodevelopmental disorders, convulsions and congenital anomalies of CNS) were included. Articles written in languages other than English were excluded. Animal studies, case reports, case series, cross-sectional studies, reviews, systematic reviews and meta-analyses were excluded.

2.3 Screening and data extraction

All articles were screened independently by two authors (PH and MC) in order to identify relevant studies based on titles and abstracts. Full texts of potentially relevant papers were also reviewed in case the titles and abstracts were not adequate for determining the relevance of the study. Data extraction was conducted independently for all the included studies using a standardised data collection form. Any discrepancies between the two reviewers were resolved through discussion. Data extraction included the year of publication, data source, method for establishing linkage between mother and child, study duration, study site, study design, sample size, types of drug used, types of CNS outcomes, inclusion criteria, exclusion criteria, identification of study groups, time period of exposure measurement, statistical method, and confounding adjustment method. Three types of data source were identified: administrative databases/registries, ad hoc disease registries and ad hoc clinical samples. Briefly, in this study we defined administrative databases/registries as electronic medical or insurance record systems, often used to facilitate the operation of hospitals, general practices or community

pharmacies. An ad hoc disease registry, on the other hand, was defined as a registration system set up for the systematic collection of data for a specific disease state or exposure group, usually for the purpose of epidemiological analysis or for carrying out follow-up studies and research. For studies not using any database and/or registry as data sources, the data source was considered to be an ad hoc clinical sample, with patients recruited in hospitals/clinics or through information services.

2.4 Review and analyses

This methodological review focused on the data collection and study designs of the included observational studies. In particular: the characteristics of the included studies with reference to the different types of data sources used, methodologies used to address underlying biases and confounders, and statistical analysis methods applied. A descriptive summary detailing study design, types of drug exposure and types of CNS outcomes is presented in Electronic Supplementary Material 3.

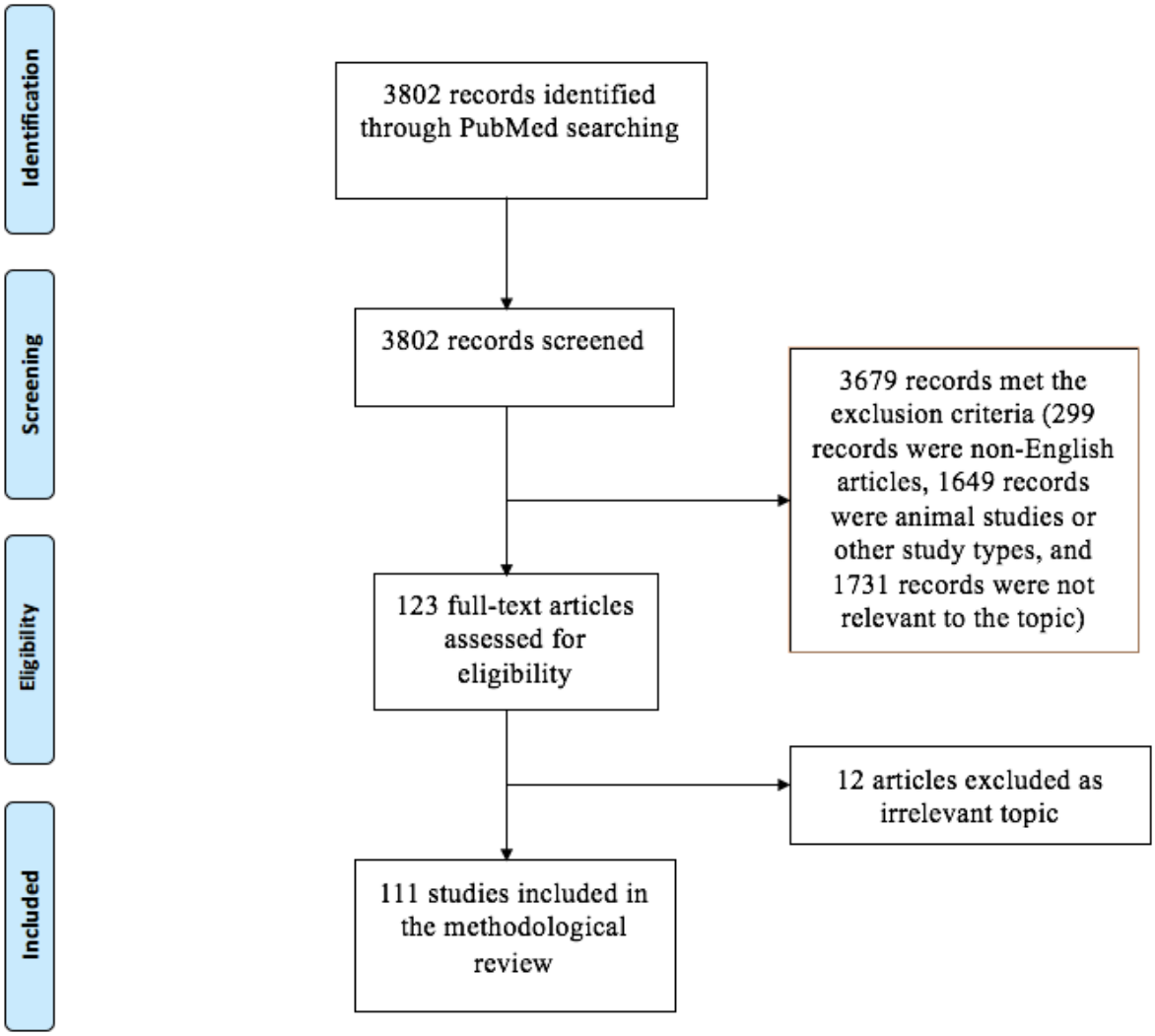

Fig 1 PRISMA flow chart for studies inclusion

3. Results

A total of 3,802 studies were retrieved from the PubMed database from 1 January 1946 to 21 September 2017 (Fig 1). One hundred and eleven were deemed to be relevant and included. The full list is found in Electronic Supplementary Material 2. Of the 111 studies, twenty-five (23%) were case-control studies (21-45) and eighty-six (77%) were cohort studies (1, 6, 7, 46-128), although five of the cohort studies did not include an unexposed group as control for comparison (73-76, 92). Sixty-one (55%) were carried out in European countries (21, 23, 24, 28, 29, 32-34, 36, 38, 39, 42, 43, 46, 48, 49, 52, 54-56, 59, 60, 62, 64, 68-72, 77, 79-81, 83, 85, 87-89, 91-94, 97, 99, 101, 103, 105-107, 110, 116-123, 125, 126, 128), twenty (18%) in the United States (1, 6, 22, 25, 26, 30, 31, 40, 41, 45, 47, 57, 61, 65, 67, 75, 76, 78, 86, 100), nine (8%) in Canada (7, 51, 53, 63, 82, 96, 100, 102, 124), seven (6%) in Australia (44, 111-115, 127), and the remaining studies were in Japan, India, Hong Kong, Israel and Egypt (23, 35, 37, 50, 58, 66, 73, 74, 84, 90, 95, 98, 104, 108, 109). In addition, the types of CNS outcomes being investigated included neurodevelopmental disorders, convulsions and congenital anomalies of CNS such as neural tube defects, spina bifida, anencephaly and microcephaly. While thirty (27%) studies specifically focused solely on one CNS outcome, others investigated all congenital malformations and included CNS as one of the outcome subgroups for analysis.

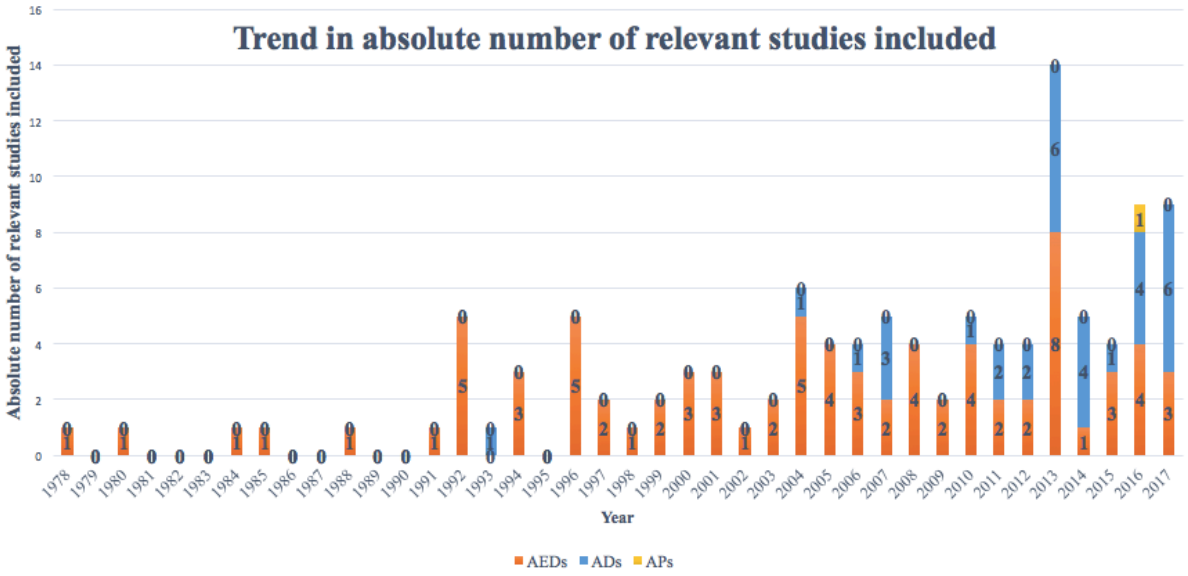

Fig 2 Trend in absolute number of relevant studies included from 1978 to 2017

3.1 General characteristics of included articles

As shown in Fig 2, the absolute number of relevant studies peaked in 2013. The number of relevant studies has increased gradually over time and the proportion of included articles over the total number of papers, found using the search terms, has remained around 2-8% in the last two decades. The first study that was included in this review, investigating gestational antiepileptic drug use, was published in 1978. Publications focused on AED use made up the majority of the included studies until

1993, when the first observational study focussed on antidepressant (fluoxetine) use in pregnancy was published (100). There has been a gradual rise in antidepressant research from 2004 onwards and these have exceeded the number of AEDs studies since 2007. In 2017, antidepressant studies contributed to the vast majority of the included studies. Only one study on antipsychotics was identified in this review (128).

3.2 Types of data sources used

Of the 111 studies, forty-six (41%) obtained their data from an administrative database/registry (6, 7, 23-30, 32-34, 40, 42, 45-49, 51, 53, 55-57, 61, 62, 69, 71, 72, 77, 82, 83, 85, 88-90, 101, 105, 106, 118, 121, 122, 124, 126, 128), twenty (18%) from an ad hoc disease registry (36, 38, 39, 41, 44, 54, 65, 68, 93, 94, 98, 100, 108, 109, 111-115, 127), forty-one (37%) from an ad hoc clinical sample (1, 21, 22, 31, 35, 37, 43, 50, 52, 58-60, 63, 64, 67, 70, 73-76, 78, 84, 86, 87, 91, 92, 95-97, 99, 102-104, 107, 110, 116, 117, 119, 120, 123, 125), and four (4%) studies did not clearly specify the data source (66, 79-81). Selection of data sources has changed over time with administrative databases/registries comprising large numbers of participants becoming the most commonly used data source in recent years.

Exposure groups were identified by using code lists or by using information from interviews or self-reports recorded during the antenatal care service in administrative databases/registries. Exposure identification methods in ad hoc disease registries and the ad hoc clinical samples usually consisted of retrospective reviews of medical records, questionnaires, or examinations. For more details, see Electronic Supplementary Material 3.

3.3 Linkage between mother and child

Few studies explicitly reported the linkage methods between mother and child, but linkage methods were ascertainable in eighty-five (77%) of the included studies (1, 7, 21, 25, 26, 28, 31-36, 38-46, 48-50, 52-60, 63-66, 68-73, 77, 78, 83, 85-90, 95-108, 110-128). In general, there are two types of mother-child linkage methods, namely deterministic linkage and probabilistic linkage. Deterministic linkage is based on a full agreement of a unique identifier or a set of common identifiers (129). Studies using administrative databases/registries mostly included mother-child pairs identified through deterministic linkages. One example of an effective deterministic linkage method is the Clinical Data Analysis and Reporting System (CDARS) in Hong Kong, which matches the identification numbers of mother and child, together with the delivery date and hospital. Accuracy is further ensured by linking the records permanently and immediately after delivery (90). Twenty-eight of the eighty-five studies (7, 25, 26, 28, 42, 49, 50, 52, 54-59, 63, 65, 70, 73, 85, 88-90, 101, 105, 108, 118, 121, 122) were conducted using deterministic linkage (129). Probabilistic linkage is an approach using a set of variables to define the unique identity of an individual, such as maternal date of birth, maternal name and residence code (130) and linking up pregnant women with children that have a high probability to be a mother-child pair. Fifty-seven studies used probabilistic linkage. An example of a study using probabilistic linkage

is the study using UK Clinical Practice Research Datalink (CPRD) which investigated the risks and benefits of psychotropic drugs use in pregnancy (128). Pregnant women and their children were linked based on the same general practice registration as well as the same family/household identifier. The maternal delivery date and child's month of birth were also required to be within 6 months.

3.4 Types of study designs adopted to deal with confounding factors

Sixty-six (59%) included studies compared women taking ADs/AEDs/APs with a control group defined as pregnant women without the corresponding exposure (21-24, 28, 32-41, 43, 45, 46, 49, 54, 56-58, 60, 62-64, 66, 68, 71-77, 79, 84, 86, 88, 91-94, 96-99, 102-105, 107, 109, 110, 113, 114, 116, 117, 119, 120, 124-128). However, there was no information regarding whether the pregnant women were untreated mothers with depression/epilepsy/schizophrenia or healthy mothers without depression/epilepsy/schizophrenia. Sibling-matched models were used to control for the shared genetic, maternal health status, familial and social factors in four (4%) studies (83, 90, 101, 106). In addition, three (3%) studies (42, 90, 106) conducted negative control analysis (131). Negative control analysis is usually applied to explore common forms of selection and measurement bias in observational studies (132).. Two of the studies conducted using negative control analysis used paternal drug exposure (Sujan et al. (2017) and Rai et al. (2013)). A recently published cohort study by Man et al. (2017) compared two negative control comparisons: pre-conception ADs users and never users; and never users with and without psychiatric disorders. To evaluate whether the exposure effect was due to the drug rather than the maternal disease state (depression/epilepsy/schizophrenia), control groups with alternative treatment were used in in thirty-three (30%) studies (1, 31, 42, 44, 47, 48, 50, 52, 55, 65, 67, 69, 70, 78, 80-82, 85, 87, 89, 90, 95, 100, 101, 108, 111, 112, 115, 118, 121-123, 128). The propensity score method was applied to minimise the effect of confounding in one (1%) study (101).

3.5 Statistical Analysis

Of the 111 included studies, forty-two (38%) conducted univariate analysis in which only the mean, standard deviation, absolute risk, percentage and incidence of adverse outcomes were reported, or the results were merely tabulated in absolute counts (21, 38, 43, 46, 47, 50, 60, 63, 64, 66-68, 73-76, 79-82, 84, 86, 87, 92, 94, 95, 97-100, 102-104, 107, 109, 110, 115-117, 119, 120, 124). The remaining sixty-nine (62%) studies used multivariable regression analysis, such as multiple linear regression, Poisson regression, logistic regression or Cox proportional hazard regression to provide adjusted risk estimates in the form of odds ratios (OR) and hazard ratios (HR) (1, 6, 7, 22-37, 39-42, 44, 45, 48, 49, 51-59, 61, 62, 65, 69-72, 77, 78, 83, 85, 88-91, 93, 96, 101, 105, 106, 108, 111-114, 118, 121-123, 125-128).

The proportion of univariate and multivariable analysis for each data source subgroup is shown in Fig 3. In total, the proportion of studies using multivariable analysis and univariate analysis is 62% and 38%, respectively. Multivariable analysis was mostly used in studies utilising administrative

databases/registries (38/46, 83%), and least in studies using ad hoc clinical samples as their data source (15/41, 37%). The reverse trend was seen for univariate analysis.

More complex methods have been used in recent studies. Studies using univariate analysis were commonly found in the early years.

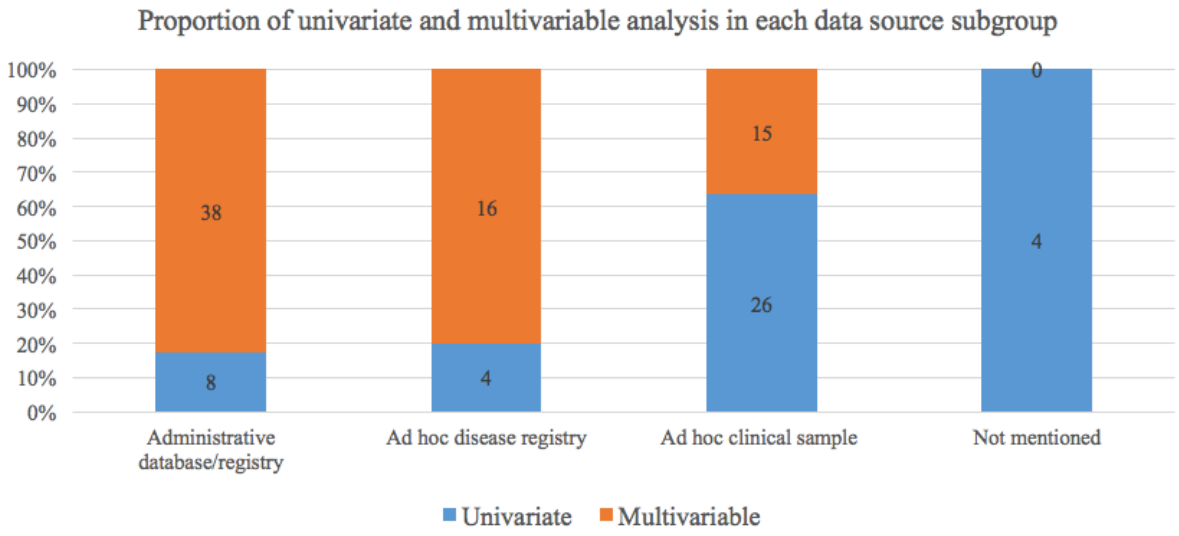

Fig 3 The proportion of univariate and multivariable analysis in each data source subgroup

4. Discussion

This is the first methodological review of observational studies of CNS drugs use in pregnant women and the CNS outcomes of their children. The findings show that most of the research to date has investigated the association between gestational CNS drugs use and infant CNS outcome using cohort studies. There has been an increase in these studies over the last 20 years and the vast majority of these have been reported in western countries. There has been more research on ADs than AEDs during the last five years.

Due to the unfavourable prognosis of epilepsy in pregnant women, such as a higher risk of death, preeclampsia, preterm labour, and stillbirth, much effort was invested in developing a registry for epilepsy patients. Registries such as the European Registry of Antiepileptic Drugs and Pregnancy (EURAP), the UK Epilepsy and Pregnancy Registry, and the North American AED Pregnancy Registry contain detailed information about participants and have become a valuable data source for research (65, 133-135). The well-established teratogenicity of AEDs may be associated with the gradual decrease in related observational studies as clinicians avoid prescribing teratogenic medications.

Only one study was found investigating the relationship between the use of antipsychotics in pregnancy and CNS outcomes in children. The prescription of APs in pregnancy has increased over the

last ten years, but the proportion of gestational APs use is still less than 1% (136, 137). Further research in this area is warranted.

4.1 Types of data source adopted

4.1.1 Administrative database/registry

A large sample size is one of the main advantages of using administrative databases/registries for observational studies. As well as being highly representative of the general population, using these registries can also increase the statistical power of the study, thus reducing standard error and improving accuracy in the detection of any effect. The pre-existing and on-going accrual of patient information in an administrative database/registry, with its primary purpose being to record health information saves time, money and the manpower involved in the data collection process compared to studies with ad hoc clinical samples as the data source.

Nonetheless, administrative databases/registries are not without some limitations. For the identification of exposures and cases, most use international coding systems such as the Anatomical Therapeutic Chemical Classification System (ATC) for medications or the International Statistical Classification of Diseases and Related Health Problems (ICD) for diagnoses. In case of misclassification or changes in coding of disease over time, significant discrepancies in diagnosis may affect the validity of the study results. For instance, the diagnostic criteria of psychiatric disorders, the Diagnostic and Statistical Manual of Mental Disorders (DSM), has been evolving constantly from DSM-III in 1980 to DSM-V in 2013. Moreover, many included studies use standard coding such as ICD codes, both 9th and 10th versions, but the accuracy of the coding varies between conditions, databases and registries (138-142). Only Rai et al., Viktorin et al. and Sujan et al., which used data from Swedish databases, performed the relevant validation for the purposes of their study (101, 106, 122, 143-145).

Biases in the collection, analysis, or interpretation of the data may result in invalid study conclusions (146). Three main types of bias are selection bias, information bias (also known as misclassification) and confounding bias (147). Limiting selection criteria to live births is common in administrative claims data and will lead to selection bias. Misclassification of the outcome disease(s), would bias the estimate towards null and consequently, underestimate the corresponding effect of the medications. Another type of misclassification, exposure misclassification, probably occurs in all observational studies as we often have data on prescriptions or dispensing, but not actual use (148). The misclassification of exposure or disease status can be considered as either differential or non-differential. Non-differential misclassification will bias the estimate towards the null (149). Conversely, differential misclassification occurs when the proportions of subjects misclassified differ between the study groups. That is, the probability of exposure being misclassified is dependent on outcome, and vice versa. The results could therefore be either overestimated or under-estimated (147, 150). An accurate exposure

assessment is vital to minimise the bias. Although measurements of drug concentration in maternal blood are not available in most of the data sources, this could potentially an ideal approach to validate exposure status. In terms of confounding bias, data from an administrative database/registry may not comprehensively cover all potential confounders, particularly lifestyle and behavioural characteristics, including diet, exercise, alcohol and tobacco use etc. (138).

Record linkages between registries are generally classified into deterministic linkage and probabilistic linkage methods (151). Deterministic linkage methods require exact agreement of the pre-determined matching variables to result in a linkage. Probabilistic linkage methods use information on some matching variables, and allow disagreement between matching variables if the degree of matching is determined to be greater than an accepted cut-off weight. Our findings showed that most studies using an administrative database/registry perform linkage through unique personal identification numbers, the deterministic linkage method. The major limitation of deterministic linkage methods is that the method is prone to entry errors and missing values, which would reduce the number of true matches, and hence the sensitivity and positive predictive value of the linkage (152). The type of identifiers used also has an effect on linkage quality. Direct identifiers, such as unique identifiable numbers (e.g. Social Security Number), are generally regarded as the gold standard (153). However, indirect identifiers (e.g. name, sex, date of birth, address, date of admission etc.) are commonly used in different studies due to regulatory and availability issues. It was shown in a validation study that record linkage using name code in place of full name record has low sensitivity but high specificity, resulting in under-estimated risks (154). This illustrates that the quality of the linkage method can significantly affect the outcome of a database-based observational study, and reporting of linkage methods is necessary, especially in database and registry settings. Lastly, medical records used in private clinics or specialist care can often not be identified in or linked with records in administrative databases/registries and this may contribute to the problem of underestimation of risk. Future studies could consider the use of probabilistic linkage to improve the quality of linkages if deterministic linkage is not possible.

4.1.2 Ad hoc disease registry

Ad hoc disease registries recruit patients with a specific exposure, for example, pregnant women with exposure to AEDs or epilepsy. They are usually set up for postmarketing surveillance and monitoring of any potential adverse effects of medication or treatment, as well as providing data for research purposes.

One strength of ad hoc disease registries is that they often have more complete data compared to administrative databases/registries, as the information on subject characteristics, treatment details and outcomes are better documented and reviewed by investigators. They also have long-term follow up, and comply with registry-specific standards and measurements, as required by the Registers of Patient Registries (RoPR), to ensure data validity (138). Data quality is further enriched by having

additional information that cannot be collected from administrative databases/registries, e.g. socioeconomic status and lifestyle characteristics of the study subjects.

However, the coverage of an ad hoc disease registry is lower as it contains a much smaller sample size and requires the voluntary enrolment of subjects, e.g. the UK Epilepsy and Pregnancy Register (68), thus reducing the representativeness and generalisability of study results. Selection bias could also be introduced as the people who are willing to enrol on the registry may be more health conscious or healthy, thus potentially underestimating the actual drug effect.

A major limitation of an ad hoc disease registry is the lack of an untreated control group. An ad hoc disease registry in general enrols subjects with the specific disease, and most likely, with the specific drug exposure (ADs/AEDs/APs) which could lead to a shortfall in calculating the incidence of the outcome of interest. However, studies using data from these ad hoc disease regstries usually have active control groups i.e. monotherapy vs polypharmacy, which has the advantage of minimising confounding by indication. For instance, a study using the North American AED Pregnancy Registry (65) compared specific AED monotherapy such as valproate, phenobarbital and topiramate with lamotrigine treatment. It is worth noting that although such comparisons help to differentiate different drugs, they can only be used when teratogenicity is already well-established in the drug class.

4.1.3 Ad hoc clinical sample

Since an ad hoc clinical sample involves the direct recruitment of patients from hospitals, clinics or information services, sample sizes are usually small and more manpower, money and time is required for the primary data collection process. Results of single centre ad hoc clinical sample studies are not very generalisable. They also have an increased risk of participants being lost-to-follow up due to their prospective nature. However, ad hoc clinical samples may have comprehensive data as any information which is not available in the database can be obtained from a questionnaire.

Summaries of the advantages and disadvantages of different data sources are shown in Table 1. An administrative database/registry might be the primary choice as it is more likely to be representative of the general population when dealing with potential bias.

Table 1 Advantages and disadvantages of different data sources

DATA SOURCE	ADVANTAGES	DISADVANTAGES
Administrative database/registry	● Large sample size ● More representative of the general population ● Higher statistical power and accuracy ● Reduction in standard error ● Time, cost and manpower saving	● May have significant discrepancies in diagnosis due to misclassifications or under-recording and/or change in coding of disease over time ● Information captured may not be adequate to address all confounding factors

		● Accurate linkage method between mothers and children may not be available ● Limited to the scope of the data coverage and may not have sufficient information from other healthcare providers ● Selection bias (i.e. limiting selection criteria to live births), information bias (i.e. misclassification of the outcome and exposure) and confounding bias (i.e. underlying confounders such as lifestyle and behavioural characteristics)
Ad hoc disease registry	● More comprehensive subjects' information ● Additional information can be collected via surveys or interviews if necessary ● Allows for long-term follow up if necessary ● Active control group involved	● Smaller sample size compared to administrative databases ● Lower coverage and representativeness of the general population ● Lack of untreated control group
Ad hoc clinical sample	● More comprehensive data than registry data ● Additional information can be collected if necessary	● Smaller sample size compared to both administrative databases and ad hoc disease registries ● More manpower, cost and time required compared to both administrative databases and ad hoc disease registries ● Lack of generalisability and representativeness ● Higher risk of loss-to-follow-up

4.2 Confounding factors management and study design

While many studies have observed that congenital malformations or neurodevelopmental disorders in infants are associated with maternal use of ADs and AEDs during pregnancy, confounders can impact the validity of estimates obtained from data and are a major source of bias (17, 90). Failing to explore the true effects of medication exposure can result in inappropriate therapies and adverse outcomes; thus, it is necessary to detect and control for confounding using suitable methods to obtain unbiased effect estimates (17, 155).

The general covariates in pregnancy observational studies are maternal age, parity, maternal smoking and alcohol use. Multivariable adjustments in regression models were commonly applied to deal with these covariates in our included studies. The use of advanced methods such as propensity score (PS) methods, which is particularly beneficial for common treatments and rare outcome observations, was still limited. Applications including matching, stratification, adjustment, and weighting (17) can be used to balance patients' characteristics in groups. PS can detect possible residual confounding and therefore decrease the potential bias (156). Logistic regression is the typical approach for estimating the PS with the exposure of interest as the dependent variable and confounders as

independent variables. Although the application of PS has increased in safety studies, it is still used far less than multivariable regression (17, 157).

Confounding by indication seems to be one of the most significant residual confounding effect in the context of our review (158). Any CNS outcome in children might be a real effect of maternal CNS drug use during pregnancy, but might also be a confounding effect due to the disease state of the pregnant mother who needs to take the medication. A straightforward analysis between users and non-users of CNS drugs fails to control for confounding by indication as the adverse effect might be due to the underlying disease of the mother, and not because of the maternal use of any medication. In our review, most included studies used control groups (matching and restriction) to deal with confounding. For example, a study using Hong Kong population based electronic medical records selected a control group using antipsychotics as an active comparator in order to adjust for confounding by indication (90). Furthermore, for some diagnoses such as depression, a scale measuring symptom severity is even better than just a dichotomous variable (e.g. depression: yes/no). For drugs used for several indications (e.g. lamotrigine and bipolar disorder/epilepsy), risks could be compared across indications as well.

We identified sibling-matched analyses and negative control analyses to adjust crude estimates for confounding factors such as socioeconomic demographics and genetic factors in our included studies. Use of sibling-matched analyses is most suitable for ascertaining the relationship between prenatal exposures to CNS substances and foetal outcomes when confounders are shared between siblings, and there are no carryover effects between siblings (159, 160). One main advantage is that, by separating the potential genetic and familial components of the disease status from exposure to medications (17), the results are less likely to be biased due to confounding. Sibling designs may be unbiased but only if all confounders are perfectly shared by within-pair members, and there is no random measurement error of the exposure (160). However, the current approach normally assumes a stable familial context, i.e. the composition of family is assumed to be static and unchanging. This might not be the case as the family might not be the same over time. The socioeconomic status of the family might change, and the birth order or the inter-pregnancy interval between different foetuses might affect various outcome such as autism (161). Since many real sibling comparisons may suffer from one or both of above biases, the application of sibling-matched analyses should be given due consideration (160).

Negative control analysis could eliminate the possibility that the adverse outcome is due to the effect of alternative variables instead of the exposure factor being studied. Measuring drug exposure before conception is common negative control method. If a significant difference in the risk of adverse CNS outcomes is found and associated with preconception drug exposure, this indicates that potentional maternal psychiatric disorders have an effect on adverse outcomes as the negative control group was not exposed to the drug of interest during pregnancy. Also, negative controls enable identification of

the existence and direction of bias, both in terms of recall bias and selection bias due to uncontrolled confounding (131). Paternal exposure to CNS substances during pregnacy period as the negative control exposure is biologically implausible as paternal exposure would not affect the fetal outcome. However, paternal exposure may, in theory, affect maternal exposure via behavioural, environmental and social influences (162). In this case, if paternal exposure during pregnancy to some extent determines maternal exposure, the outcomes would be considered to be due to the confounding of unmeasured factors within the families rather than the exposure of interest.

Marginal structural models (MSMs) and instrumental variable methods are advanced methods for confounding control in pregnancy medication safety studies (17). MSM use time-varying exposures and measure confounders which are highly related in pregnancy studies due to the variation in foetal vulnerability and the tendency of women to alter their gestational medication use (17, 163, 164). However, MSMs cannot provide unbiased effect estimates when confounders are unmeasured. On the other hand, instrumental variable analyses can address both measured and unmeasured confounding factors, and so instruments which meet all the strict assumptions may imitate the results from a randomised trial (17), whereas untestable assumptions could result in bias amplification. As no included study has adopted these two methods, it is worth noting that there are alternatives for researchers to consider as primary or secondary analyses in further research.

We identified some issues in the included studies such as inadequate follow-up, unspecified time to exposure, or even use inappropriate confounding approaches, which could lead to overestimation or underestimation of potential risks. An example is the inconsistent findings by several observational studies investigating the association between ADs and ADHD (25, 26, 61, 83, 106). While ADHD is often clinically diagnosed after the age of five (90), few studies (61, 90) have restricted the samples to children at least five years old. Therefore, the resulting estimates may not truly reflect the actual risk. Methods such as the use of adequate follow-up and specified exposure time are therefore necessary to avoid underlying bias, imprecision and confusing interpretation of estimates. When focusing on congenital malformations, investigators should attempt to study the time period of exposures relevant to the pathogenesis of the condition where appropriate. For instance, the critical period for neural tube development is 17-30 days of gestation (165). Thus, for any of the neural tube defects, e.g. anencephaly and spina bifida, they are more likely to be influenced by exposure factors in the first trimester and cannot be caused by exposure later in pregnancy. However, many included studies did not specify the time period of the drug exposure, or merely set it as ‘during pregnancy’, which could potentially affect the accuracy of results. Moreover, the definition of pregnancy period should be considered carefully that when counting gestational days, it could preferably be clarified that ‘days of gestation’ are claculated from the first day of the last menstrual bleeding day rather than the fertilisation day which is two weeks later.

4.3 Limitations and challenges

A limitation of this methological review is that we only seached articles in PubMed and we may not have included all potential studies on maternal CNS drug use and infant CNS outcomes. For the purposes of this review, we selected a wide varity of observational studies focusing on pregnancy exposure with different methodological characteristics.

It is hard to define whether the quality assessment such as Newcastle-Ottawa Scale (NOS) can provide the true study quality although we often consider a higher NOS score represent a higher study quality. Researchers are supposed to be critical when conducting a meta-analysis that the more 'inferior' studies included in the meta-analysis, the more misleading the conclusion could be. To exclude the 'inferior' studies from the meta-analysis might be a better choice which can provide reliable risk calculations.

4.4 Clinical implication and recommendation

Although there are some drawbacks of observational studies, they are currently the only way of assessing medication safety during pregnancy. There is no perfect study design for all studies. However, several suggestions for further studies could be considered. Firstly, using an appropriate time period of exposure (by trimester or even week of pregnancy) and adequate follow-up are vital for accurate results. Failure to evaluate the right observation period could mask a potential effect, i.e. bias towards null. Secondly, an administrative database/registry is a good first choice for a representative study sample, providing accurate and reliable record linkage between mothers and their children is possible. Inaccurate linkage between mother-child pairs could results in misclassification of both exposures and outcomes and would underestimate the study findings. Third, regardless of the types of data source selected, it is important to address confounding, preferably with more than one of the above mentioned advanced methods in order to avoid potential biases. In particular, confounding by indication is the most important factor to consider in observational studies on CNS drugs use in pregnancy and CNS outcomes in offspring. Unmeasured or unaddressed confounding could lead to biased results and subsequently to incorrect conclusions. Last but not least, in order to account for multiple confounding factors, multivariable analyses such as logistic regression analysis are recommended to provide more precise risk estimates. A flow chart of the study design process can be seen in Electronic Supplementary Material 4.

5. Conclusion

While publications of observational studies investigating the association between gestational CNS drug use and adverse CNS outcome in neonates have increased over the years, the findings have been inconsistent and sometimes contradictory. This could be due to multiple factors, such as the underlying limitations of different study designs and estimations used. The discrete choices of control

groups and data sources, whether potential confounders are addressed appropriately, the sample size involved, or even study period, duration, inclusion and exclusion criteria may all also contribute to differences in the final results and conclusions. Investigators should be mindful of these issues and focus on optimising study designs as well as adopting the most suitable statistical analysis method for their hypothesis in order to minimise potential bias and confounders. Addresing these factors will achieve better precision, validity and generalisability of results.

Compliance with Ethical Standards:

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