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Review article

Seizure prediction in pregnant women with epilepsy: An umbrella review of clinical practice guidelines and systematic reviews

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ABSTRACT

Objective: To identify risk factors for seizure in pregnant women, and in the general population with epilepsy.
Study design: Umbrella review of clinical practice guidelines and systematic reviews on risk factors or prediction models for seizure occurrence in pregnant women with epilepsy, adults with epilepsy, or all individuals with epilepsy. Guidelines or systematic reviews exclusively for children were excluded. We searched MEDLINE, Emcare, Embase, CINAHL, TRIP PRO, Epistemonikos, World Health Organisation, Guideline International Network, DANS, and grey literature (2000-2023) without language restrictions. Risk factors or predictors listed in the final guidelines or systematic reviews were collated and thematically analysed.
Results: From 3406 citations, we included 13 articles (ten guidelines, three systematic reviews) reporting 26 risk factors in pregnant women and the general adult population with epilepsy: eight factors in guidelines for pregnant women only; five in both pregnant women and general adult populations (four in both guidelines and systematic reviews, one in guidelines only); and 13 factors in the general adult population (four in both guidelines and systematic reviews, eight in guidelines, and one in a systematic review). Risk factors were categorised into five broad themes: seizure type; seizure control; anti-seizure medication; neurological; and epilepsy and medical history. Three risk factors for seizure ocurrence were cited in more than two guidelines or systematic reviews: seizure freedom (reduced risk), immediate initiation of anti-seizure medication after first seizure (reduced risk), and abnormal electroencephalogram (increased risk). Three risk factors were linked to a more

Abbreviations: ASM, anti-seizure medication; EEG, electroencephalogram; HR, hazard ratio; OR, odds ratio; RR, relative risk; SUDEP, sudden unexpected death in epilepsy.

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than two-fold chance of seizures in pregnant women with epilepsy: tonic-clonic seizures in the last three months (RR 7.20, 95% CI 6.63-11.93), a history of non-tonic-clonic seizures (RR 2.11, 95% CI 1.88—2.62), and seizures in the pre-pregnancy year compared to no seizures (RR 3.51, 95% CI 3.13-3.94).
Conclusion: Multiple risk factors have been recommended for use in practice across different guidelines and reviews to identify those at increased risk of seizures in the adult population with epilepsy, and specifically in pregnant women with epilepsy. Further research is needed on the implementation of tools for predicting seizures to improve maternal and neonatal outcomes.

Introduction

In the United Kingdom (UK), one in 200 women who give birth have epilepsy, but one in 14 women who die during pregnancy or after childbirth have epilepsy [1]. Epilepsy is now the third leading cause of indirect maternal death in the UK, and the main cause of death is poor seizure control [2]. This is often due to a lack of recognition of the women's high-risk status by healthcare professionals, and women discontinuing their anti-seizure medication (ASM) due to concerns about effect of the drug on their unborn baby [3].

Seizure control is critical during pregnancy, as uncontrolled seizures pose significant risks to both the mother and baby, including seizure-related accidents, miscarriages, preterm birth, and sudden unexpected death in epilepsy (SUDEP) [4–6]. Even brief absence seizures, which cause temporary unconsciousness, can have a major impact on a woman's life, like losing a driver's licence [7 8]. Effective antenatal risk stratification and clinical management rely on being able to accurately identify pregnant women with epilepsy who are at increased risk of seizures, and prioritise those most in need of urgent specialist epilepsy care [1].

Risk factors for seizures have been reported in various clinical practice guidelines and systematic reviews on epilepsy management during pregnancy [9 10]. While these guidelines and reviews often identify similar risk factors, they are often presented in different formats, leading to variability in their clinical interpretation and application. This inconsistency can contribute to differences in risk assessment, management decisions, and overall maternal care [11].

Sex-specific differences in seizures, including hormonal and pregnancy-related changes complicates risk prediction in women [12]. The historical and persistent sex and gender disparities in research have led to limited data on women-specific seizure risk, especially in pregnancy [13–14]. We carried out an umbrella review to map the risk factors recommended by both pregnancy-specific and general adult epilepsy guidelines and systematic reviews, to assess any differences in reported seizure risk factors, assess the quality of identified guidelines and reviews, and determine whether additional risk factors should be considered for inclusion in current pregnancy-specific recommendations.

Methods

The systematic review was prospectively registered with PROSPERO (CRD42023425551) and reported according to PRISMA guidelines [15].

Literature search

We searched MEDLINE, Emcare, Embase, CINAHL, TRIP PRO, Epistemonikos, World Health Organisation, Guideline International Network, DANS, and grey literature from January 2000 to August 2023 using combinations of relevant medical subject heading (MeSH) terms for "epilepsy", "seizures", "risk factors", "guidelines", and "systematic reviews". We included guidelines or systematic reviews that reported risk factors or prediction models for epileptic seizures in general adult or pregnancy-specific population. We excluded guidelines and reviews aimed at non-epileptic seizures, those limited to paediatric populations, or those published before 2000.

Study selection and data extraction

Three independent reviewers (FJ, STariq, BD) reviewed titles and abstracts, with any conflicts resolved by consensus. Two independent reviewers (FJ, BD) performed full-text screening to identify guidelines or systematic reviews that reported on risk factors for seizures or seizure risk prediction. We defined a clinical practice guideline as a publication that uses a search of the literature to provide recommendations, strategies, or information to guide decisions about appropriate health care, and defined a review as systematic if it included a method of searching literature from more than one database. Two reviewers (FJ, BD) independently extracted data on publication year, publishing organisation, geographical region of organisation, population, population size, seizure definition, number of reported risk factors, and effect sizes of individual risk factors (relative risk, odds ratio or hazard ratio) or prediction models (discrimination and calibration). Discrepancies in data extraction were resolved through discussion.

Quality assessment

Each publication was independently quality assessed by reviewers (FJ, BD) with the relevant tool: Appraisal of Guidelines for Research and Evaluation II (AGREEII) was used to assess clinical practice guidelines; and A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR2) was used to assess systematic reviews [16–18]. Where the guideline included a systematic review or prediction model, the quality assessment was of the review or model, rather than the guideline. We used the Prediction model Risk Of Bias ASsessment Tool (PROBAST) to assess the methodological quality of prediction models. The degree of overlap in the citation of primary publications in the guidelines and systematic reviews was quantified using the corrected covered area (CCA) index [19].

Data analysis and reporting

We performed a narrative synthesis of the extracted data to compare risk factors recommended by both pregnancy-specific and general adult epilepsy guidelines and systematic reviews. Clinical practice guidelines and systematic reviews were analysed separately in each population, before comparing across sources. We categorised risk factors based on common clinical themes, such as: seizure type; seizure control; anti-seizure medication; neurological; and epilepsy and medical history. Where available, we compared effect sizes to assess the strength and consistency of associations across different sources. No meta-analyses were undertaken so as not to conflate the calculated effect sizes of the different seizure risk factors identified. We also compared variations in the definition of seizure outcomes and assessed geographical distribution of the included guidelines and reviews. We interpreted our findings in the context of improving seizure prediction in pregnant women during antenatal risk assessment.

Results

The literature search identified 3406 citations. After abstract screening, 223 full-text papers were reviewed, of which 210 were excluded. Thirteen citations were included for data extraction (Fig. 1).

The final papers comprised ten guidelines and three systematic reviews (Table 1). Ten of the guidelines or reviews were from Europe and three were from North America. The guidelines or reviews were published between 2009 and 2022. There were five guidelines and one systematic review for pregnant women with epilepsy, and five guidelines and two systematic reviews for the general or general adult population with epilepsy.

The guidelines or reviews incorporated results from eighteen primary studies (Appendix 2). There was a slight overlap of the primary research in the guidelines and reviews, as determined by a low corrected covered area (CCA) index of 1.2%. Three of the guidelines or reviews did not provide references to primary studies specifically regarding risk

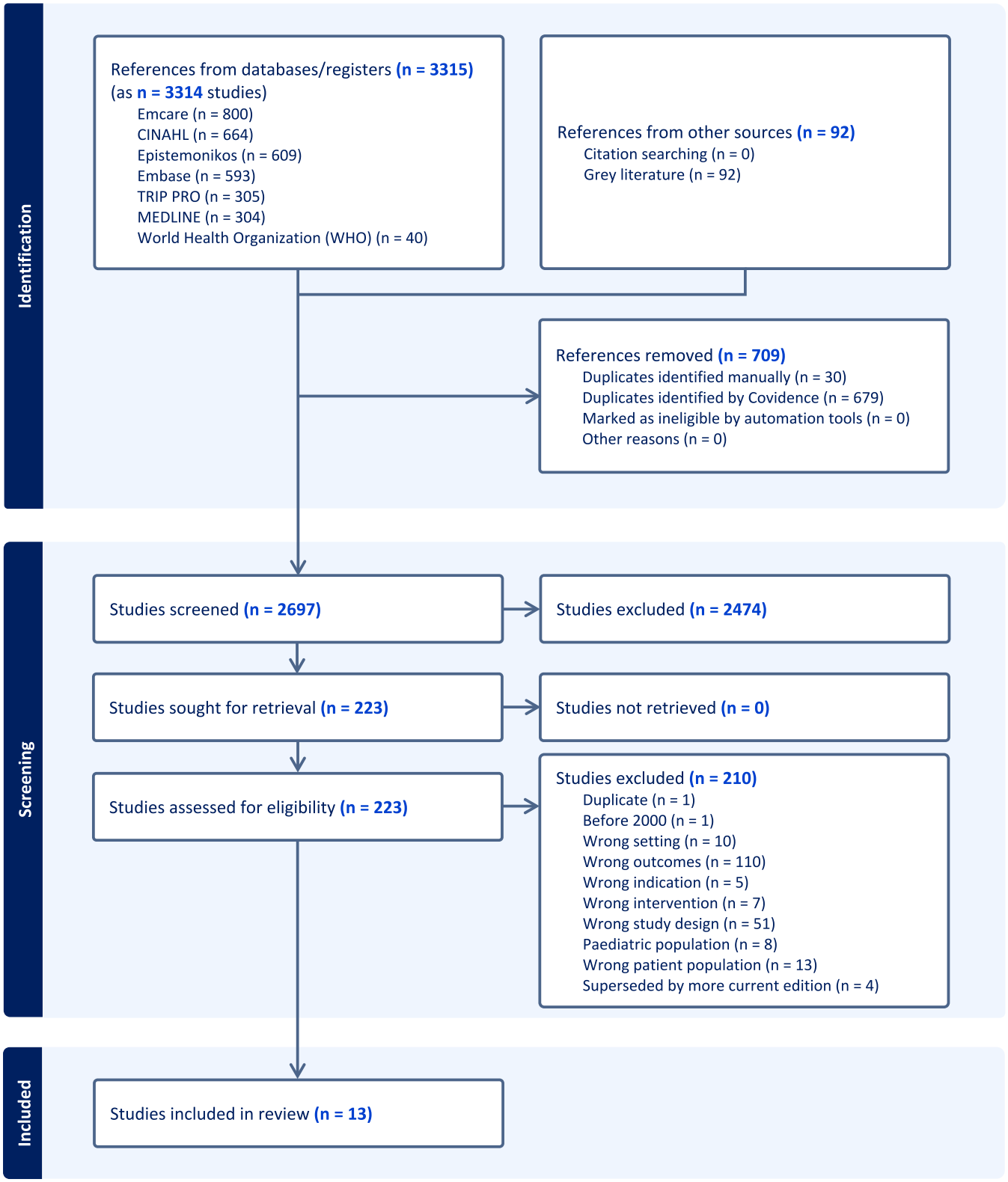

Fig. 1. PRISMA flow chart. Flow chart detailing literature search and screening of articles.

Table 1
Characteristics of guidelines and studies

Ref	Title	Year	Group	Region	Type	Population	Outcome	List of predictors or risk factors
20	Epilepsies in children, young people and adults	2022	NICE	Europe	guideline	general	frequency of monitoring, likely due to reduced independence, "high risk" and risk of adverse events	learning disability, < 16 years old, have active epilepsy (seizure last 12 months), bilateral tonic-clonic seizures, modifiable risk factors for SUDEP: (non-adherence to medication, alcohol and drug misuse, having focal to bilateral tonic-clonic seizures or generalised tonic-clonic seizures, having uncontrolled seizures, living alone, sleeping alone without supervision)
21	The management of pregnant women with epilepsy: a multidisciplinary collaborative approach to care	2017	n/a	Europe	guideline	pregnant women	factors contributing to deterioration of epilepsy during pregnancy	seizure frequency >1/month, multiple seizure types, drug-resistant epilepsy, high-dose polytherapy, poor compliance with ASMs, nausea and vomiting, sleep deprivation
22	First seizure presentations in adults: beyond assessment and treatment	2019	n/a	Europe	systematic review	adult	risk of seizure recurrence after first seizure	number of seizures prior to presentation, presence of a neurological disorder, epileptiform activity on EEG
23	Consensus statement for the management of generalized tonic-clonic seizures in Spain	2020	n/a	Europe	guideline	general	risk of seizure recurrence and prognosis	type of seizure, precipitating factors, age of onset, family history, relation to the wake/sleep cycle and other characteristics that can determine the risk of recurrence and prognosis.
24	Antiseizure Medication Withdrawal in Seizure-Free Patients: Practice Advisory Update Summary	2021	AAN	North America	systematic review	adults	seizure recurrence within 1-2 years	>/= 16 years old, > 1 ASM, history of seizures after starting an ASM, history of tonic-clonic seizures, history of myoclonic seizures, abnormal EEG in the past year
25	Practice Parameter update: Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): Obstetrical complications and change in seizure frequency	2009	AAN	North America	systematic review	pregnant women	seizure-free in pregnancy	seizure-free for at least 9 months to 1 year prior to pregnancy
26	Evidence-based guideline: Management of an unprovoked first seizure in adults	2015	AAN	North America	guideline	adults	seizure recurrence 1-5years after first seizure	ASM use, prior brain lesion or insult causing the seizure, an EEG with epileptiform abnormalities, a significant brain-imaging abnormality, nocturnal seizure
27	The Spanish Society of Neurology's official clinical practice guidelines for epilepsy	2016	SEN	Europe	guideline	general	risk of seizure after first generalised tonic-clonic seizure	type of epilepsy or epileptic syndrome (provoked seizure or symptomatic epilepsy), family history of epilepsy, neurological anomalies, epileptiform anomalies on EEG, lesions in neuroimaging study
28	Overview of the management of epilepsy in adults	2023	UpToDate	Europe	guideline	adults	risk of seizure in 2-5 years after ASM withdrawal, for people with epilepsy who are seizure-free with ASMs	epilepsy duration before remission, seizure-free interval before ASM withdrawal, age at onset of epilepsy, history of febrile seizures, number of seizures before remission, absence of a self-limiting epilepsy syndrome, epileptiform abnormality on EEG before withdrawal
9	Epilepsy in Pregnancy: Green-top Guideline No. 68	2016	RCOG	Europe	guideline	pregnant women	seizure-free in pregnancy	seizure free for at least 9 months to 1 year prior to pregnancy, idiopathic generalised vs focal epilepsies
10	Epilepsy in pregnancy: The role of the midwife in risk management	2018	n/a	Europe	guideline	pregnant women	risk of seizures in pregnancy	active seizures in the pre-pregnancy year, non-adherent with ASMs in early pregnancy, focal epilepsy, ASM polytherapy
29	Epilepsy in Pregnancy	2022	NHS Wales	Europe	guideline	pregnant women	risk factors for seizures	sleep deprivation and stress; adherence to ASMs; and seizure type and frequency.

(*continued on next page*)

Table 1 (*continued*)

Ref	Title	Year	Group	Region	Type	Population	Outcome	List of predictors or risk factors
11	Guidance for maternal medicine services in the coronavirus (COVID-19) pandemic	2020	RCOG	Europe	guideline	pregnant women	risk of seizures in pregnancy and up to 6 weeks postpartum	age at first seizure, seizure classification, booking dose of levetiracetam, booking dose of lamotrigine, non-tonic clonic seizures in 3 months before pregnancy, tonic clonic seizures in 3 months before pregnancy, learning disability or mental health disorder, admitted to hospital for seizures during previous pregnancy

Key: Y: Yes, N: No, AAN: American Academy of Neurology (USA), ASM: anti-seizure medication, EEG: electroencephalogram, NICE: National Institute for Health and Care Excellence (UK), RCOG: Royal College of Obstetricians and Gynaecologists (UK), SEN: Spanish Society of Neurology (Spain), SUDEP: sudden unexpected death in epilepsy

factors for seizures.

Quality assessment

Guidelines and reviews were quality assessed for risk of bias (Fig. 2, Appendices 2A-D). The clinical guidelines included ranged from lower quality (AGREE II score 3), to the highest quality score (AGREE II score 7) (Fig. 2A). Key AGREE II domains that were often incompletely covered in guidelines were sufficient detail in rigor of development and in stakeholder involvement. Guidelines with the lowest scores were insufficient in all AGREE II domains. Of the three systematic reviews included, two were judged to have a high confidence in the results of the review [24 25], and one with critically low confidence in its results [22], using the AMSTAR 2 tool to assess risk of bias (Fig. 2B). Of the two prediction models, both were judged to have a low risk of bias [11,28,3]. The AED Withdrawal Risk Tool was judged to have an unclear risk of concerns regarding applicability [28]; the EMPiRE tool, low risk [11].

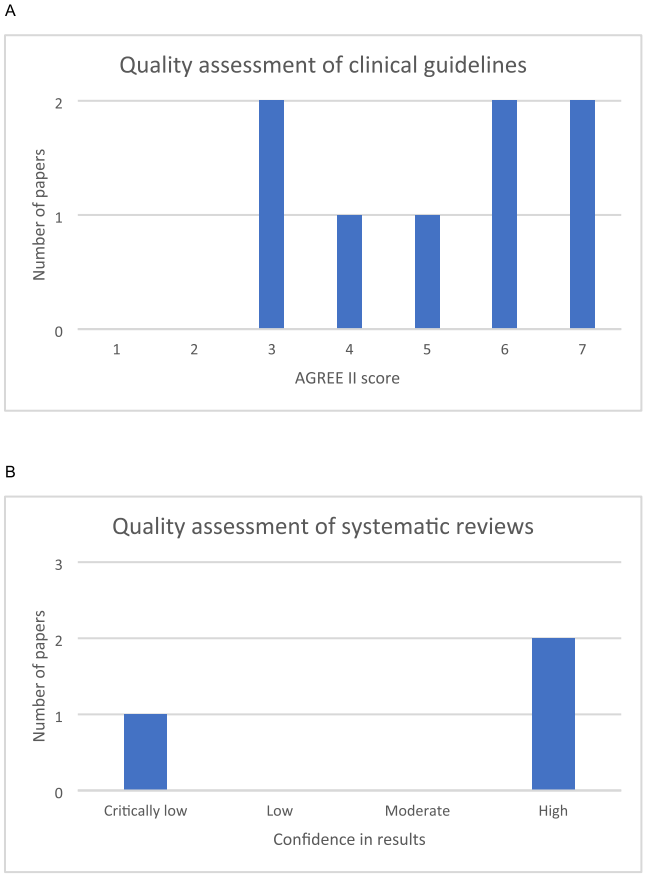

Fig. 2. Quality assessment of risk of bias. A – Quality assessment of clinical guidelines based on AGREE II score. B- Quality assessment of systematic reviews based on AMSTAR2 tool

Risk factors for seizures and outcomes

Twenty-six individual risk factors were identified across all papers (Table 2). Five factors were identified both in guidelines and reviews for pregnant women specifically and in the general adult population. These were: presence of a neurological disorder, learning disability or mental illness; focal seizures; seizure-freedom; polytherapy of anti-seizure medications (ASMs); and age of onset of epilepsy. Eight factors were identified only in guidelines for pregnant women. Of the 13 factors identified only in among the general population, eight were in both guidelines and systematic reviews, four were from guidelines only, and one was from a systematic review only

Table 2
Risk factors for seizure prediction. Risk factors identified in both guidelines and systematic reviews with asterisk* (eight factors), risk factors identified in guidelines only are unmarked (17 factors), and risk factor identified in systematic reviews only *italicised* (one factor).

Theme	Pregnant women only	Pregnant and general population	General population
Seizure type	Non-tonic-clonic Not specified	Focal*	Tonic-clonic* Provoked seizure *Myoclonic* Self-limiting syndrome (e.g. absence)
Seizure control	Hospital admission for seizures Tonic-clonic seizures in last 3 months Non-tonic-clonic seizures in last 3 months	Seizure-free >9-12months*	Recent recurrent seizures* Seizures with ASM* Nocturnal seizure
Anti-seizure medication	Lamotrigine dose Levetiracetam dose Non-compliance	Polytherapy*	Immediate ASM initiation after first seizure
Neurological		Neurological deficit, learning disability, or mental illness*	Abnormal brain imaging Abnormal electroencephalogram*
Medical and epilepsy history		Age of onset of epilepsy	Family history of epilepsy Epilepsy duration Female sex

Guidelines or reviews provided an estimated risk of seizure recurrence: either at all, or within a time frame, for example, in pregnancy, or in the next one to two years. Exact outcomes from each citation are listed in Appendices 3 and 4. Where guidelines or reviews included a reference as evidence for including a risk factor in their recommendations, these references were followed up and data extracted from the original study (Appendices 3 and 4). Numbers of studies for each risk factor were too small to undertake a meta-analysis.

Five of the guidelines or reviews did not give a numerical value of the association between the risk factor and seizure risk [20 21,23,27,29] (Appendices 3 and 4). Of the remaining eight guidelines or reviews, odds ratio, hazard ratio, relative risk, or likelihood of seizure were used as measures of association. Most of the identified risk factors increased the risk of seizure recurrence, with the relative risk or hazard ratio between 1.0 and 2.0 (Table 3).

Risk factors for seizures and outcomes in pregnant women

Nine risk factors identified in the pregnant women population were taken originally from the EMPiRE prediction model, which scored highly in quality assessment, with a low risk of bias and low concerns regarding applicability (Appendices 2A-D). [30] The four other factors identified in the pregnant women population were from guidelines of moderate to high quality. Two categories of risk factors were identified in more than one guideline or review for pregnant women: seizure-freedom was listed in four guidelines or reviews, and focal seizures was listed in two guidelines (Table 3).

Three risk factors were identified as having a larger association with seizure recurrence in pregnant women, all from the EMPiRE prediction model: tonic-clonic seizures in the three months preceding pregnancy (OR 7.20, 95% CI 6.63-11.93), a history of non-tonic-clonic seizures (OR 2.11, 95% CI 1.88—2.62), and seizures in the pre-pregnancy year compared to no seizures (OR 3.51, 95% CI 3.13-3.94) [11].

One risk factor was identified as having a decreased probability of seizure recurrence in pregnant women, from the EMPiRE prediction model: late onset of epilepsy (OR 0.98, 95% CI 0.97-0.99) [11].

Risk factors for seizures and outcomes in the general population

Seven risk factors associated with seizures in the general population were only identified in the AED Withdrawal Risk Tool prediction model, which scored moderately in quality assessment, with a low risk of bias and uncertain concerns regarding applicability [28]. One risk factor was identified both in the AED Withdrawal Risk Tool and a systematic review with a high risk of bias. The remaining ten factors were from systematic reviews and guidelines of high quality.

Six categories of risk factors were identified in more than one paper for the general population: immediate initiation of ASM after first seizure (five guidelines or reviews); abnormal electroencephalogram (four); neurological disorder, learning disability, or mental illness (two); provoked seizure (two); recent recurrent seizures (two); and ASM polytherapy (two).

Four risk factors were identified as having an even higher probability of seizure recurrence in the general population, all from the 2015 American Academic of Neurology guideline, which scored highly on quality assessment: seizures secondary to brain injury (RR 2.55, 95% CI 1.44-4.51); abnormal brain imaging (RR 2.44, 95% CI 1.09-5.44); abnormal electroencephalogram in one paper (RR 2.16, 95% CI 1.07-4.38); and nocturnal seizure (RR 2.10, 95% CI 1.00-4.30). [26]

Four risk factors were identified as having a decreased probability of seizure recurrence in the general population, from the 2015 American Academic of Neurology guideline and UpToDate guideline (both of which scored highly on quality assessment): self-limiting epilepsy syndrome (HR 0.57, 95% CI 0.39-0.68) [26]; childhood onset of epilepsy (before age ten years) (HR 0.75, 95% CI 0.60-0.92) [26]; immediate initiation of ASM after first seizure (absolute risk reduction 35%, 95% CI 23-46%) [28]; and longer seizure-free interval prior to stopping ASM (HR 0.94, 95% CI 0.91-0.98) [26].

Discussion

This review identified 26 individual risk factors for seizure prediction in the adult population or population of pregnant women with epilepsy, which were grouped into five broad themes: type of seizure or epilepsy, seizure control, ASM factors, neurological factors, and epilepsy or medical history. The review uncovers the role of medical history in determining likelihood of further seizures in the future. Demographic factors, like the current age of the patient or ethnicity, mostly did not feature as risk factors in the guidelines or reviews (except female sex, identified in one review). This suggests the possibility of risk factors for seizure recurrence being mainly modifiable with the appropriate treatment and management.

The strength of an umbrella review in risk factor identification is that it collates a list of factors that have already undergone screening and assessment and have been judged to be clinically or scientifically useful or relevant. This approach has not been previously applied to comprehensively assess seizure risk before. As a result, this review has brought together the practical recommendations from the research and deliberations of several leading international organisations in the care of people with epilepsy. This provides a broad oversight of the current advice regarding and understanding of seizure risk, and therefore a strong foundation from which to use the review to improve patient care or identify areas for future research. Several of the papers are of the highest quality in risk of bias assessment, adding weight to recommendations of risk factors. Also, limiting the search to guidelines produced after the year 2000 ensures the results are contemporary.

However, this comes with limitations. Many of the risk factors have only been cited in a single guideline or review, meaning meta-analysis cannot be undertaken. The guidelines included in this review have all originated from the global north, that is, Europe or North America. This means the generalisability of findings to other geographic regions or ethnicities is unknown. Little data exists regarding the role of ethnicity in adverse outcomes for pregnant women with epilepsy, and this gap in research must be addressed [31]. There is evidence that low socioeconomic impact is associated with increased seizure frequency in pregnancy, but this has not been identified in any of the systematic reviews or guidelines [32]. The clinical effectiveness of either the list of risk factors or the prediction models suggested is also untested.

In order to maximise our scope in an umbrella review and identify all possible risk factors that may be useful and applicable to pregnant women, we broadened our search to include risk factors identified in the general adult population. This review highlights the differences in approach in predicting seizure risk between the pregnant women and general population, one key difference being the use of brain imaging in the general population, which was not present in guidelines for pregnant women. Whether doing so would be both beneficial and acceptable to pregnant women and logistically possible, would be something to consider further in future research. It is known that there are sex differences in epilepsy between men and women, including differences in the epidemiology and type of epilepsy, and susceptibility to seizures [33–34]. Men are more likely to have seizures, but women are more likely to experience variation in seizure control. These sex differences are likely due to sexual dimorphism in brain structure, neural circuits, and steroid hormones [33]. Despite this understanding, how to implement its findings and further personalise epilepsy-care based on sex is yet to be determined [34]. The current literature regarding pregnancy and epilepsy broadly assesses incidence, anti-seizure medication use, serum levels, and effects on the fetus, seizure frequency, and maternal and fetal outcomes [35–37] However, few papers directly address risk factors regarding increased seizure frequency in pregnancy [35]. The only prediction tool for pregnant women with epilepsy to date, EMPiRE, identified risk factors based on a Delphi consensus of a multidisciplinary

Table 3
Evidence table of risk factors.

Risk factor	Pregnant women Y/N (no. of studies)	Author (year; sample size)	RR/OR/HR (95%CI)	Quality assess-ment	General population Y/N (no. of studies)	Author (year; sample size)	RR/OR/HR (95% CI)	Quality assess-ment
Neurological disorder, deficit or impairment, delayed development, learning disability, or mental illness	Y (1)	Allotey (2019; 527 women)	OR 1.96 (1.68 - 2.89)	high	Y (2)	Kim (2006; 1443 patients), Lamberink (2017; 1769 patients)	Kim: HR 1·35 (1·07–1·72), Lamberink: HR 1·31 (1·05–1·63)	Low, mod
Abnormal brain imaging	N				Y (1)	Hui (201; 132 patients)	HR 2.44 (1.09-5.44)	High
Abnormal electroencephalogram	N				Y (4)	Kim (2006; 1443 patients), Lamberink (2017; 1769 patients), MRC AED Group (1993, 1013 patients), Hauser (1990; 2008 patients)	Kim HR 1·54 (1·27–1·86), MRC RR 1.32 (1.01–1.73), Hauser RR 2.16 (1.07-4.38), Lamberink: HR 1·48 (1·23–1·77)	Low, mod, high
Seizure/epilepsy type - focal	Y (2)	Vajda (2018; 1939 pregnancies), Battino (2013; 3806 pregnancies)	Vadja RR 1.31 (1.18 - 1.45), Battino RR 1.54	Mod, high	Y (1)	Lamberink (2017; 1769 patients)	HR 1·75 (1·19–2.57)	Mod
Seizure/epilepsy type - tonic-clonic	N				Y (1)	MRC AED Group (1993, 1013 patients)	RR 1.56 (1.09–2.22)	High
Seizure/epilepsy type - non-tonic-clonic	Y (1)	Allotey (2019; 527 women)	OR 2.11 (1.88 - 2.62)	High	N			
Seizure/epilepsy type - not specified	Y (1)	Allotey (2019; 527 women)	OR 1.85 (1.64 - 4.30)	High	N			
Seizure/epilepsy type - myoclonic	N				Y (1)	MRC AED Group (1993, 1013 patients)	RR 1.84 (1.13–3.01)	High
Seizure/epilepsy type - self-limiting syndrome (eg absence, benign)	N				Y (1)	Lamberink (2017; 1769 patients)	HR 0·57 (0·43–0·77)	Mod
Provoked seizure	N				Y (2)	Lamberink (2017; 1769 patients), Hauser (1990; 2008 patients)	Hauser RR 2.55 (1.44-4.51), Lamberink HR 1·38 (1·11–1·70)	Mod, high
Seizure control - hospital admission for seizures	Y (1)	Allotey (2019; 527 women)	OR 1.19 (1.08 - 1.92)	High	N			
Seizure control - seizure-free >9 to 12 months	Y (4)	Vajda (2018; 1939 pregnancies), Gjerde (1998; 78 pregnancies); Tomson (1994; 93 pregnancies)	Vajda RR 3.51 (3.13 - 3.94). Likelihood seizure-free pregnancy: Vajda 74%, Tomson 84%, Gjerde 92%.	Mod, high	Y (1)	Lamberink (2017; 1769 patients)	HR 0·94 (0·91–0·98)*	Mod
Seizure control - recent recurrent seizures	N				Y (2)	MRC AED Group (1993, 1013 patients); Lamberink (2017; 1769 patients)	MRC RR 1·56 (1·42–1·72), Lamberink HR 1·35 (1·13–1·60)	Mod, high
Seizure control - tonic-clonic seizures in last 3 months	Y (1)	Allotey (2019; 527 women)	OR 7.20 (6.63 - 11.93)	High	N			
Seizure control - non-tonic-clonic seizures in last 3 months	Y (1)	Allotey (2019; 527 women)	OR 1.94 (1.71 - 2.38)	High	N			
Seizure control - seizures with ASM	N				Y (1)	MRC AED Group (1993, 1013 patients)	RR 1.56 (1.19–2.04)	High
ASM: non-compliance	Y (1)	Vajda (2018; 1939 pregnancies)	RR 1.21 (1.04 - 1.40)	Mod	N			
ASM: polytherapy	Y (1)	Vajda (2018; 1939 pregnancies)	RR 1.67 (1.51 - 1.85)	Mod	Y (2)	MRC AED Group (1993, 1013 patients); Lamberink (2017; 1769 patients)	MRC RR 1.83 (1.40–2.39), Lamberink HR 1·34 (1·09–1·64)	Mod, high
ASM: lamotrigine dose	Y (1)	Allotey (2019; 527 women)	OR 1.34 (1.00 - 1.44)	High	N			

(*continued on next page*)

Table 3 (*continued*)

Risk factor	Pregnant women Y/N (no. of studies)	Author (year; sample size)	RR/OR/HR (95%CI)	Quality assess-ment	General population Y/N (no. of studies)	Author (year; sample size)	RR/OR/HR (95% CI)	Quality assess-ment
ASM: levetiracetam dose	Y (1)	Allotey (2019; 527 women)	OR 1.02 (1.01-1.03)	High	N			
ASM: immediate initiation after first seizure	N				Y (5)	Leone (2006; 397 patients), Marson (2005; 812 patients), Das (2000; 76 patients), Chandra (1992, 228 patients), Gilad (1996; 87 patients)	Absolute risk reduction 35% (23-46%)	High
Age of onset of epilepsy (childhood)	Y (1)	Allotey (2019; 527 women)	OR 0.98 (0.97-0.99)	High	Y (1)	Lamberink (2017; 1769 patients)	HR 0·75 (0·60–0·92)*	Mod
Epilepsy duration	N				Y (1)	Lamberink (2017; 1769 patients)	HR 1·04 (1·03–1·05)*	Mod
Family history of epilepsy	N				Y (1)	Lamberink (2017; 1769 patients)	HR 1·22 (1.03–1·45)	Mod
Nocturnal seizure	N				Y (1)	Bora (1995; 147 patients)	OR 2.10 (1.00-4.30)	High
Female sex	N				Y (1)	Lamberink (2017; 1769 patients)	HR 1·48 (1·04–2.10)	Mod

Data extracted from primary studies. Full references in Appendix 1. Key: ASM: anti-seizure medication, HR: hazard ratio, OR: odds ratio, RR: relative risk, CI: confidence interval, MRC AED Group: Medical Research Council Anti-Epileptic Drug Withdrawal Study Group.
Quality assessment key: High = AGREE II 7, AMSTAR2 high, PROBAST low risk bias. Mod (moderate) = AGREE II 4/5, PROBAST uncertain concerns of applicability. Low= AMSTAR2 critically low. Data from Lamberink2017 are given as multivariate odds, except data with *, which are univariate odds.

team of experts drawing on existing evidence and expertise [30]. The systematic nature of this review provides a more comprehensive list of potential risk factors for seizures in pregnant women with epilepsy, that may then be used to improve prediction tools or used as a basis for further research into how significant these factors are in seizure susceptibility.

Including both recommendations from guidelines and results from systematic reviews in this study casts a wide net to collect all identified risk factors for seizure. All five risk factors captured in both the general adult and pregnant women population were also present in both guidelines and systematic reviews, further strengthening their validity for use in clinical situations. The remaining risk factors in pregnant women only were derived from guidelines, whereas most of the risk factors from the general population were derived from guidelines and reviews. This is indication of the data gaps and fewer systematic reviews published regarding pregnant women with epilepsy.

By collating the recommendations of several guidelines, the results of this review may aid clinicians in identifying those patients at highest risk of further seizure occurrence. A comprehensive clinical history, including in follow-up appointments, can identify patients with some of these risk factors so they can be considered for closer monitoring or specialist clinical support. They should also be counselled regarding their increased seizure risk and identify ways to mitigate this. This is especially the case in the pregnant women population, and antenatal screening may ensure pregnant women with epilepsy receive the timely specialist care they need. The need for improved preconception information and antenatal care for women with epilepsy is evidenced by previous systematic reviews [38–40]. However, as more than half of pregnancies in women with epilepsy in the UK are unplanned, specialist antenatal advice and care remains vital in improving maternal outcomes in this group of patients [41,42]. Seizure freedom has been shown here to be a key risk factor in predicting likelihood of seizures in both the general and pregnant population. This therefore flags patients with recurrent seizures to be especially vulnerable and requiring additional intervention, support, or counselling. The role of epilepsy in preventable maternal deaths in the UK provides urgency to identify ways of improving the care of women with this condition. It is hypothesised that a better understanding of the risk of seizures within this group of women will lead to improved antenatal care and therefore better outcomes for mother, baby, and their families. Multiple recent reports into safety of maternity services emphasise that antenatal care must be woman-centred and must be personalised [43,44]. Identifying the highest risk women of those who have epilepsy, through detection of the most significant risk factors and how it applies to them, can allow for specialised senior obstetric and neurologic input into their care, and thorough counselling regarding anti-seizure medications and pregnancy. This may take the form of earlier referral to a specialist antenatal clinic, to an epilepsy specialist midwife, or to a maternal medicine network for further advice and support with the antenatal management of the patient. This can ensure that women are supported in making more informed decisions regarding their epilepsy and their pregnancy. It may also allow maternity services to prioritise women with epilepsy at the highest risk, based on multiple risk factors for seizure, to ensure sufficient resources and support is provided in managing them safely and effectively.

Further research is needed to address the evidence gaps identified in this review, specifically seizure risk in ethnically diverse populations and the impact of socioeconomic status. Further research is also required to determine whether some of the seizure risk factors identified in guidelines for the general population, like nocturnal seizures, are also risk factors in the pregnant women population. Taking the EMPiRE prediction model as an example, the model remains under-utilised despite recommendations for its use. There is little data on the EMPiRE model's effectiveness in improving maternal and seizure outcomes [45]. Therefore, research is necessary to determine how to calculate seizure risk, explain this to patients, and if knowledge of seizure risk can have an impact in improving outcomes – both clinically, for the patient, as well as for the health service more broadly.

Conclusions

This umbrella review has identified 26 individual risk factors for seizure recurrence, across the pregnant women and general adult populations. Seizure type, timing, and control are key to determining the likelihood of seizures for patients. Understanding this personalised risk is key to improving counselling and care both for epilepsy patients

overall, and for pregnant women with epilepsy, who are particularly vulnerable to adverse outcomes secondary to their condition. This may direct clinicians to see women with epilepsy at the highest risk of seizures and adverse outcomes earlier, in more specialised clinics, or by a more specialised team of healthcare professionals.

Our understanding of seizure risk may be better improved by more studies from ethnically diverse populations, and those considering the impact of socioeconomic factors and sex differences. Further research is needed to determine the effectiveness of combinations of risks factors in determining seizure recurrence in pregnancy and the efficacy of personalised prediction of seizure risk on maternal and fetal outcomes.

Contribution to authorship

FJ planned and carried out the search, screening, and data extraction and analysis, and drafted the manuscript. BD contributed to abstract and full text screening, and data extraction. STariq contributed to abstract and full text screening. JZ contributed to study design. NM, MB, AWilson, JD, AWeckesser, JC, RB contributed to data interpretation. SThangaratinam and JA conceived of the study and directed its design. All authors reviewed and edited the manuscript.

Details of ethics approval

No ethics approval was required for this systematic review, in keeping with the National Research Ethics Service assessment.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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