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Review

Do premature and postterm birth increase the risk of epilepsy? An updated meta-analysis☆

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ABSTRACT

Background: Many studies have reported that premature birth is associated with a higher incidence of epilepsy, and postterm birth also increases the risk of epilepsy. The effects of different gestational ages (GAs) on epilepsy have become a research hotspot, but the findings of these studies remain controversial, and no systematic review has been performed until now.
Objective: The aim of this study was to evaluate the impact of different GAs on the incidence of epilepsy.
Data sources: The main databases, including PubMed, Medline, Embase, Cochrane Library, and Web of Science, were searched using the terms "preterm/premature/early/postterm/postmature/late/delayed delivery/birth", "gestational age", and "epilepsy/seizure" for eligible studies published up to April 1, 2019. The search was limited to English-language articles.
Study selection: Observational studies investigating the association between epilepsy and premature or postterm birth were included in this meta-analysis. We only selected studies that had clearly reported GA and the occurrence of epilepsy.
Data extraction and analysis: Two reviewers independently extracted the data. The quality of the included studies was examined in accordance with the Newcastle-Ottawa criteria, and the heterogeneity and publication bias were tested. We used sensitivity and subgroup analyses to determine the source of heterogeneity. A logistic randomized-effects model was used to assess the collected data when $I^2 \geq 50\%$.
Main outcomes: The primary outcome was the odds ratio (OR) of epilepsy.
Results: The research included eleven eligible studies with a total of 4,513,577 participants. Studies involving premature birth showed that the risk of epilepsy was 2.16 times higher in the premature birth group (<37 weeks) than in the full-term birth group (≥37 weeks) (OR [99% confidence interval [CI]] = 2.16 [1.80, 2.58]; $P < 0.001$). Those born before 32 weeks were associated with an increased occurrence of epilepsy when compared with those born at 32–36 weeks (OR [99% CI] = 2.73 [1.90, 3.94]; $P < 0.001$). However, the difference in the incidence of epilepsy between postterm children (41 weeks or more) and full-term children (37–40 weeks) was not statistically significant (OR [99% CI] = 1.05 [0.98, 1.12]; $P = 0.067$).
Conclusions: Preterm birth was closely associated with a higher risk of epilepsy throughout childhood that persisted into adulthood, and the association became stronger as GA decreased, while there was no significant difference in the risk of developing epilepsy between postterm and full-term offspring.

1. Introduction

Epilepsy is one of the most common chronic neurological diseases [1,2]. Nearly 120,000 people die because of epilepsy every year worldwide [3,4]. It has been listed as one of the five major neurological and psychiatric diseases by the World Health Organization and has become a research focus in the field of neuroscience. Gestational age (GA) plays a critical role in neurological diseases [5], preterm brain is particularly vulnerable to cerebral white matter injury [6], while postterm relates to increased severe asphyxia and cerebral damage [7]. Prematurity can increase the risk of cerebral palsy [8,9], intellectual disability [10], mental retardation [11], and adult epilepsy [12–14]. Hirvonen's cohort study involving 1,033,349 infants showed that 5611 (0.54%) children developed epilepsy over the 7-year follow-up period, and the incidence of epilepsy was 2.53% in the very preterm (<32 weeks), 1.08% in the moderately preterm (32–33 weeks), 0.75% in the late preterm (34–36 weeks), and 0.51% in the term group (≥37 weeks) [15]. Preterm birth was associated with an elevated incidence of epilepsy in the rest

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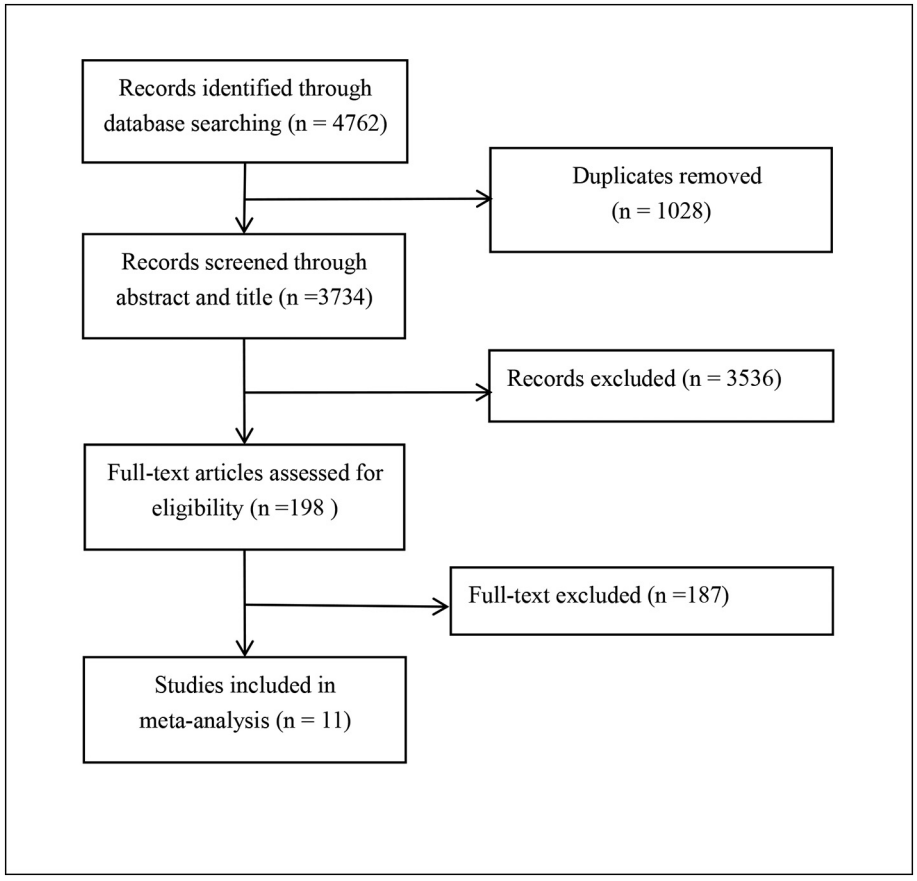


Fig. 1. Flowchart of literature search and study selection.

of life, while postterm birth predicted an increased risk of epilepsy in the first year of life [16]. The incidence of epilepsy increased with decreasing GA for children born before 37 weeks, but this phenomenon was not true for postterm birth. However, Sellier's study reported that the odds of epilepsy increased with GAs among patients with cerebral palsy [9]. Thus, no consensus has been reached regarding the relationship between GAs and epilepsy.

The aim of this study was to evaluate the impact of different GAs on the incidence of epilepsy. We searched all the existing literature about GAs and epilepsy and collected and analyzed the related data on the topic. By applying evidence-based methods to a large sample size, the pooled estimates may help to clarify the influence of different GAs on the incidence of epilepsy and illuminate the underlying epileptogenic mechanisms.

2. Method

Our study report conformed to the guidelines recommended for meta-analyses in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [17].

2.1. Search strategy

We searched PubMed, Medline, Embase, Cochrane Library, and Web of Science from inception to April 1, 2019. Combining both MeSH (Medical Subject Headings) and free text terms, we searched using the terms "preterm or premature or early or postterm or postmature or late or delayed or gestational age" and "delivery or birth or labour or labor" and "epilepsy or seizure" for eligible studies. The language was restricted to English. The search strategies were developed under the guide of an information expert. In addition, we searched references of relevant studies and review articles to avoid missing documents, and we contacted the author via email for necessary data.

2.2. Inclusion and exclusion criteria

We included observational studies, including both cohort studies and case–control studies, which compared the occurrence of epilepsy in different GAs. These studies explicitly reported the circumstances of birth, the specified diagnosis method of epilepsy, and the incidence of epilepsy. Duplicate publications and studies with insufficient analytical data did not meet our inclusion criteria. Studies that only concerned specific epileptic attacks, symptomatic epileptic attacks, seizures, or epileptic syndromes were excluded. Studies conducted in specific populations, such as cerebral palsy, neonatal convulsions, and congenital anomalies, were excluded, because those factors were recognized to increase the risk of epilepsy. As well, unrelated studies, letters, comments, reviews, meta-analyses, animal experiments, and cell experiments were excluded. When studies with overlapping cases were identified, we included the one with the larger number of participants.

2.3. Data extraction

Two reviewers independently selected the eligible studies by screening titles, abstracts, and full texts. They separately extracted the data by using standardized forms with detailed instructions. Disagreements were resolved through consensus or adjudication by a third reviewer. We collected data involving the basic information of the included studies (e.g., first author, publication year, country and ethnicity of the participants, data source, data collection methods, inclusion and exclusion criteria, definition of GAs, diagnosis and definition of

Table 1
Study characteristics.

Study ID	Country	Ethnicity	Source	Data obtain method	Study types	Inclusion/exclusion criteria	Gestational age	Diagnosis and definition of epilepsy
Odd 2018	UK	Caucasian	Sweden 1983–1993	Swedish Birth Register	Cohort	Exclude congenital abnormalities	NA; early term = 37–38, full-term = 39–40, postterm ≥ 41	H; ICD-8, ICD-9, ICD-10
Thygesen 2018	Denmark	Caucasian	Danish 1978–2009	Medical Birth Registry; Danish National Patient Registry	Cohort	All	BR; 32–36	H; ICD-8, ICD-10
Hirvonen 2017	Finland	Caucasian	Finland 1991–2008	Medical Birth Register; Hospital Discharge Register; Care Register for Health Care; The registers of Social Insurance Institution.	Cohort	All	PU + LMP; preterm < 37, term = 37–41, postterm ≥ 42	H; ICD-9, ICD-10
Bhalla 2012	Cambodia	Asian	Prey Veng	Questionnaire	Case–control	All	NA	H; ILAE 1981, ILAE 1993
Lekoubou 2012	Cameroon	African	Bafut	Questionnaire	Case–control	All	NA	H; ILAE 1993
Crump 2011	Sweden	Caucasian	Sweden 1973–1979	Swedish Birth Registry; Swedish Hospital Discharge Registry; The National Pharmacy Register; Prenatal and Birth Records in the Birth Registry	Cohort	Exclude significant congenital anomalies	LMP; preterm < 37, term = 37–42, postterm ≥ 43	L; ICD-10
Kannoth 2009	India	Asian	Kerala 2005–2007	Questionnaire	Case–control	All	NA; preterm < 37, term ≥ 37	H; ILAE 1989
Sun 2008	Denmark	Caucasian	Denmark 1979.1–2002.12	Danish Medical Birth Registry; The Danish Civil Registration System; Danish National Hospital Register	Cohort	Include singletons	LMP + PU; preterm < 37, term = 37–41, postterm ≥ 42	H; ICD-8, ICD-10
Ehrenstein 2007	Denmark	Caucasian	Three Danish counties 1980.1–2001.12	The Danish National Birth Registry; The Local Hospital Discharge Registries	Cohort	Include singletons	LMP + PU; term = 39–42, postterm ≥ 43	H; ICD-8, ICD-10, ILAE 1989
Whitehead 2006	Canada	Caucasian	Nova Scotia 1986.1–2001.12	The Nova Scotia Atlee Perinatal Database; The Canadian Epilepsy Database and Registry	Cohort	All	LMP; preterm < 37, term = 37–40, postterm ≥ 41	L; ILAE 1993
Sidenvall 2001	Sweden	Caucasian	Sweden 1985.11–1987.6	Doctor assessment and medical records	Case–control	Exclude neonatal seizures	LMP; preterm < 37, term = 37–42, postterm ≥ 43	H; ILAE 1981

Study ID	Age	Number of children				Number of epilepsy				Follow-up (year)	NOS score
		Total	Preterm	Term	Postterm	Total	Preterm	Term	Postterm		
Odd 2018	0–20	1,030,168	0	766,169	263,999	4594	0	3369	1225	20	7
Thygesen 2018	0–15	95,026	95,026	0	0	2326	2326	0	0	15	8
Hirvonen 2017	0–7	1,033,349	55,249	930,507	47,593	5611	575	4779	257	7	9
Bhalla 2012	3–70	288	51	237		96	27	69		–	7
Lekoubou 2012	15–74	170	20	150		85	12	73		–	7
Crump 2011	25–37	630,090	27,953	583,571	18,566	5327	403	4767	157	5	8
Kannoth 2009	6–85	724	127	597		362	93	269		–	7
Sun 2008	0–24	1,324,203	33,790	921,614	368,799	1233	68	833	332	24	9
Ehrenstein 2007	0–12	277,435	0	274,039	3396	2805	0	2754	51	NA	7
Whitehead 2006	0–15	121,957	7128	85,220	29,609	636	80	405	151	8.5	7
Sidenvall 2001	0–15	167	14	151	2	58	10	46	2	–	7

All, include all kinds of population; NA, not available; BR, birth record; PU, pregnancy ultrasound; LMP, last menstrual period; H, the diagnosis process is highly reliable (doctor's diagnoses of epilepsy during a hospital admission, emergency room visit, or outpatient visit; diagnoses of epilepsy based on reliable records); L, less reliable (diagnoses of epilepsy based on self-report of patients, antiepileptic drug prescription data, or electroencephalogram (EEG) data); ILAE, Commission on Classification and Terminology of the International League Against Epilepsy; ICD, International Classification of Diseases; NOS, the Newcastle-Ottawa Scale.

epilepsy, follow-up time, sample size of groups, age) and the outcomes (the occurrence of epilepsy in different groups).

2.4. Risk of bias assessment

The quality of the included cohort studies was assessed using the Newcastle-Ottawa scale (NOS) (Supplementary Table S2 shows the Newcastle-Ottawa criteria) [18]. The total scores on the NOS range from 0 to 9, with higher scores indicating better quality. The NOS evaluated the selection bias, information bias, confounding bias, and withdrawal bias. Studies with an NOS score of at least 8 were considered to be highly reliable, those with NOS scores ranging from 6 to 7 were moderate reliable, and those with NOS scores less than 6 were considered to be of low quality.

2.5. Data analyses and exploration of heterogeneity

We used pooled odds ratios (ORs) and 99% confidence intervals [CIs] to evaluate the rates of epilepsy among different GA groups. Pooled results were shown in forest plots by using Stata software (version 12.0, StataCorp LP: 800-STATA-PC). A logistic randomized-effects model was used to assess the collected data when $I^2 \geq 50\%$, and fixes-effects model was used when $I^2 < 50\%$. We also assessed publication bias and heterogeneity. Statistical heterogeneity was evaluated using I^2 tests with the χ^2 test to calculate P values, and we used sensitivity and subgroup analyses to determine the source of heterogeneity. The potential for publication bias was assessed by Begg's and Egger's tests, and the funnel plots were presented. We choose different cutoff values for GAs and made different comparisons to evaluate their specific effects on

Table 2
The pooled data on occurrence of epilepsy in the meta-analysis.

Variables	N[a]	Sample size[b]	Pooled data		Heterogeneity		Begg's test	Egger's test
Total	11	4,513,577	OR (99%CI)	P	I^2	Ph		
Preterm								
<37 weeks vs ≥37 weeks	8	3,110,948	2.16 [1.80, 2.58]	<0.001	60.0%	0.014	0.386	0.085
By ethnicity								
Caucasian	5	3,109,766	2.05 [1.73, 2.42]	<0.001	61.8%	0.033		
Asian	2	1012	3.13 [1.96, 4.96]	<0.001	<0.1%	0.606		
African	1	170	1.58 [0.45, 5.52]	0.344	–	–		
By study types								
Cohort study	4	3,109,599	2.01 [1.73, 2.34]	<0.001	60.0%	0.058		
Case–control study	4	1349	3.01 [1.95, 4.66]	<0.001	4.7%	0.369		
By inclusion/exclusion criteria								
Exclude some specific population	3	1,954,460	2.07 [1.42, 3.02]	<0.001	67.9%	0.044		
All kinds of population	5	1,156,488	2.29 [1.80, 2.91]	<0.001	42.5%	0.138		
By diagnosis methods of epilepsy								
Highly reliable	6	2,358,901	2.34 [1.80, 3.05]	<0.001	44.9%	0.106		
Less reliable	2	752,047	1.99 [1.41, 2.82]	<0.001	77.1%	0.037		
By sample size								
≥10,000	4	3,109,599	2.01 [1.73, 2.34]	<0.001	60.0%	0.058		
<10,000	4	1349	3.01 [1.95, 4.66]	<0.001	4.7%	0.369		
By follow-up								
≥5 years	4	3,109,599	2.01 [1.73, 2.34]	<0.001	60.0%	0.058		
<5 years or NA	4	1349	3.01 [1.95, 4.66]	<0.001	4.7%	0.369		
By NOS score								
<8	5	123,306	2.63 [1.91, 3.62]	<0.001	62.2%	0.071		
≥8	3	2,987,642	1.96 [1.67, 2.28]	<0.001	18.0%	0.300		
By different cutoff								
Preterm (<37 weeks) vs term (37–40/41/42 weeks)	5	3,109,766	2.20 [1.73, 2.80]	<0.001	82.8%	<0.001		
<37 weeks vs 37–40 weeks	1	121,957	2.38 [1.73, 3.26]	<0.001	–	–		
<37 weeks vs 37–41 weeks	2	2,357,552	2.36 [2.15, 2.59]	<0.001	<0.1%	0.645		
<37 weeks vs 37–42 weeks	2	630,257	2.71 [0.64, 11.48]	0.076	71.8%	0.060		
<32 weeks vs 32–36 weeks	3	2,987,642	2.73 [1.90, 3.94]	<0.001	62.4%	0.070		
<34 weeks vs 34–36 weeks	3	1,250,332	1.93 [1.04, 3.59]	0.006	94.8%	<0.001		
<35 weeks vs 35–36 weeks	2	725,116	1.47 [1.04, 2.10]	0.005	84.0%	0.012		
Postterm								
Postterm (=;≥41/42/43 weeks) vs term (37–40/41/42 weeks)	6	4,139,934	1.05 [0.98, 1.12]	0.067	<0.1%	0.688	0.707	0.244
By study types								
Cohort study	5	4,139,767	1.05 [0.98, 1.11]	0.073	<0.1%	0.947		
Case–control study	1	167	11.34 [0.20, 629.44]	0.119	–	–		
By inclusion/exclusion criteria								
Exclude some specific population	4	2,984,628	1.04 [0.97, 1.12]	0.131	<0.1%	0.394		
All kinds of population	2	1,155,306	1.06 [0.92, 1.21]	0.286	<0.1%	0.859		
By diagnosis methods of epilepsy								
Highly reliable	4	3,387,887	1.05 [0.96, 1.12]	0.100	<0.1%	0.394		
Less reliable	2	752,047	1.05 [0.90, 1.23]	0.419	<0.1%	0.774		
By sample size								
=; ≥10,000	5	4,139,767	1.05 [0.98, 1.11]	0.073	<0.1%	0.947		
<10,000	1	167	11.34 [0.20, 629.44]	0.119	–	–		
By follow-up								
=; ≥5 years	5	4,139,767	1.05 [0.98, 1.11]	0.073	<0.1%	0.947		
<5 years or NA	1	167	11.34 [0.20, 629.44]	0.119	–	–		
By NOS score								
<8	3	1,152,292	1.06 [0.98, 1.15]	0.069	14.6%	0.310		
=; ≥8	3	2,987,642	1.03 [0.93, 1.14]	0.515	<0.1%	0.831		
By different cutoff								
Postterm (=;≥41 weeks) vs late term (39–40 weeks)	2	2,354,371	1.11 [1.03, 1.21]	0.001	34.3%	0.217		
=; ≥43 weeks vs 37–42 weeks	3	907,692	1.27 [0.76, 2.15]	0.233	72.7%	0.026		
=; ≥42 weeks vs 37–41 weeks	2	2,357,552	1.02 [0.91, 1.15]	0.621	<0.1%	0.551		
=; ≥41 weeks vs 37–40 weeks	2	1,152,125	1.06 [0.98, 1.15]	0.077	<0.1%	0.868		

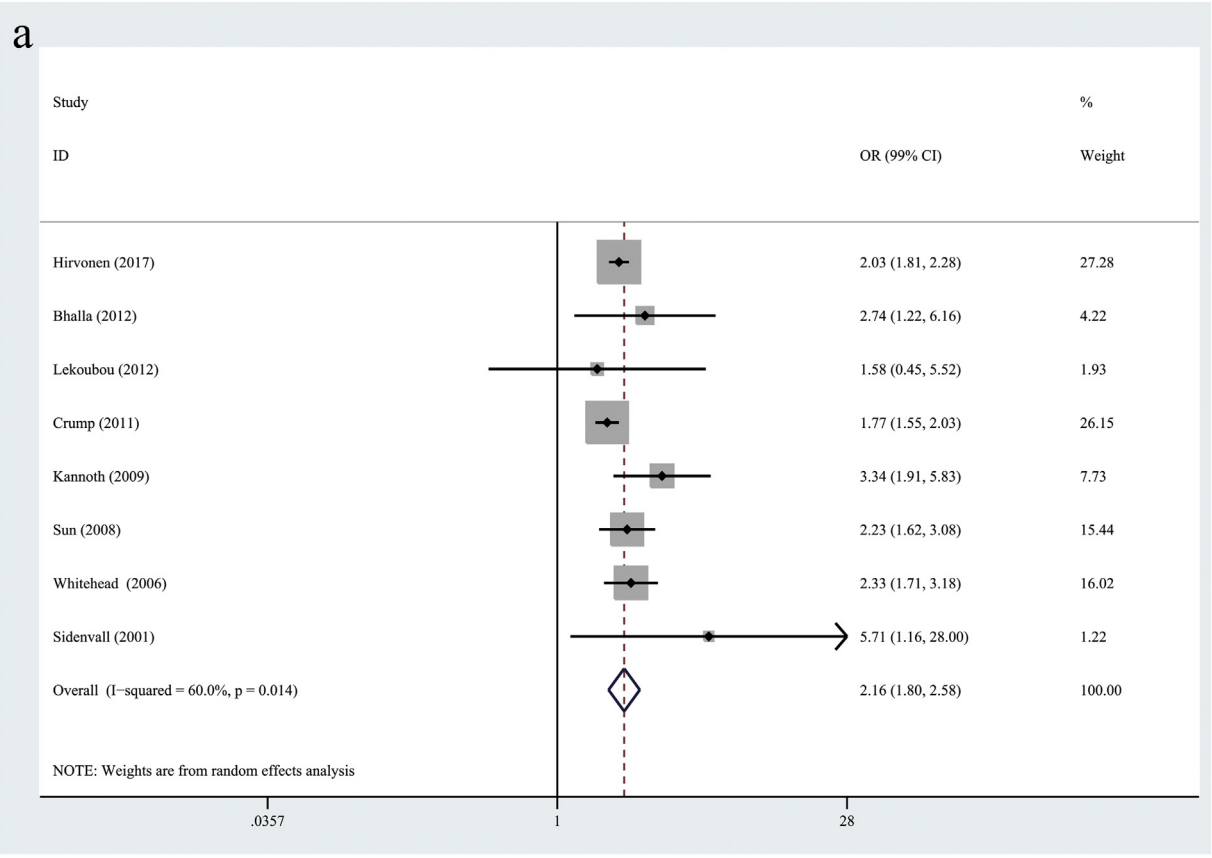
OR: odds ratio; 99% CI: confidence interval; P: P value of pooled OR; I^2: value of Higgins I-squared statistics.
[a] Numbers of studies included in the meta-analysis.
[b] Number of participants in the included studies.

epilepsy. All statistical tests were two-sided, and the 1% level (P value <0.01) was considered to be statistically significant.

3. Results

3.1. Literature search and study selection

We initially retrieved 4762 potentially relevant reports from the databases and removed a total of 1028 duplicate publications. Through a selection process involving screening of abstract and titles (n = 3734), we selected 198 publications. On full-text screening, we excluded the following 5 studies: Demesi-Drljan et al., Pong et al., and Ronen et al. did not report the specific definition and diagnosis method of epilepsy [19–21]; Petrini et al. and Wu Wen et al. focused on seizures instead of epilepsy [22,23]. Sellier et al. and Jauhari et al. evaluated the effect of GAs on the risk of epilepsy in neonate with cerebral palsy [8,9]; Pisani et al. investigated the effect in patents with neonatal seizure [14]; and our study did not use those data for analyses to avoid increasing heterogeneity. Animal experiments (n = 6), reviews (n = 3), and studies with smaller overlapping populations (n = 1), publications without



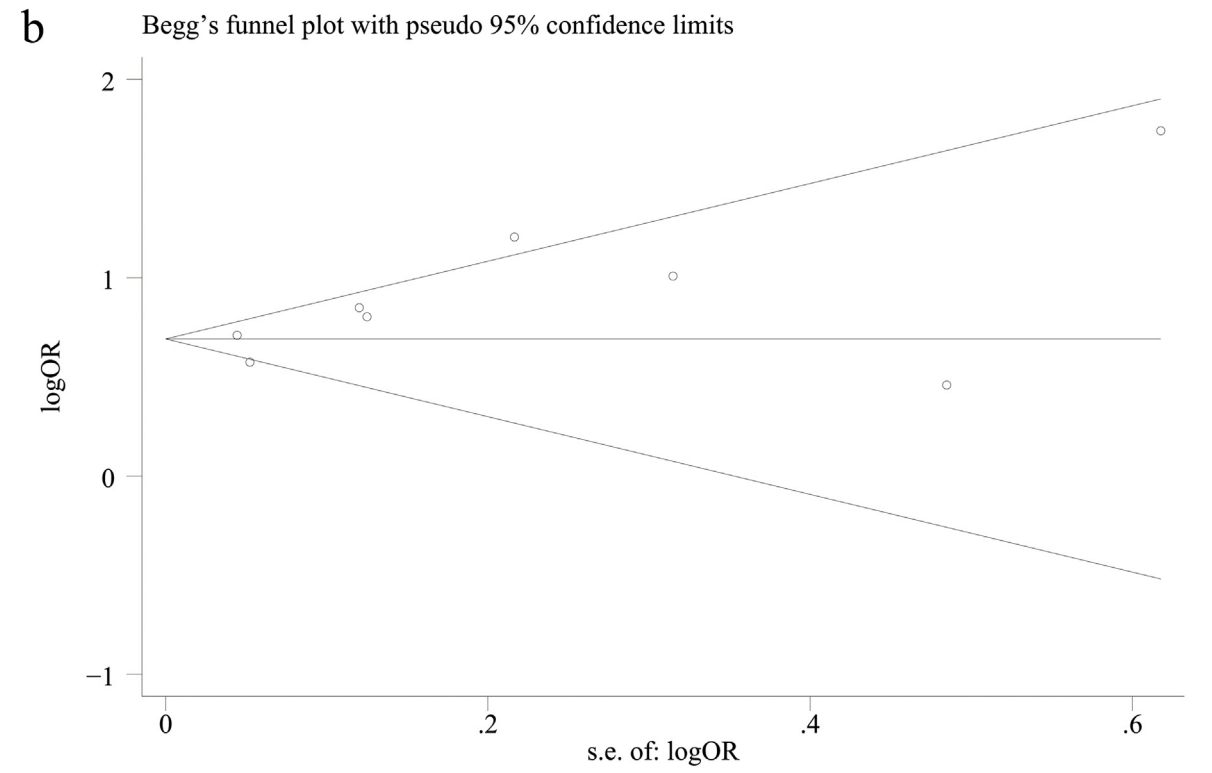


Fig. 2. The odds ratio of individuals born before 37 weeks vs those born after 37 weeks (a), and the Begg's funnel plot for accessing publication biases (b).

sufficient data to estimate outcomes (n = 7), and irrelevant publications (n = 173) were excluded (Fig. 1). Thus, eleven studies, involving 4,513,577 patients, reported the occurrence of epilepsy in different GA groups [12,15,16,24–31]. Among them, four studies assessed preterm birth; five studies assessed both preterm and postterm births; and two study evaluated postterm births only.

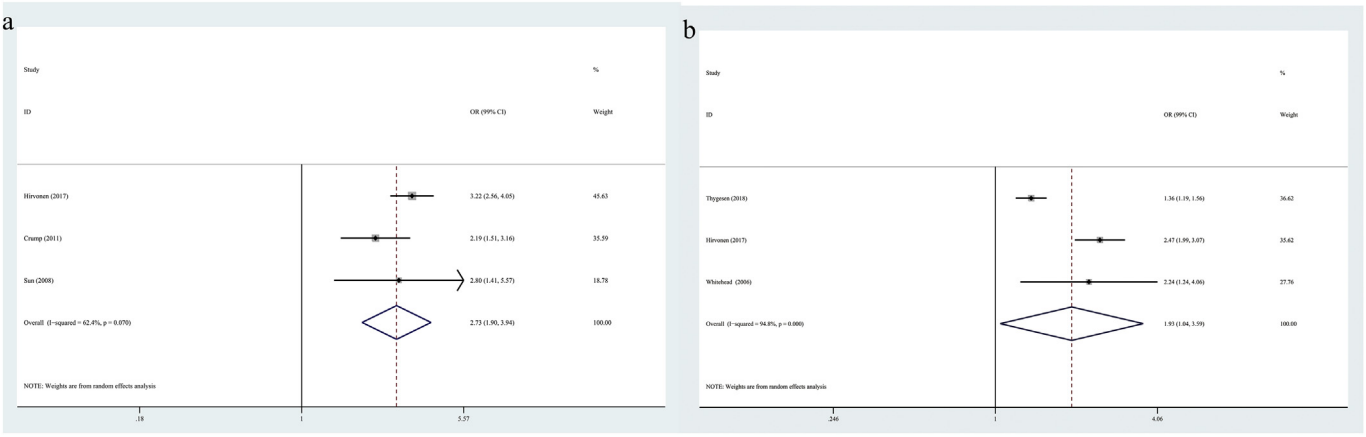


Fig. 3. The odds ratio of individuals born before 31 weeks vs those born at 32–36 weeks (a), and the risk ratio of individuals born before 33 weeks vs those born at 34–36 weeks (b).

3.2. Study characteristics

The main features of the eleven selected studies are shown in Table 1. Eight studies were performed in Caucasian populations (three from Denmark, others from Finland, UK, Sweden, Canada, and America), two in Asia (Cambodia and India), and one in Africa (Cameroon). Nine studies (n = 3,205,974) investigated preterm birth and epilepsy, while seven studies (n = 4,417,369) reported the effects of postterm birth on the risk of epilepsy. The extracted data in detail are presented in Supplementary Table S1, while detailed NOS scores of each included study are presented in Supplementary Table S3.

3.3. Premature birth increases the risk of epilepsy

Eight studies containing 3,110,948 participants compared the occurrence of epilepsy between offspring born before 37 weeks and those born 37 weeks and above, which showed heterogeneity across the studies ($I^2 = 60.00\%$). The results showed that the risk of epilepsy was 2.16 times higher in the premature birth group (<37 weeks) than in the full/postterm birth group (≥37 weeks) (OR [99% CI] = 2.16 [1.80, 2.58]; P < 0.001) (Table 2; Fig. 2a). There was no significant publication bias among the included studies (Fig. 2b). Subgroup analysis showed that preterm birth increased the risk of epilepsy in each subgroup except African. There was no heterogeneity in the subgroup including five studies with all kinds of population (OR [99% CI] = 2.29 [1.80, 2.91]; P < 0.001; $I^2 = 42.5\%$; Ph = 0.138) and the subgroup including six studies with highly reliable diagnosis method of epilepsy (OR [99% CI] = 2.34 [1.80, 3.05]; P < 0.001; $I^2 = 44.9\%$; Ph = 0.106). We further noted that increasing GA was associated with a decreasing risk of epilepsy among people born before 37 weeks. Patients born before 32 weeks were more likely to have epilepsy than those born in 32–36 weeks (OR [99% CI] = 2.73 [1.90, 3.94]; P < 0.001) (Table 2; Fig. 3a). The risk of epilepsy was significantly higher in infants born before 34 weeks than in those born at 34 to 36 weeks (OR [99% CI] = 1.93 [1.04, 3.59]; P = 0.006) (Table 2; Fig. 3b).

3.4. Postterm birth has little effect on the risk of epilepsy

In addition, we examined the association between postterm birth and the risk of epilepsy. We found that the difference in the incidence of epilepsy between postterm offspring (41 weeks or more) and full-term offspring (37–40 weeks) was not statistically significant (OR [99% CI] = 1.05 [0.98, 1.12]; P = 0.067; $I^2 < 0.1\%$; Ph = 0.688) (Table 2; Fig. 4a). There was no significant publication bias among the included postterm studies (Fig. 4b). There was an increased risk of epilepsy for postterm (41 weeks or more) (OR [99% CI] = 1.11 [1.03, 1.21]; P = 0.001; $I^2 = 34.3\%$; Ph = 0.217) when compared to late term (39–40 weeks) (Table 2; Fig. 5a). The OR for epilepsy was 1.27 (99% CI, [0.76, 2.15]; P = 0.233; $I^2 = 72.7\%$; Ph = 0.026) for birth later than 43 weeks versus birth at 37–42 weeks (Table 2; Fig. 5b). The OR for epilepsy was 1.02 (99% CI, [0.91, 1.15]; P = 0.621; $I^2 < 0.1\%$; Ph = 0.551) for birth later than 42 weeks versus birth at 37–41 weeks (Table 2; Fig. 5c). The OR for epilepsy was 1.06 (99% CI, [0.98, 1.15]; P = 0.006; $I^2 < 0.1\%$; Ph = 0.868) for birth later than 41 weeks versus birth at 37–40 weeks (Table 2; Fig. 5d).

3.5. Sensitivity analysis and publication bias

To identify the source of heterogeneity across the selected studies, sensitivity analysis was conducted by removing each study in turn from the analysis. The pooled ORs did not significantly change, indicating the stability of our analyses. The funnel plots were largely symmetrical for OR in prematurely born patients, and the result of Begg's test was P = 0.386, which indicated that there was no apparent publication bias in our study (Table 2; Fig. 2b).

4. Discussion

Although GA has been reported to be associated with epilepsy, the findings were controversial, and no meta-analysis on this association has been reported. This meta-analysis included eleven individual studies of 4,513,577 patients with various follow-up periods. The results showed that preterm birth was strongly associated with an increased risk of epilepsy throughout childhood and persisting into adulthood, and the association became stronger as GA decreased. Dassi's meta-analysis including case–control study showed that preterm birth increases the risk of epilepsy, and the results of that study were in line with ours [32].

Hirvonen's study (n = 1,033,349) involved follow-up assessments until 7 years of age and Crump's study (n = 630,090) only included those aged 25–37 years. However, in both of these studies, the risk of epilepsy in preterm births was approximately twice as high as that in term births [15,27]. The longer the follow-up period, the greater is the likelihood of identifying cases of epilepsy. Because of their limited follow-up periods, both studies may have missed potential cases and thus underreported the outcome of interest and underestimated the results. It was thus reassuring that despite this, the results still showed an increased risk. The underlying mechanisms of the elevated epilepsy risk in preterm offspring are as follows: Premature birth increases the risk directly because of impaired brain development [33]. The third trimester of fetal life is a critical period for the increase in cortical gray matter and the medulla. Diffuse white and gray matter abnormalities have been found in premature infants, and these anomalies continued to

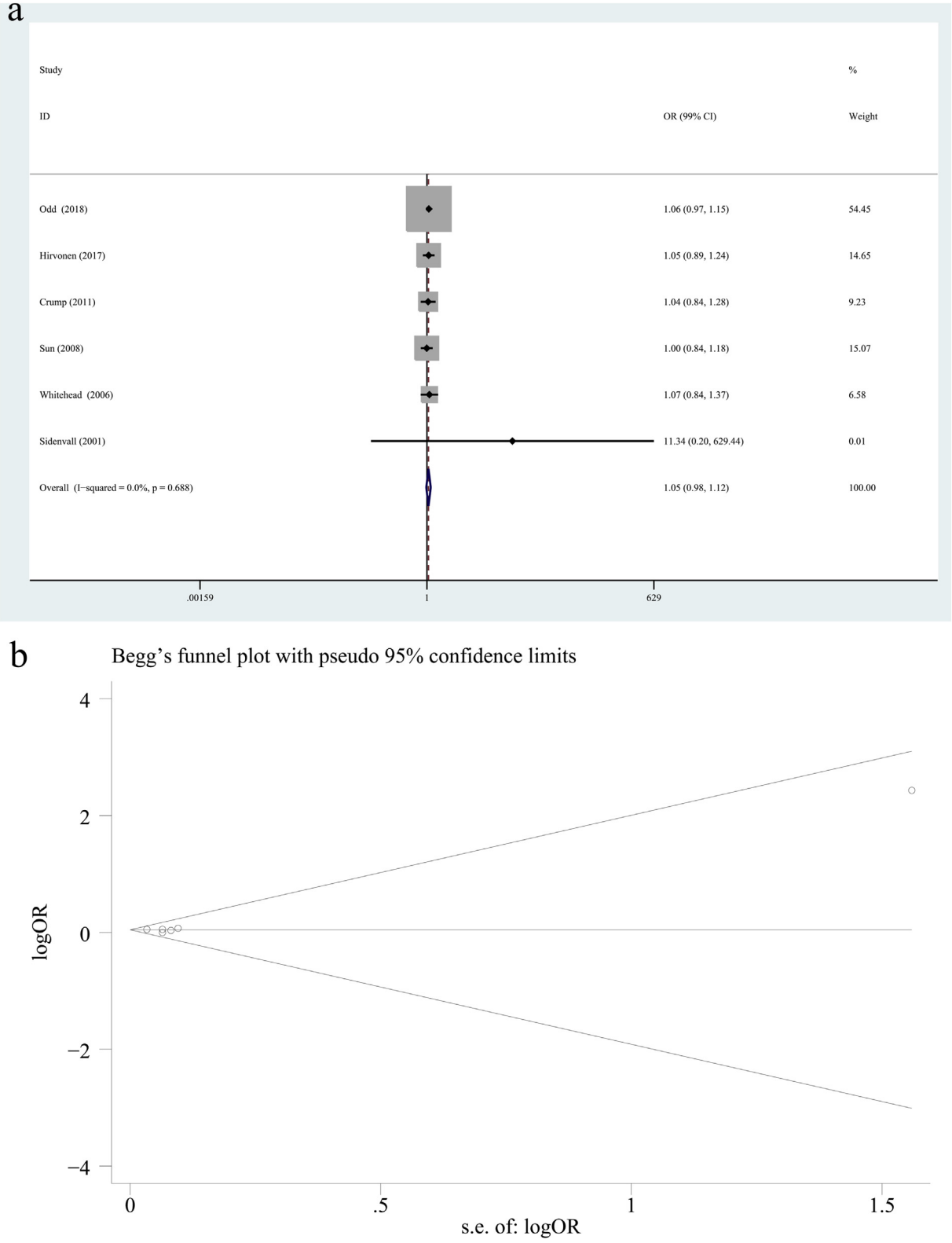


Fig. 4. The odds ratio of late/postterm births vs term birth (a), and the Begg's funnel plot (b).

exist when they reach the same full-term age after birth, which has been associated with the occurrence of epilepsy [34,35]. Preterm birth can lead to cerebral white matter gliosis, hippocampal sclerosis, and subarachnoid hemorrhage, which are common pathological manifestations of the brain in patients with epilepsy. On the other hand, preterm offspring are also susceptible to epilepsy because of hypoxic ischemic brain damage, which starts the epileptogenic process and creates epileptic neuronal circuits [27]. Intrauterine infection and preeclampsia are reported to be related to both hypoxic–ischemic fetal brain injury and preterm birth [35]. Considering the adverse effects of preterm birth on the nervous system and the increasing number of premature infants, multidisciplinary management of pregnant women must be

carried out to reduce preterm birth and thus reduce the burden of epilepsy. Clinicians need to learn more about the prevention and treatment of epilepsy in preterm offspring.

However, the findings were different in the postterm group. The study results showed no increased risk associated with postterm birth when compared to term birth, and this phenomenon existed in all subgroups (including 37–40 weeks vs ≥41 weeks, 37–41 weeks vs ≥42 weeks, 37–42 weeks vs ≥43 weeks, and so on) except one (≥41 weeks vs 39–40 weeks). We found an elevated risk of developing epilepsy in offspring born 41 weeks and above, when compared to those born at 39–40 weeks gestation, this result should be treated with caution considering the modest OR (OR = 1.3) with the lower end of the CI at 1.03. One of the possibilities for explaining this result is that the finding might be a false positive and postterm gestation overall does not increase epilepsy risk. In this case, there is no difference in the risk of epilepsy between postterm and full-term offspring, and the incidence of epilepsy does not change with GAs after 37 weeks. But, here is another interpretation for the finding. The positive result of postterm (≥41 weeks) vs late term (39–40 weeks) subgroup analysis is reliable and statistically significant, not caused by type 1 errors. Odd's study results are consistent with ours, which showed a higher risk of epilepsy for postterm infants with 41 weeks or more GAs [24]. Sun's study (n = 1,324,203) only had follow-up assessments until 5 years of age [29]. It also showed an increased incidence rate ratio (IRR) in the 42+ week group compared to the 39–41 week group (IRR [95% CI] = 1.04 [0.91–1.08]). The modest OR with the lower end of the CI at 1.03 can be explained in two ways: First, the limited follow-up duration may have resulted in underestimation of the total number of cases. Second, on comparing the findings for 39–41 weeks versus those for ≥42 weeks, the trend showed a protective effect for the former. Ehrenstein concluded that prolonged gestation is a risk factor for early epilepsy (epilepsy occurs in the first year of life) and the increased risk for instrument-assisted and cesarean deliveries could be attributable to factors that are related to both birth complications and epilepsy [16]. Predictors of postterm delivery include anencephaly, hormonal disturbances, nullipara, young maternal age, and history of prolonged pregnancy [36]. Therefore, clinicians and medical caregivers should provide thorough consideration and carefully decide whether to induce childbirth and the appropriate time to induce delivery. It would be prudent to conduct multidisciplinary consultations and offer enhanced surveillance on enhanced monitoring to these pregnant women in order to minimize any potential impact. Since the postterm finding results should be treated with caution, more standardized and high quality studies are needed to explore the risk of epilepsy in postterm offspring.

There were many limitations in our systematic review. First, the inclusion and exclusion criteria of the included studies varied greatly. Some of the involved studies excluded newborns with other diseases affecting the risk of epilepsy, such as cerebral palsy, severe brain injury, and brain infections. This selection bias might result in the heterogeneity, and we performed subgroup analysis to address this issue. Secondly, this meta-analysis assessed the independent influence of GA towards epilepsy, and a variety of factors, such as low birth weight associated with preterm birth, may be confounding factors resulting in confounding bias. Besides, given the sample size, small effects are more likely to be "statistically significant at the P = 0.05 level." The chance of a type I error is increased in meta-analyses because results are repeatedly updated over time [37,38]. In such situations, a larger CI is often applied to minimize the chances of a type 1 error. In this study, P < 0.01 was considered statistically significant, considering the large sample size, and our study had a high probability of containing type 1 errors. Third, the lack of registration of the systematic review was a major limitation of this study, which should be done before the start of the study to help

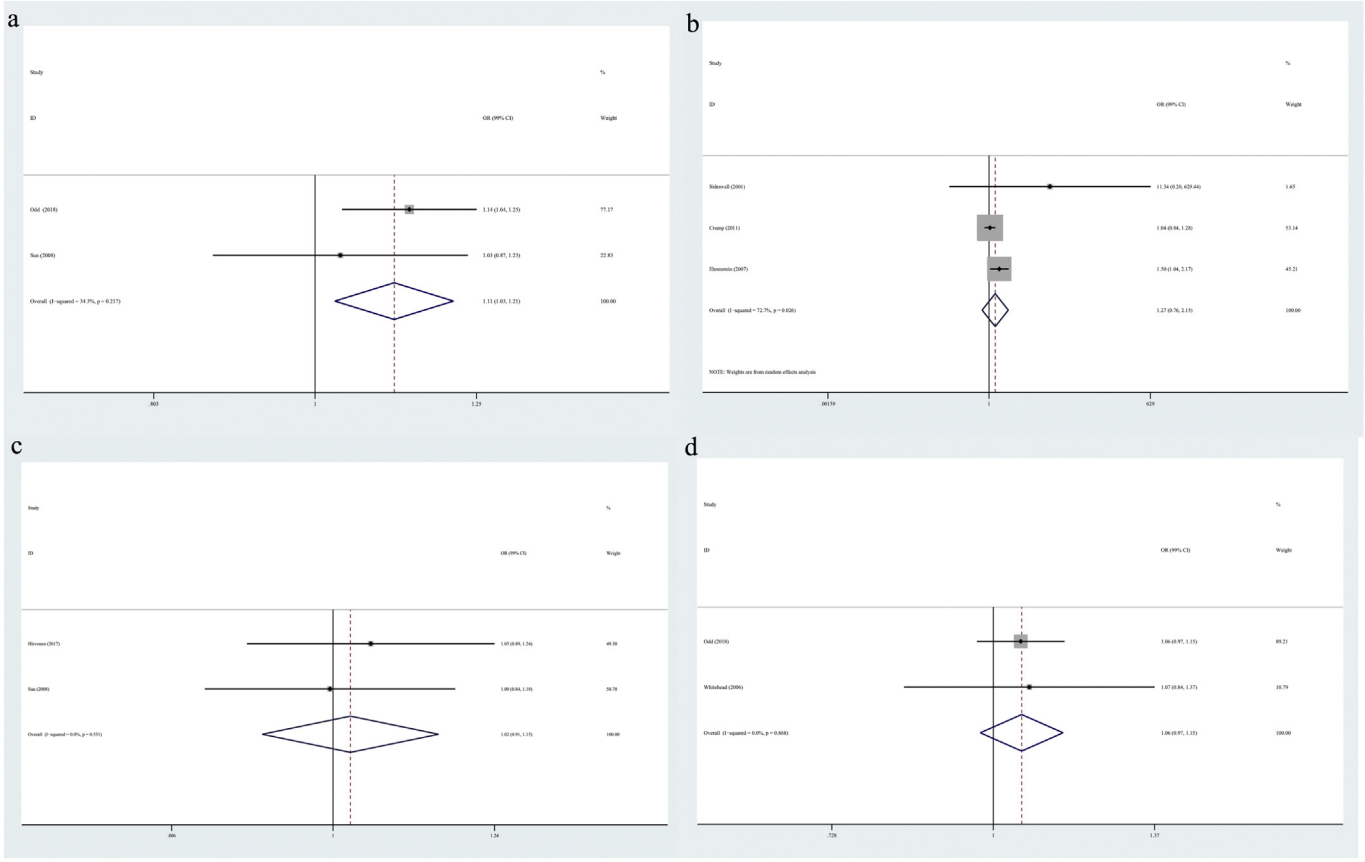


Fig. 5. The odds ratio of postterm births vs late term birth (a), the odds ratio of individuals born after 43 weeks vs those born at 37–42 weeks (b), the odds ratio of individuals born after 42 weeks vs those born at 37–41 weeks (c), and the odds ratio of individuals born after 41 weeks vs those born at 39–40 weeks (d).

avoid duplication and reduce opportunity for reporting bias. Finally, the modest number of included studies was another limitation. The strength of this study was the large sample size. We included all current eligible relative studies with very large sample sizes; therefore, this meta-analysis has strong persuasiveness in terms of the large sample.

In conclusion, preterm birth increases the risk of epilepsy, and the effect is more obvious as GA decreases, while postterm birth has little effect on developing epilepsy.

Abbreviations

GA	gestational age
OR	odds ratio
99% CI	99% confidence interval
NOS	the Newcastle-Ottawa Scale
IRR	incidence rate ratio

Authors' contributions

Lei Chen and Wanling Li conceived the study idea and designed the study. Anjiao Peng, Shuyue Deng, Wanlin Lai, and Xiangmiao Qiu reviewed the literature and collected the data. Lin Zhang and Shuyue Deng performed statistical analyses. Wanling Li drafted the manuscript. Lei Chen reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Declaration of competing interest

The authors have declared no conflict of financial interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.05.016.

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