# RESEARCH



# Impact of prenatal, neonatal, and postnatal factors on epilepsy risk in children and adolescents: a systematic review and meta-analysis

Imen Ketata<sup>1,2\*</sup>, Emna Ellouz<sup>1,2</sup> and Rahil Mizouri<sup>1,3</sup>

# Abstract

**Background** Epilepsy is a common, long-term neurological condition. Several previous case-control, cohort and cross-sectional studies have highlighted the role of prenatal, delivery and postnatal factors in the onset of epilepsy. In this systematic review, we evaluate the impact of these factors on the development of epilepsy in children and adolescents.

**Methods** We searched PubMed and Google Scholar for literature on the relationship between prenatal, delivery and postnatal factors and the occurrence of epilepsy. The research was performed according to the PRSIMA 2020 flowchart and checklist. Data were extracted and pooled according to the ReviewManager 5.3 software using a random-effects model. Sensitivity analysis and subgroup analysis were used to evaluate the source of heterogeneity.

**Results** We identified 25 reports, including 45,044 cases with confirmed epilepsy and 2,558,210 controls. Premature birth is significantly associated with the risk of epilepsy (pooled OR = 4.36 [95% CI: 1.26–15.09], P = 0.02). Smoking during pregnancy significantly increases this risk by 28% (pooled OR = 1.28 [95% CI:1.1–1.49], P = 0.002). Furthermore, maternal epilepsy confers a pooled OR of 2.06 [95% CI:1.26–3.36]. Eclampsia is linked to a 16.9-fold increased risk of epilepsy. In addition, both pregnancy metrorrhagia and maternal infection are significantly associated with the epilepsy risk (pooled OR = 2.24 [95% CI: 1.36–3.71] and 1.28 [95% CI: 1.17–1.41], respectively). For delivery conditions, cord prolapse (pooled OR = 2.58 [95% CI: 1.25–5.32]), prolonged labor (> 6 h) (OR = 6.74 [95% CI: 3.57–12.71]) and head trauma (pooled OR = 2.31 [95% CI: 1.54–3.48]) represent a meaningful risk of epilepsy occurrence. Moreover, birth complications (OR = 3.91 [95% CI: 2.43–6.29]), low birth weight (pooled OR = 1.83 [95% CI: 1.5–2.23]) and male birth (pooled OR = 1.18 [95% CI: 1.06–1.32]) are associated with an elevated risk of epilepsy in childhood and adolescence.

**Conclusions** Epilepsy in children and adolescents can be attributed to a multitude of intricate factors, notably those during pregnancy, delivery and the postnatal period. These findings highlight the crucial role of prenatal and postnatal care in reducing the impact of these factors on epilepsy occurrence.

Keywords Prenatal factors, Delivery factors, Postnatal factors, Epilepsy, Children, Adolescents

imen.ketata.fmss@gmail.com

<sup>1</sup> Neurology Department, University Hospital of Gabes, Gabes 6014,

Tunisia

<sup>2</sup> Sfax University, Sfax 3029, Tunisia

<sup>&</sup>lt;sup>3</sup> Monastir University, Monastir 5000, Tunisia



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

<sup>\*</sup>Correspondence:

Imen Ketata

# Background

Epilepsy is a common chronic neurological disorder marked by a pathological tendency toward recurring and unprovoked seizures [1]. Epilepsy poses a burden for parents, children, and medical doctors. The annual incidence of epilepsy is 61.4 per 100,000 persons [2]. Notably, the incidence of epilepsy is highest in the first year of life, with a rate of ~150 cases/100,000 persons per year [3]. Additionally, the occurrence of repeated and unprovoked seizures in childhood reaches 0.8% by the age of 15 [3]. For those aged under 20, epilepsy can affect 1% of the population [4]. The etiology of epilepsy can be divided into three types: cryptogenic, symptomatic, and idiopathic [1]. Meanwhile, the underlying risk factors for epilepsy in childhood and adolescence vary from those associated with epilepsy in adults [1]. A risk factor for epilepsy is defined as a situation that increases the occurrence of epilepsy [5]. Although certain risk factors are well documented, such as infection in the central nervous system and metabolic disorders, others remain poorly understood, notably those associated with pregnancy characteristics [5]. In fact, 20% of epilepsy cases have no identifiable causes [6]. While extensive research has been conducted to understand the etiology and management of epilepsy, there is a growing interest in investigating the roles of prenatal factors, delivery conditions, and postnatal factors in the development and progression of epilepsy. Understanding the risk factors can help prevent epilepsy onset, decrease epilepsy prevalence in children and adolescents as well as its associated comorbidities, and aid healthcare professionals in identifying high-risk populations and making plausible preventive strategies. Hence, the impacts of prenatal factors, delivery condition and postnatal factors on epilepsy are still a subject of debate, with different studies yielding conflicting results. In this systematic review, we aim to establish the relationships of prenatal characteristics, newborn delivery situations and postnatal conditions with the risk of epilepsy.

# Methods

### Study design

This systematic review and meta-analysis was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 [7]. It has not been recorded or registered in any registry site. The checklist is provided as a supplementary material.

# Literature search

We searched for literatures on the relationship between perinatal/postnatal characteristics and the risk of epilepsy development in children and adolescents in Pub-Med and Google Scholar using the MeSH (Medical Subject Heading) terms with the assistance of the HeTOP site (https://www.hetop.eu/hetop/). The terms identified were combined by Boolean search operators, and we used the following phrases for the search: "Epilepsy" AND ("prenatal" OR "prenatal care" OR "prenatal injuries" OR "pregnancy" OR "postnatal" OR "postnatal care" OR "postpartum" OR "postpartum care" OR "postnatal injuries") AND ("child" OR "children" OR "childhood" OR "adolescent" OR "infant" OR "adolescence"). We specifically looked for case-control, cohort and cross-sectional studies. The last search was made in September 2023. No language or date restrictions were set during the search. Only studies in humans and full-free papers were included. The title and abstract of the collected papers were reviewed by two investigators to assess whether the records covered risk factors for epilepsy, and then the full-texts were evaluated for eligibility. In the event of a disagreement, a third author would rejudge the article.

#### **Eligibility criteria**

The inclusion criteria for literature are listed as below: (1) case-control, cohort or cross-sectional papers aiming to establish epilepsy risk factors in children or adolescents according to prenatal factors, newborn delivery conditions and postnatal characteristics; (2) free full-text; (3) reporting cases aged 0 to 20 years; (4) reporting epilepsy cases with normal birth without stroke, cerebral palsy, malformation or encephalopathy; and (5) reporting cases of confirmed epilepsy regardless of the seizure type (two or more unprovoked seizures or one seizure with abnormal electroencephalogram). Reports that included adult seizures or reported only one seizure with normal electroencephalogram or with hypoglycemia as a cause of neonatal seizure or febrile seizure were excluded.

We considered the following prenatal factors: maternal age, gestational age, maternal infection regardless of the type of infection, preeclampsia, gestational hypertension, gestational diabetes, eclampsia, smoking during pregnancy, maternal epilepsy, and pregnancy metrorrhagia regardless of the term. The factors that were considered to occur during newborn delivery conditions are as follows: cesarean section, forceps, breech presentation, cord prolapses, prolonged labor and meconium. Finally, the following factors were incorporated into the category of postnatal factors: birth complications (infection excluding nervous central system infection, respiratory distress, feeding or crying or breathing complications, Apgar < 6), male newborn (male gender), weight at birth under 2.5 kg and head trauma.

# **Quality of studies**

The validated Newcastle-Ottawa quality assessment scale (NOS) was applied to assess the quality of reports [2].

Two investigators independently screened the quality of articles based on three key aspects: (i) participant selection, (ii) comparability of groups, and (iii) determination of the exposure of interest for a case-control study and the outcome of interest for a cohort study.

# **Data extraction**

For each report, the following information was retrieved: first author, year of publication, country or region of the paper, study design, gender, number of cases, number of control groups, number of evaluated perinatal/postnatal factors in cases and controls and the odds ratio (OR) and 95% confidence interval (95% CI).

#### Statistical analysis

The ReviewManager 5.3 software developed by the Cochrane Collaboration was used to analyze the data and pooled the odds ratio. For the pooled effect, statistical significance was set at P < 0.05. Meanwhile, when P = 0.05, we defined it as statistical significant when the 95% CI did not contain 0. OR was combined for dichotomous data and DerSimonian and Laird's general inverse variance technique [8] was used to estimate the betweenstudy variance, in which each study's weight was inversely proportional to its variance. Given the possibility of high variability among studies due to differences in

study origins and populations, we chose a random-effects model over a fixed-effects model. To analyze the heterogeneity across the different studies, the Cochran Q test (P < 0.1 was deemed significant) and  $I^2$  statistic were used. The heterogeneity was categorized as minimal ( $I^2$  value, 0-25%), low (25–50%), moderate (50–75%), and severe (>75%). If considerable heterogeneity was found, a sensitivity analysis was performed by eliminating studies one by one to determine the likely causes of this heterogeneity. We ran a subgroup analysis if the sensitivity analysis failed to identify the source of heterogeneity. Because there were fewer than 10 combined studies in each risk factor analysis, it remained unnecessary to study the bias risk by funnel plot or Begg test, and Egger test [9, 10].

#### Results

# Characteristics of the studies and evaluation of their quality

The initial search identified 6296 records from PubMed and Google Scholar. After screening the title, abstract, and full-text for eligibility, we identified 25 reports [5, 11–34]. Figure 1 illustrates the flowchart of the selection procedure. Overall, we collected 45,044 cases with confirmed epilepsy and 2,558,210 controls. Epilepsy was confirmed by clinical criteria (two or more unprovoked

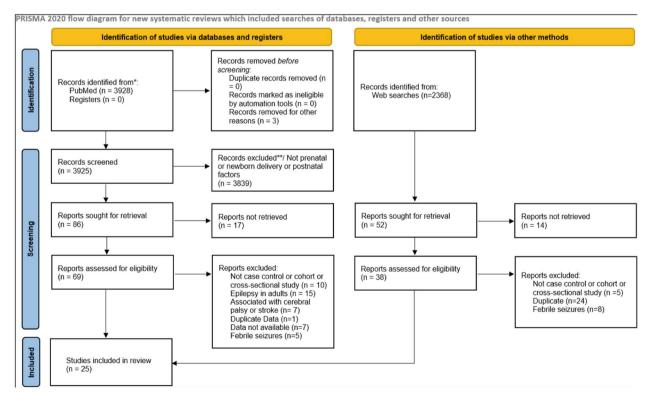


Fig. 1 PRISMA flowchart showing the processes of literature search and screening for systematic review and meta-analysis

seizures) or one seizure coupled with an abnormal electroencephalogram.

Each of the case-control studies included was evaluated using the NOS. One study received a score of 4 and another had a score of 5. Seven reports had a score of 6, 11 had score of 7 and four had a score of 8. Only one study had a score of 9. Table 1 summarizes the features of the included studies.

#### Meta-analysis

The number and the type of prenatal, newborn delivery and postnatal risk factors varied among studies. Some risk factors could not be pooled for analysis since their association with epilepsy was only reported in one study (alcohol consumption during pregnancy, vacuum extraction delivery, cephalic presentation and breastfeeding). Overall, we analyzed 20 factors (10 prenatal factors, 6 newborn delivery factors and 4 postnatal factors) for epilepsy occurrence in children or adolescents (age < 20).

#### **Prenatal factors**

#### Gestational age (< 37 weeks or > 42 weeks)

Gestational age <37 weeks or >42 weeks was not significantly associated with the risk of epilepsy in children or adolescents with significant heterogeneity (pooled OR = 2.58 [95% CI: 0.68–9.73], P=0.16,  $I^2$ =100%, Cochran's Q test < 0.00001) (Fig. 2a). Sensitivity analysis by excluding studies one-by-one showed no decrease in heterogeneity. Subgroup analysis revealed that premature birth was significantly associated with the risk of epilepsy

#### Table 1 Characteristics of the studies included

Study	Country/Region	Study design	Epilepsy diagnosis	Patient with epilepsy (n)	Control without epilepsy (n)	NOS score
Henderson et al. (1964) [32]	United States	Case-control	Clinical <sup>a</sup>	283	283	6
Maheshwar et al. (1990) [31]	India	Cohort study	Clinical <sup>a</sup>	381	372	7
Kuenneth et al. (1996) [30]	United States	Case-control	Clinical <sup>a</sup>	78	408	7
Daoud et al. (2003) [5]	Jordan	Case-control	Clinical <sup>a</sup>	200	200	6
Asadi-Pooya et al. (2005) [14]	Iran	Case-control	Clinical <sup>a</sup>	142	138	6
Krebs et al. (2006) [17]	Denmark	Case-control	Unavailable	290	580	6
Mung'ala-Odera et al. (2008) [29]	United Kingdom	Case-control	Clinical <sup>a</sup>	110	816	8
Cansu et al. (2007) [23]	Turkey	Case-control	Clinical <sup>a</sup>	805	848	7
Masri et al. (2008) [28]	Jordan	Case-control	Seizure and EEG <sup>b</sup>	55	111	6
McDermott et al. (2010) [16]	United States	Case-control	ICD codes	2185	125,563	7
Attumalil et al. (2011) [25]	India	Case-control	Clinical <sup>a</sup>	82	160	4
Burton et al. (2012) [22]	Tanzania	Cross-sectional	Clinical <sup>a</sup>	112	113	8
Miller et al. (2012) [3]	Denmark	Cohort study	ICD codes	2848	444,781	7
Ngugi et al. (2013) [12]	Sub-Saharan Africa	Cross-sectional and case- control	Clinical <sup>a</sup>	825	1031	9
Sun et al. (2008) [13]	United States	Cohort study	Clinical <sup>a</sup>	664	89,973	8
Ae-Ngibise et al. (2015) [11]	Ghana	Cross-sectional and case- control	Clinical <sup>a</sup>	144	172	6
Cruz-Cruz (2017) [24]	Mexico	Case-control	Clinical <sup>a</sup>	118	118	6
Thygesen et al. (2018) [34]	Denmark	Cohort study	Clinical <sup>a</sup>	2326	92,700	7
Hirvonen et al. (2017) [18]	Finland	Cohort study	Seizure and EEG <sup>b</sup>	5611	1,027,738	7
Kakooza-Mwesige (2017) [27]	United Kingdom	Case-control	Clinical <sup>a</sup>	155	171	8
Odd et al. (2018) [19]	United Kingdom	Cohort study	ICD codes	4594	467,038	7
Chou et al. (2020) [21]	Taiwan region of China	Cohort study	ICD codes	21,474	94,720	7
Whitehead et al. (2006) [20]	Canada	Cohort study	Seizure and EEG <sup>b</sup>	648	124,207	7
Chowdhury et al. (2020) [26]	Bangladesh	Cross-sectional	Unavailable	55	55	5
Gumisiriza et el (2021) [33]	Belgium	Case-control	Clinical <sup>a</sup>	154	153	7
Total	-	-	-	45,044	2,558,210	-

<sup>a</sup>, Two unprovoked seizures; NOS Newcastle-Ottawa Scale, ICD International Classification of Diseases, EEG electroencephalogram

<sup>b</sup>, abnormal

(pooled OR = 4.36 [95% CI: 1.26–15.09], P=0.02). Meanwhile, the heterogeneity was also significant ( $I^2$ =100%, Cochran's Q test < 0.00001). Furthermore, postterm was not linked to the risk of epilepsy (OR=0.52 [95% CI: 0.16–1.77], P=0.3) (Fig. 2b). The study by Attumalil et al. was excluded because it combined preterm and postterm births into a single variable [25].

#### Smoking

Smoking during pregnancy was associated with an increased prevalence of epilepsy in children or adolescents with significant heterogeneity (37% vs 31.1%, pooled OR=1.91 [95% CI: 1.01–3.61], P=0.05,  $I^2=84\%$ , Cochran's Q test=0.002) (Fig. 2c). Meanwhile, after sensitivity analysis by excluding the study by Attumalil et al. [25], smoking during pregnancy was shown to significantly increase the risk of epilepsy in children or adolescents by 28%, with insignificant and negligible heterogeneity (38% vs 31.1%, pooled OR=1.28 [95% CI:1.1–1.49], P=0.002,  $I^2=0\%$ , Cochran's Q test=0.6) (Fig. 2d).

#### Maternal epilepsy

Maternal epilepsy significantly elevated the risk of epilepsy in children or adolescents, with significant heterogeneity (1.32% vs 0.4%, pooled OR=2.62 [95% CI: 1.42–4.84], P=0.002,  $I^2$ =57%, Cochran's Q test=0.03) (Fig. 2e). After sensitivity analysis by excluding the study by McDermott et al. [16], this risk factor was significantly associated (1.15% vs 0.5%) with the epilepsy occurrence (pooled OR=2.06 [95% CI:1.26–3.36], P=0.004,  $I^2$ =0%, Cochran's Q test=0.64) (Fig. 2f).

#### Eclampsia

Eclampsia was not significantly associated with the risk of epilepsy in childhood or adolescence (0.6% vs 0.02%, pooled OR=3.46 [95% CI: 0.13–89.52], P=0.45,  $I^2=82\%$ , Cochran's Q test=0.004) (Fig. 2g). Sensitivity analysis by excluding studies one-by-one did not show a decrease in heterogeneity. Subgroup analysis revealed that study design (cohort study/cross-sectional study or case–control study) represented the source of heterogeneity ( $I^2=81.9\%$ , Cochran's Q test=0.02). Additionally, sub-group analysis showed that eclampsia was associated with

a 16.9- fold increase of the risk of epilepsy in children/ adolescents with insignificant heterogeneity in cohort/ cross-sectional studies (prevalence of epilepsy, 0.85% vs 0.02%, pooled OR = 16.9 [95% CI: 2.05–139.53], P=0.009,  $I^2$ =48%, Cochran's Q test=0.16) (Fig. 2h).

### Pregnancy metrorrhagia

Pregnancy metrorrhagia, regardless of the term, was significantly associated with the risk of epilepsy occurrence in children or adolescents (prevalence of epilepsy, 2.8% vs 0.8%, pooled OR=2.24 [95% CI: 1.36–3.71], P=0.002,  $I^2$ =0%, Cochran's Q test=0.83). The heterogeneity was low and insignificant (Fig. 3a).

## Maternal infection

Maternal infection was shown to raise the risk of developing epilepsy by 28% with negligible and insignificant heterogeneity (26.2% vs 22.1%, pooled OR = 1.28 [95% CI: 1.17–1.41], P<0.001,  $I^2$ =18%, Cochran's Q test=0.29) (Fig. 3b).

# Other factors

Gestational diabetes (Fig. 3 c), hypertension (Fig. 3d,e), preeclampsia (Fig. 3f), and maternal age (Fig. 3g,h) were not related to an increased risk of epilepsy in childhood or adolescence.

# Newborn delivery factors

#### Cord prolapse

Children/adolescents with epilepsy had a significantly higher prevalence of cord prolapse than the control groups (2.1% vs 0.3%) (pooled OR = 2.58 [95% CI: 1.25–5.32], P=0.01,  $I^2$ =0%, Cochran's Q test=0.88) (Fig. 3i).

#### Prolonged labor > 6 h

Prolonged labor >6 h was not significantly connected to the risk of epilepsy in childhood or adolescence with significant heterogeneity (37% vs 35.5%, pooled OR=3.4 [95% CI: 0.78–14.75], P=0.1,  $I^2=93\%$ , Cochran's Q test < 0.00001) (Fig. 4a). Sensitivity analysis by eliminating the study of Whitehead et al. [20] revealed a significant decrease in heterogeneity ( $I^2=0\%$ , Cochran's Q test=0.71). Prolonged labor (>6 h) was associated

(See figure on next page.)

**Fig. 2** Forest plot of the associations of gestational age, smoking, maternal epilepsy and eclampsia with the epilepsy risk. **a** Forest plot of the association between gestational age and the epilepsy risk. **b** Forest plot of the association between gestational age and the epilepsy risk after subgroup analysis. **c** Forest plot of the association between smoking during pregnancy and the epilepsy risk. **d** Forest plot of the association between smoking during pregnancy and the epilepsy risk. **d** Forest plot of the association between maternal epilepsy risk after sensitivity analysis. **e** Forest plot of sociation between maternal epilepsy and the epilepsy risk after sensitivity analysis. **e** Forest plot of the association between maternal epilepsy risk after sensitivity analysis. **e** Forest plot of the association between maternal epilepsy risk after sensitivity analysis. **e** Forest plot of the association between maternal epilepsy risk after sensitivity and the epilepsy risk after sensitivity analysis. **e** Forest plot of the association between maternal epilepsy risk after sensitivity analysis. **e** Forest plot of the association between maternal epilepsy risk after sensitivity analysis. **e** Forest plot of the association between eclampsia and the epilepsy risk. **h** Forest plot of the association between eclampsia and the epilepsy risk after subgroup analysis

	Study or Subgroup	Epileps Events	y Total	Conf Events		Moight	Odds Ratio		Odds Ratio IV, Random, 95% Cl
a	Asadi-Pooya et al (2005) Attumalil et al (2011)	8 11	142 82	5 12	138 160	9.5% 9.8%	IV, Random, 95% CI 1.59 [0.51, 4.98] 1.91 [0.80, 4.54]		
a	Chou et al (2020)	604 2	1474	331	94720	10.2%	8.25 [7.21, 9.44]		· ·
	Cruz-Cruz (2017) Gumisiriza et el (2021)	13 20	118 154	8 8	118 153	9.8% 9.8%	1.70 (0.68, 4.27) 2.71 (1.15, 6.35)		
	Hinvonen et al (2017) Masri et al (2008)	575 11	5611 55	54674 9	1027738 111	10.3% 9.7%	2.03 [1.86, 2.22] 2.83 [1.10, 7.32]		•
	McDermott et al (2010) Odd et al (2018)	1842	2185 4594	11949 262774	125563 467038	10.3% 10.3%	51.06 [45.43, 57.39] 0.28 [0.26, 0.30]		
	Whitehead et al (2006)	243	648	39392	124207	10.2%	1.29 [1.10, 1.52]		+
	Total (95% CI) Total events	3 4552	5063	369162	1839946	100.0%	2.58 [0.68, 9.73]		-
	Heterogeneity: Tau <sup>a</sup> = 4.47; Test for overall effect: Z = 1	Chi <sup>2</sup> = 665	5.90, d	f=9 (P<0	0.00001);	I <sup>a</sup> = 100%		0.01	0.1 1 10 100
	resciol orerail ellect 2 - 1	Epileps		Cont	ral		Odds Ratio		Control Epilepsy Odds Ratio
1.	Study or Subgroup		, Total	Events		Weight		1	IV, Random, 95% CI
b	26.2.1 Preterm Chou et al (2020)	604 2		331	94720		8.25 [7.21, 9.44]		-
	Cruz-Cruz (2017) Gumisiriza et el (2021)	13 20	118 154	8 8	118 153		1.70 [0.68, 4.27] 2.71 [1.15, 6.35]		
	Hirvonen et al (2017) Masri et al (2008)	575 11	5611 55	54674 9	1027738	11.3% 10.7%	2.03 [1.86, 2.22] 2.83 [1.10, 7.32]		•
	McDermott et al (2010) Whitehead et al (2006)	1842 80	2185 648	11949 7048	125563	11.3%	51.06 [45.43, 57.39] 2.34 [1.85, 2.96]		÷ *
	Subtotal (95% CI) Total events	3 3145	0245	74027	1372610	77.4%	4.36 [1.26, 15.09]		-
	Heterogeneity: Tau <sup>a</sup> = 2.73	; Chi <sup>2</sup> = 19	84.74,	df = 6 (P	<0.00001	); I² = 100	1%		
	Test for overall effect: Z = :	2.33 (P = 0	.02)						
	26.2.2 post-term Odd et al (2018)			262774	467038		0.28 [0.26, 0.30]		
	Whitehead et al (2006) Subtotal (95% CI)		648 5242	29458	124207 591245	11.3% 22.6%	0.98 [0.81, 1.17] 0.52 [0.16, 1.77]		-
	Total events Heterogeneity: Tau <sup>2</sup> = 0.76	1376 Chi <sup>2</sup> = 15	7.01. d	292232 f=1 (P<	0.00001)	P = 99%			
	Test for overall effect Z =	.04 (P = 0	.30)		,				
	Total (95% CI) Total events	3 4521	5487	366259	1963855	100.0%	2.69 [0.68, 10.69]		-
	Heterogeneity: Tau <sup>2</sup> = 4.39	; Chi <sup>2</sup> = 66	87.12,	df= 8 (P	<0.00001	); I <sup>z</sup> = 100	1%	0.01	0.1 1 10 100
	Test for overall effect Z = Test for subgroup differen	1.41 (P = 0. ces: Chi <sup>2</sup> =	7 <i>6)</i> 5.71, (	df= 1 (P =	0.02), I <sup>2</sup>	= 82.5%			Control Epilepsy
		Epilep	sy	Cont	rol		Odds Ratio		Odds Ratio
С	Study or Subgroup Asadi-Pooya et al (2005)	Events 65	Total 142	Events 51	138	33.8%	IV, Random, 95% Cl 1.44 (0.89, 2.32)		IV, Random, 95% Cl
	Atturnalil et al (2011) Whitehead et al (2006)	23 235	82 648	11 38639	160 124207	25.7% 40.5%	5.28 [2.42, 11.51] 1.26 [1.07, 1.48]		
	Total (95% CI)		872		124505	100.0%	1.91 [1.01, 3.61]		•
	Total events Heterogeneity: Tau <sup>a</sup> = 0.26	323 CDF=12	55 df	38701					
	Test for overall effect Z = "			- 2 (F - 0	.002),1 =	0430		0.01	0.1 i 10 100 Control Epilepsy
	Study or Subgroup	Epileg Events	osy Total	Con Events		Moinht	Odds Ratio IV, Random, 95% Cl		Odds Ratio IV, Random, 95% Cl
d	Asadi-Pooya et al (2005)	65	142	51	138		1.44 [0.89, 2.32]		
•	Whitehead et al (2006)	235	648	38639	124207	89.9%	1.26 [1.07, 1.48]		
	Total (95% CI)		790		124345	100.0%	1.28 [1.10, 1.49]		•
	Total events Heterogeneity: Tau <sup>2</sup> = 0.0	300 0: Chi² = 0	.27. df:	38690 = 1 (P = 0	.60);  ² =	0%		L	
	Test for overall effect: Z =	3.15 (P=	0.002)					0.01	0.1 1 10 100 Control Epilepsy
	Study or Subgroup	Epile Events			ntrol Total	Weight	Odds Ratio IV, Random, 95% Cl	I	Odds Ratio IV, Random, 95% Cl
•	Ae-Ngibise et al (2015) Henderson et al (1964)	2			172	5.4%	0.30 [0.03, 3.32] 5.04 [0.24, 105.36]		
C	Kakoooza-Mwesig (2017) Kuenneth et al (1996)		155	5 2	171	9.1%	2.24 [0.40, 12.39] 2.15 [0.66, 7.04]		
	McDermott et al (2010) Ngugi et al (2013)	34 19	2185	355		28.3%	5.57 [3.91, 7.95] 2.69 [1.21, 5.97]		+
	Whitehead et al (2006)	5			124207	18.9%	1.71 [0.71, 4.13]		+
	Total (95% CI)		5315			100.0%	2.62 [1.42, 4.84]		<b>•</b>
	Total events Heterogeneity: Tau <sup>z</sup> = 0.3	70 1; Chi² = 1	3.86, di	940 = 6 (P =	0.03);   <sup>2</sup> =	57%		0.01	0.1 1 10 100
	Test for overall effect: Z =	3.09 (P = 0 Epile		<b>C</b> -1			Odda Datia	0.01	Control Epilepsy
•	Study or Subgroup	Events	Tota	Events			Odds Ratio IV, Random, 95% CI		Odds Ratio IV, Random, 95% Cl
f	Ae-Ngibise et al (2015) Henderson et al (1964)		283	з о	283	2.6%	0.30 [0.03, 3.32] 5.04 [0.24, 105.36]		
	Kakoooza-Mwesig (2017 Kuenneth et al (1996)	) 4					2.24 [0.40, 12.39] 2.15 [0.66, 7.04]		
	Ngugi et al (2013)	19	82:	2 9	1031	37.5%	2.69 [1.21, 5.97]		
	Whitehead et al (2006)	:	641	3 563	124207	30.6%	1.71 [0.71, 4.13]		+
	Total (95% CI) Total events	36	3130	585		100.0%	2.06 [1.26, 3.36]		<b>◆</b>
	Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect: Z =	10; Chi² = 3	41. df			1%		0.01	0.1 1 10 100
	Test for orefull click. 2 -	Epilep		Conf	rol		Odds Ratio		Control Epilepsy Odds Ratio
	Study or Subgroup Chowdhury et al (2020)	Events 1	Total 55	Events 0	Total 55	Weight 29.5%	N, Random, 95% Cl 3.06 [0.12, 76.64]		IV, Random, 95% Cl
g	Henderson et al (1964) Whitehead et al (2006)	0 5	283 648	2	283 124207	30.4%	0.20 [0.01, 4.16] 33.30 [12.85, 86.29]	•	
U	Total (95% CI)	5	986	20	124545		3.46 [0.13, 89,52]		
	Total events	6		31			5.40 [0.15, 65.52]		
	Heterogeneily: Tau <sup>a</sup> = 6. Test for overall effect: Z	64; Chi*= 1 = 0.75 (P =	0.45)	at = 2 (P =	0.004);1	= 82%		0.01	0.1 1 10 100 Control Epilepsy
	Study or Subgroup	Epile Events		Cor Events	trol Total	Weight	Odds Ratio IV, Random, 95% Cl		Odds Ratio IV, Random, 95% Cl
h	6.2.1 cohort/cross-se Chowdhury et al (2020	0 1	1 55			29.5%	3.06 [0.12, 76.64]		
11	Whitehead et al (2006 Subtotal (95% CI)	) (	5 648 703		124207 124262	40.1% 69.6%	33.30 [12.85, 86.29]		
	Total events Heterogeneity: Tau <sup>a</sup> =	6 1.38: Chi <sup>z</sup> =	3 :194.0	29 if = 1/P =	0.16) · F =	48%			
	Test for overall effect:								
	6.2.2 control Henderson et al (1964	) (	283	3 2	283	30.4%	0.2010.01 4.44	←	
	Subtotal (95% CI)	, i	283		283	30.4%	0.20 [0.01, 4.16] 0.20 [0.01, 4.16]	_	
	Heterogeneity: Not app	licable		2					
	Test for overall effect:	L= 1.04 <i>(P</i> =			42454-	100 00	2 40 10 10 00		
	Total (95% CI) Total events			31		100.0%	3.46 [0.13, 89.52]		
	Heterogeneity: Tau <sup>e</sup> = Test for overall effect: 2	Z = 0.75 (P	= 0.45)					0.01	0.1 1 10 100 Control Epilepsy
	Test for subgroup diffe	rences: Ch	i²= 5.5	4, df = 1 ()	P = 0.02).	l <sup>2</sup> = 81.99			Control Chickey

Fig. 2 (See legend on previous page.)

with a 6.74-fold increase of epilepsy risk (34.3% vs 7% pooled OR=6.74 [95% CI: 3.57–12.71], P < 0.001,  $I^2 = 0$ %, Cochran's Q test=0.71) (Fig. 4b).

#### Other factors

Cesarean section (Fig. 4c, d), forceps (Fig. 4e), breech presentation (Fig. 4f, g) and meconium (Fig. 5a) were not associated with the risk of epilepsy in children or adolescents.

### **Postnatal factors**

#### Head trauma

Head trauma was correlated with an elevated likelihood of epilepsy in children or adolescents (9.5% vs 3.8%, pooled OR=3.39 [1.84–6.25], P < 0.001,  $I^2 = 74\%$ , Cochran's Q test=0.0007) (Fig. 5b). The sensitivity analysis showed that after excluding the study by Cansu et al. [23], there remained a significant association between head trauma and epilepsy during childhood or adolescence, but with insignificant heterogeneity (9.5% vs 5.1%, pooled OR=2.31 [95% CI: 1.54–3.48], P < 0.001,  $I^2 = 33\%$ , Cochran's Q test=0.19) (Fig. 5c).

### **Birth complications**

Birth complications including feeding complications, crying, respiratory complications, infection (excluding central nervous system infection) and Apgar < 6, were significantly associated with a higher risk of epilepsy (12.4% vs 8.3%, pooled OR = 3.91 [95% CI: 2.43–6.29], P < 0.001). Meanwhile, the heterogeneity was high and significant ( $I^2$ =90%, Cochran's Q test < 0.00001). Sensitivity analysis did not show any decrease in heterogeneity. Subgroup analysis showed that the complication type (infection, respiratory distress) was not the source of heterogeneity across studies ( $I^2$ =0%, Cochran's Q test=0.41). Figure 5d shows that the most significant risk factor was infection (OR = 19.49 [95% CI: 1.03–368.71], P=0.05]).

#### Low birth weight (< 2.5 kg)

Low birth weight significantly increased the risk of epilepsy in childhood or adolescence by 83% (18.2% vs 10.7%, pooled OR=1.83 [95% CI: 1.5–2.23],  $I^2=0\%$ , Cochran's Q test=0.57) (Fig. 5e).

#### Gender

The male gender was not associated with the risk of epilepsy with high heterogeneity (28.6% vs 50.7%, pooled OR=0.7 [95% CI: 0.2–2.45], P=0.58,  $I^2=99\%$ , Cochran's Q test<0.00001) (Fig. 5f). After sensitivity analysis by excluding the study by McDermott et al. [16], this risk factor was significant with negligible and insignificant heterogeneity (56% vs 50.7%, pooled OR=1.18 [95% CI: 1.06–1.32], P=0.003,  $I^2=0\%$ , Cochran's Q test=0.41) (Fig. 5g).

Table 2 provides a concise overview of the variables associated with epilepsy occurrence in childhood and adolescence, categorized by prenatal, delivery, and postnatal periods.

#### Discussion

The present systematic review and meta-analysis is the first to evaluate factors associated with epilepsy occurrence in childhood or adolescence. Meta-analysis based on the 25 studies revealed that the prenatal risk factors for epilepsy included preterm birth (<37 weeks), smoking during pregnancy, maternal epilepsy, eclampsia, pregnancy metrorrhagia regardless of the term, and maternal infection regardless of the term. Newborn delivery factors that increase the risk of epilepsy were cord prolapse, head trauma and prolonged labor >6 h. Regarding postnatal factors, the risk of epilepsy was significantly elevated with birth complications, low-weight birth (<2.5 kg), and male gender.

Prenatal factors were more commonly studied in various papers [16, 18–21, 28, 33]. Of the studies addressing the relationship between preterm/postterm birth and the risk of epilepsy, we identified six case-control studies [14, 16, 24, 25, 28, 33] and four cohort studies [19–21, 33]. It is worth noting that these studies had comparable weights in terms of their impact on the overall results of the meta-analysis. Subgroup analysis and sensitivity analysis indicated that preterm birth doubled the risk of epilepsy in children or adolescents. The study conducted by Li et al. was in line with our findings, in which the risk was

#### (See figure on next page.)

**Fig. 3** Forest plot of the associations of pregnancy metrorrhagia, infection, preeclampsia, gestational diabetes and hypertension, maternal age, and cord prolapse with the epilepsy risk. **a** Forest plot of the association between pregnancy metrorrhagia and the risk of epilepsy. **b** Forest plot of the relationship between maternal infection and the risk of epilepsy in children or adolescents. **c** Forest plot of association between gestational diabetes and the epilepsy risk. **d** Forest plot of the association between gestational hypertension and the epilepsy risk. **e** Forest plot of the association between gestational hypertension and the epilepsy risk after sensitivity analysis. **f** Forest plot of the association between preeclampsia and the epilepsy risk. **g** Forest plot of the association between maternal age and the epilepsy risk after sensitivity analysis. **i** Forest plot of the association between cord prolapse and the epilepsy risk after sensitivity analysis. **i** Forest plot of the association between cord prolapse and the epilepsy risk after sensitivity analysis. **i** Forest plot of the association between cord prolapse and the epilepsy risk after sensitivity analysis. **i** Forest plot of the association between cord prolapse and the epilepsy risk

dy or Subgroup wwdhury et al (2020) hderson et al (1964) itehead et al (2006) al (95% CI) al events erogeneity: Tau <sup>2</sup> = 0.00 it for overall effect: Z = 3	Events 10 7 11 28	55 283		Tota	Al Moigh	t N/D	dds Ratio andom, 95%	CI.		N/ Dand	om, 95% Cl	1	
itehead et al (2006) al <b>(95% CI)</b> al events erogeneity: Tau <sup>2</sup> = 0.00	11	283	5	5	5 19.39	% 2	.22 [0.71, 6.	99]				-	
al events erogeneity: Tau² = 0.00	28	648	2 1010	283 12420		% 3.5	56 (0.73, 17. .11 (1.16, 3.)	30]					
		986	1017		5 100.0%	% 2.	24 [1.36, 3.7				•		
	8.15 <i>(P</i> =	0.002)			= 0%	04	Patio	0.01	0.1		1 Epilepsy	10	100
tudy or Subgroup	Epileps Events		Contro vents		Weight N	Odds F V, Rando	Ratio m, 95% Cl			lds Ratio Idom, 95%	CI		
tumalil et al (2011)	6	82	7	160	0.7%	1.73 [0	0.56, 5.31]			-			
ansu et al (2007) ruz-Cruz (2017)	8 67	805 118	2 52	848 118	0.4% 3.1%		90, 20.05] 1.00, 2.79]			-			
enderson et al (1964)	7	283	5	283	0.6%	1.41 [0	0.44, 4.50]		-	-	-		
										-			
un et al (b) (2008)	137	643	18292	89667	18.0%	1.06 [0	0.87, 1.28]			+			
otal (95% CI)		5428	43							٠			
eterogeneity: Tau <sup>2</sup> = 0.00	l; Chi² = 8.	.54, df=		?9); I* = 1	8%		Ĕ	1.01 0	.1 Cont	1 rol Epile	10 psy	100	
dv or Subaroup					l Weigh			CI					
malil et al (2011)	5	82	4							-	•	_	
owdhury et al (2020)	6	55	2			6 3.2	4 [0.63, 16.8	34]			-		
nderson et al (1964) itehead et al (2006)	1 19	283 648								-	-		
											•		
al events	31		3176			~ 1.							
			= 3 (P = 0	0.39);   <b>*</b> :	= 0%			0.01	0.1	Control	1 Enilenev	10	100
			Con	trol		Od	lds Ratio						
udy or Subgroup	Events	s Tota				t IV, Ra	ndom, 95%						
howdhury et al (2020)	1:	3 55	5 1	55	13.5%	16.71	[2.10, 132.9	93]					
enderson et al (1964)	13	3 283	3 13	3 283	28.3%	5 1.	00 [0.46, 2.2	20]		_			
tal (95% CI)					100.0%	2.5	58 [0.98, 6.8	2]			-		
otal events eterogeneity: Tau² = 0.3					3);  ² = 70	96		<u> </u>					
				- 0.003				0.01	0.1	Control	1 Epilensv	10	100
	-	nilor		ont			Odde Defi						
Study or Subaroup					otal Wei	ight IV							
Attumalil et al (2011)		8	82									_	
lenderson et al (1964	)	13 2	283	13 2	283 59	.4%	1.00 [0.46	6, 2.20]					
otal (95% CI)		3	365	4	143 100	0.0%	1.17 [0.64	, 2.141			-		
fotal events		21		24							Γ		
				P = 0.5	5); I² = 09	%		L 0	.01	0.1	trol Entro	1	0
who ar Culture					L 147-1-1			c		Odds	Ratio	, i/ ay	
	Events 20									w, Kando	mi, 95% Cl		
uz-oluz (zolir)			3 1				56 [0.26, 1.2				1		
nderson et al (1964)	11		1								Ť		
nderson et al (1964) tal (95% CI)		40			100.0%	6 0.0	69 [0.42, 1.1	3]		•			
nderson et al (1964) tal (95% CI) tal events	31		4	3		6 0.0	69 [0.42, 1.1			•		-t	
nderson et al (1964) tal (95% CI)	31 0; Chi² = 1.47 (P =	0.47, df = <i>0.14)</i>	4 f = 1 (P =	3 0.49); I²		6 0.0		1 <b>3]</b> 0.01	0.1		Epilepsy	10	100
nderson et al (1964) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.0 st for overall effect: Z =	31 0; Chi <sup>2</sup> = 1.47 (P = El	0.47, df = 0.14) pilepsy	4 f = 1 (P = )	3 0.49); I² Control	= 0%		Odds Ratio	0.01	0.1	Odd	ls Ratio		100
nderson et al (1964) tal (95% CI) tal events terogeneity: Tau <sup>#</sup> = 0.0 st for overall effect: Z = <b>idy or Subgroup</b> owdhury et al (2020)	31 0; Chi <sup>2</sup> = 1.47 (P = El	0.47, df = 0.14) pilepsy ents To 1	4 f = 1 (P = ) (0 tal_Even 55	3 0.49); I² Control <u>nts T</u> 18	= 0% <u>otal We</u> 55 7	ight IV,	Odds Ratio Random, 95	0.01 5% CI 0.30] ←	0.1	Odd			100
nderson et al (1964) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.0 st for overall effect Z = tdy or Subgroup owdhury et al (2020) enneth et al (1996)	31 0; Chi <sup>z</sup> = 1.47 (P = El Eve	0.47, df = 0.14) pilepsy ents To 1 2	4 f=1(P= 0 <u>tal Even</u> 55 78	3 0.49); I <sup>≈</sup> Control tts T 18 16	<sup>2</sup> =0% <u>fotal We</u> 55 7 408 11	ight IV,	Odds Ratio Random, 95 0.04 [0.00, 0.64 [0.15,	0.01 5% CI 0.30] ← 2.86]	0.1	Odd	ls Ratio		100
nderson et al (1964) tal (95% CI) tal events terogeneity: Tau <sup>#</sup> = 0.0 st for overall effect: Z = <b>idy or Subgroup</b> owdhury et al (2020)	31 0; Chi <sup>2</sup> = 1.47 (P = Eve Eve	0.47, df = 0.14) pilepsy ents To 1 2 24 1	4 f=1(P= 0 <u>tal Even</u> 55 78	3 0.49); I <sup>≥</sup> Control 1ts T 18 16 89	<sup>2</sup> = 0% <u>otal We</u> 55 7 408 11 816 35	ight IV,	Odds Ratio Random, 95	0.01 5% CI 0.30] ← 2.86] 1.50]	0.1	Odd	ls Ratio		100
Inderson et al (1964) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.0 st for overall effect Z = <b>idy or Subgroup</b> owdhury et al (2020) enneth et al (1986) mg/ala-Odera et al (2000) ittehead et al (2006) tal (95% CI)	31 0; Chi <sup>2</sup> = 1.47 (P = Eve Eve	0.47, df = 0.14) pilepsy ents To 1 2 24 1 172 6	4 f = 1 (P = 0 tal Even 55 78 10 1	3 0.49); I <sup>≥</sup> Control tts T 18 16 89 71 124	<sup>2</sup> = 0% <u>otal We</u> 55 7 408 11 816 35	ight IV, .0% .7% 5.9% 5.4%	Odds Ratio Random, 95 0.04 [0.00, 0.64 [0.15, 0.93 [0.57,	0.01 5% CI 0.30] ← 2.86] 1.50] 1.12]	0.1	Odd	ls Ratio		100
nderson et al (1964) tal (95% CI) tal events terogeneik; Tau <sup>2</sup> = 0.0 st for overall effect: Z = idy or Subgroup owdhury et al (2020) owdhury et al (2020) ng'ala-Odera et al (2006) tal (95% CI) tal events	31 0; Chi <sup>2</sup> = 1.47 ( <i>P</i> = Eye 8) 1	0.47, df = 0.14) pilepsy ents To 1 2 24 1 172 6 8 199	4 f=1(P = 0 tal Even 55 78 10 1 48 345 91 347	3 0.49);   <sup>2</sup> Control <u>its T</u> 18 16 89 71 124 125 94	e 0% 55 7 408 11 816 35 207 45 486 100	ight IV, .0% .7% 5.9% 5.4%	Odds Ratio Random, 95 0.04 (0.00, 0.64 (0.15, 0.93 (0.57, 0.94 (0.79,	0.01 5% CI 0.30] ← 2.86] 1.50] 1.12] 1.29]		Odd	ls Ratio	1	
Inderson et al (1964) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.0 st for overall effect Z = <b>idy or Subgroup</b> owdhury et al (2020) enneth et al (1986) mg/ala-Odera et al (2000) ittehead et al (2006) tal (95% CI)	31 0; Chi <sup>2</sup> = 1.47 ( <i>P</i> = Eye 8) 1 1; Chi <sup>2</sup> = 9	0.47, df e 0.14) pilepsy ents To 1 2 24 1 172 6 8 199 3.47, df=	4 f=1(P = 0 tal Even 55 78 10 1 48 345 91 347	3 0.49);   <sup>2</sup> Control <u>its T</u> 18 16 89 71 124 125 94	e 0% 55 7 408 11 816 35 207 45 486 100	ight IV, .0% .7% 5.9% 5.4%	Odds Ratio Random, 95 0.04 (0.00, 0.64 (0.15, 0.93 (0.57, 0.94 (0.79,	0.01 5% CI 0.30] ← 2.86] 1.50] 1.12]		Ode IV, Rano	ls Ratio	1	100
Inderson et al (1964) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.0 st for overall effect: Z = <b>idy or Subgroup</b> owdhury et al (2020) enneth et al (1986) ing <sup>1</sup> al-Odera et al (2006) titehead et al (2006) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.19	31 0; Chi <sup>2</sup> = 1.47 ( <i>P</i> = Er Eve 8) 1 1; Chi <sup>2</sup> = 9 .12 ( <i>P</i> =	0.47, df = 0.14) pilepsy ents To 1 2 24 1 172 6 8 199 3.47, df = 0.26)	4 f=1(P = 0 tal Even 55 78 10 1 48 345 91 347	3 0.49);   <sup>2</sup> Control tts T 18 16 89 71 124 125 94 02);   <sup>2</sup> =	<sup>2</sup> = 0% <b>otal We</b> 55 7 408 11 816 35 207 45 <b>486 100</b> 68%	ight IV, 10% 17% 59% 54%	Odds Ratio Random, 95 0.04 (0.00, 0.64 (0.15, 0.93 (0.57, 0.94 (0.79,	0.01 5% CI 0.301 ← 2.86] 1.501 1.12] 1.29]		Ode IV, Rand	Is Ratio Iom, 95% C	1 10 1	
nderson et al (1964) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.0 st for overail effect: Z = <b>idy or Subgroup</b> owdhury et al (2020) ng'ala-Odera et al (2006) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.19 st for overail effect: Z = 1 <b>idy or Subgroup</b>	31 0; Chi <sup>2</sup> = 1.47 ( <i>P</i> = Er Eve 8) 1 1; Chi <sup>2</sup> = 9 .12 ( <i>P</i> =	0.47, df = 0.14) pilepsy ents To 1 2 24 1 172 6 8 199 3.47, df = 0.26)	4 f= 1 (P = 0 (1) 55 78 10 1 148 345 91 347 : 3 (P = 0. 0 (0) (0) (0) (0) (0) (0) (0) (0) (0) (	3 0.49);   <sup>2</sup> control <u>nts T</u> 18 16 89 71 124 125 94 02);   <sup>2</sup> = ents	otal         We           55         7           408         11           816         35           207         45           6486         100           68%         Total	ight IV, .0% .7% .9% .4% 0.0% Veight I	Odds Ratio Random, 91 0.04 [0.00, 0.64 [0.15, 0.93 [0.57, 0.94 [0.79, 0.71 [0.40, V, Random,	0.01 5% CI 0.30] ← 2.86] 1.50] 1.12] 1.29] 0.0 95% CI		Ode IV, Rand	Is Ratio tom, 95% C	1 10 1	
Inderson et al (1964) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.0 st for overall effect: Z = <b>idy or Subgroup</b> ovdhury et al (2020) enneth et al (1996) ngraia-Odera et al (2006) titehead et al (2006) tal events terogeneity: Tau <sup>2</sup> = 0.19 st for overall effect: Z = 1	31 0; Chi² = 1.47 (P = Eve 8) 1; Chi² = 9 .12 (P = 1 Eve	0.47, df = 0.14) pilepsy ents To 1 2 2 4 1 172 6 8 199 3.47, df = 0.26)	4 f = 1 (P = <u>(P =</u> <u>55</u> 78 10 1 148 345 91 347 3 (P = 0. <u>otal Eve</u> 78 110	3 0.49);   <sup>2</sup> Control tts T 18 16 89 71 124 125 94 02);   <sup>2</sup> =		ight IV, 10% 17% 59% 54%	Odds Ratio Random, 95 0.04 [0.00, 0.64 [0.15, 0.93 [0.57, 0.94 [0.79, 0.71 [0.40,	0.01 0.30] ← 2.86] 1.50] 1.12] 1.29] 95% Cl 5, 2.86] 7, 1.50]		Ode IV, Rand	Is Ratio tom, 95% C	1 10 10	
Inderson et al (1964) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.0 st for overall effect: Z = <b>idy or Subgroup</b> owdhury et al (2020) owdhury et al (2020) itehead et al (2006) tal events terogeneity: Tau <sup>2</sup> = 0.16 tof overall effect: Z = 1 <b>idy or Subgroup</b> enneth et al (1996) ong'ala-Odera et al (2006) itehead et al (2006)	31 0; Chi² = 1.47 (P = Eve 8) 1; Chi² = 9 .12 (P = 1 Eve	0.47, df = 0.14) pilepsy ents To 1 2 24 1 172 6 8 199 3.47, df - 0.26) - - - - - - - 2 4 172	4 f = 1 (P = ( <u>tal Even</u> 55 78 10 1 148 345 991 347 347 347 347 347 347 347 347	3 0.49);   <sup>2</sup> control 18 16 89 71 124 125 94 02);   <sup>2</sup> = ents 16 189 571 12	e 0% otal We 55 7 408 11 816 35 207 45 408 100 68% Total W 408 816 1 24207 8	ight IV, .7% .9% .4% 0.0% Veight I 1.2% 11.5% 37.3%	Odds Ratio Random, 95 0.04 [0.00, 0.93 [0.57, 0.94 [0.79, 0.71 [0.40, V, Random, 0.64 [0.11 0.93 [0.5 0.94 [0.7]	0.01 0.301 ← 2.86] 1.50] 1.12] 1.29] 95% Cl 5, 2.86] 7, 1.50] 9, 1.12]		Ode IV, Rand	Is Ratio tom, 95% C	1 10 10	
Inderson et al (1964) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.0 st for overall effect: Z = udy or Subgroup owdhury et al (2020) itehead et al (2020) itehead et al (2006) tal events terogeneity: Tau <sup>2</sup> = 0.19 teroseneity: Tau <sup>2</sup> = 0.19 teroseneity: Tau <sup>2</sup> = 0.19 itehead et al (1996) ing'ala-Odera et al (2006) tal events tal events tal events tal events tal events tal events tal events	31 0; Chi <sup>#</sup> = 1.47 ( <i>P</i> = Eve 8) 1; Chi <sup>#</sup> = 9 .12 ( <i>P</i> = Eve	0.47, df = 0.14) pilepsy ents To 1 2 24 1 172 6 8 199 9.47, df = 0.26) - 	4 (= 1 (P = 55 78 10 1 48 345 91 347 347 347 347 347 347 347 347 347 347	3 0.49);   <sup>2</sup> Control its T 18 18 71 124 94 125 94 02);   <sup>2</sup> = ents 16 189 571 12 12 776	i= 0%         55       7         408       11         816       35         207       45         486       100         68%       100         7000       8%         408       816         408       816         816       124207         25431       10	ight IV, .7% .9% .4% 0.0% Veight I 1.2% 11.5% 37.3%	Odds Ratio Random, 95 0.04 (0.00, 0.64 (0.15, 0.93 (0.57, 0.94 (0.79, 0.71 (0.40, V, Random, 0.64 (0.11, 0.93 (0.5	0.01 0.301 ← 2.86] 1.50] 1.12] 1.29] 95% Cl 5, 2.86] 7, 1.50] 9, 1.12]		Ode IV, Rand	Is Ratio tom, 95% C	1 10 10	
nderson et al (1964) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.0 st for overall effect: Z = <b>idy or Subgroup</b> owdhury et al (2020) ng*ala-Odera et al (2000) itehead et al (2006) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.18 st for overall effect: Z = 1 <b>idy or Subgroup</b> enneth et al (1996) ng*ala-Odera et al (2001) itehead et al (2006) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.0	31 0; Chi <sup>2</sup> = 1 1.47 ( <i>P</i> = Eve 8) 1; Chi <sup>2</sup> = 9 .12 ( <i>P</i> = 1 Eve 08)	0.47, df e 0.14) pilepsy ntts Too 1 2 24 1 172 6 8 8 199 8,47, df= 0.26) 2 24 172 24 172 24 172	4 (= 1 (P = 55 78 10 1 48 345 91 347 347 347 347 347 347 347 347 347 347	3 0.49);   <sup>2</sup> Control its T 18 18 71 124 94 125 94 02);   <sup>2</sup> = ents 16 189 571 12 12 776	i= 0%         55       7         408       11         816       35         207       45         486       100         68%       100         7000       8%         408       816         408       816         816       124207         25431       10	ight IV, .7% .9% .4% 0.0% Veight I 1.2% 11.5% 37.3%	Odds Ratio Random, 95 0.04 [0.00, 0.93 [0.57, 0.94 [0.79, 0.71 [0.40, V, Random, 0.64 [0.11 0.93 [0.5 0.94 [0.7]	0.01 0.30] 4 2.86] 1.50] 1.12] 1.29] 0.0 95% CI 5, 2.86] 7, 1.50] 9, 1.12] 9, 1.10]		Contro IV, Rand	Is Ratio lom, 95% C	10 % CI	
Inderson et al (1964) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.0 st for overall effect: Z = udy or Subgroup owdhury et al (2020) itehead et al (2020) itehead et al (2006) tal events terogeneity: Tau <sup>2</sup> = 0.19 teroseneity: Tau <sup>2</sup> = 0.19 teroseneity: Tau <sup>2</sup> = 0.19 itehead et al (1996) ing'ala-Odera et al (2006) tal events tal events tal events tal events tal events tal events tal events	31 0; Chi <sup>2</sup> = 1.47 ( $P = E_{i}$ Even 8) 1; Chi <sup>2</sup> = 9 .12 ( $P = 1$ Even 08) 0; Chi <sup>2</sup> = 1 0.85 ( $P = 1$	0.47, df e 0.14) pilepsy ntts Too 1 2 24 1 172 6 8 8 199 8,47, df= 0.26) 2 24 172 24 172 24 172	$\begin{array}{c} 4\\ f = 1 \ (P = \\ \hline \\ tal \ Even \\ 55\\ 78\\ 10 \ 1 \\ 148 \ 345\\ 991\\ 347\\ 347\\ 347\\ 347\\ 78\\ 110\\ 648 \ 34\\ 836\\ 836\\ 34\\ = 2 \ (P = 4) \end{array}$	3 0.49);   <sup>2</sup> Control its T 18 18 71 124 94 125 94 02);   <sup>2</sup> = ents 16 189 571 12 12 776	i= 0%         55       7         408       11         816       35         207       45         486       100         68%       100         7000       8%         408       816         408       816         816       124207         25431       10	ight IV, .0% .7% .9% .4% 0.0% Veight I 1.2% 11.5% 87.3% 00.0%	Odds Ratio Random, 95 0.04 [0.00, 0.93 [0.57, 0.94 [0.79, 0.71 [0.40, V, Random, 0.64 [0.11 0.93 [0.5 0.94 [0.7]	0.01 0.30] 4 2.86] 1.50] 1.12] 1.29] 0.0 95% CI 5, 2.86] 7, 1.50] 9, 1.12] 9, 1.10]	1 0.	Control	Is Ratio tom, 95% C	10 % CI	
nderson et al (1964) tal (95% CI) tal events terogeneity. Tau <sup>2</sup> = 0.0 st for overall effect. Z = <b>idy or Subgroup</b> owdhury et al (2020) ng*ala-Odera et al (2000) itehead et al (2006) tal (95% CI) tal events terogeneity. Tau <sup>2</sup> = 0.18 st for overall effect. Z = 1 <b>idy or Subgroup</b> enneth et al (1996) intehead et al (2006) tal (95% CI) tal events terogeneity. Tau <sup>2</sup> = 0.0 st for overall effect. Z = Study or Subgroup	31 0; Chi <sup>#</sup> = 1.47 ( <i>P</i> = Eve 8) 1, Chi <sup>#</sup> = 9 1.12 ( <i>P</i> = Even 0; Chi <sup>#</sup> = 1 0.85 ( <i>P</i> = Epilit Event Even	0.47, df pilepsy pilepsy 1 2 2 4 1 172 6 8 8 199 .47, df - .24 172 2 4 172 2 4 172 2 2 4 172 198 0.24, df 172 2 4 172 198 0.24, df 199 199 199 199 199 199 199 199 199 19	4 4 1 (P = (C tal Even 55 78 10 1 148 345 991 347 347 347 347 347 348 346 48 36 24 24 24 24 24 24 24 24 24 24	3 0.49);   <sup>2</sup> Control 18 18 18 18 18 125 94 02);   <sup>2</sup> = ents 16 189 571 12 12 12 12 577 6 0.89);   <sup>2</sup> 10 57 12 12 12 12 12 12 12 12 12 12	image: state of the state o	ight IV, .0% .9% .9% .4% Veight I 1.2% .00% Veight IV, .00.0%	Odds Ratio Randorn, 99 0.04 (0.00, 0.84 (0.15, 0.93 (0.57, 0.94 (0.78, 0.71 (0.40, V. Randorn, 0.84 (0.1 0.93 (0.6 0.93 (0.6 0.94 (0.7) 0.93 (0.7) 0.93 (0.7)	0.01 5% CI 2.86] 1.50] 1.12] 1.29] 0.0 95% CI 5, 2.86] 7, 1.50] 9, 1.12] 9, 1.10] 5, 2.86 5, 2.86	1 0.	1 Contro IV, Rand	Is Ratio lom, 95% C	10 % CI	
nderson et al (1964) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.0 st for overall effect Z = <b>udy or Subgroup</b> owdhury et al (2020) owdhury et al (2020) rg*ala-Odera et al (2006) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.16 st for overall effect Z = 1 <b>udy or Subgroup</b> enneth et al (1996) ng*ala-Odera et al (2006) tal events terogeneity: Tau <sup>2</sup> = 0.0 st for overall effect Z = <b>Study or Subgroup</b> Enneth et al (2020) tal events terogeneity: Tau <sup>2</sup> = 0.0 st for overall effect Z = <b>Study or Subgroup</b> Enneth et al (2020)	31 31 1.47 (P = Eve 8) (; Chi <sup>2</sup> = 9 1.2 (P = 1.2 (P = 1.2 (P = Even 0.55 (P = Even 1.2 (P = 1.2 (P =	0.47, di e, 0.43, pilepsy ents To 1 2 24 1 172 6 8 199 8.47, df 1 2 2 4 198 0.269	$\begin{array}{c} 4\\ r=1 \ (P= & c\\ c\\ tal \ Even \\ 65\\ 78\\ 10 \ 1 \\ 148\\ 345\\ 5\\ 891\\ 347\\ 347\\ 78\\ 3(P=0, \\ c\\ c$	3 Control Its T 18 71 125 94 125 94 125 94 125 94 125 94 125 94 125 94 125 94 125 94 125 94 125 94 125 94 125 94 125 94 125 125 125 125 125 125 125 125	i= 0%           total         We           55         7           408         11           816         35           2207         45           486         100           68%         101           408         11           4108         11           4207         2           25431         11           = 0%         10%           tal         Wei           55         3.5.	Hight IV. 10% 10% 10% 10% 10% 10% 11.2% 11.5% 11.5% 11.5% 11.5% 11.5% 11.5% 11.5% 11.5% 11.2% 11.5% 11.	Odds Ratio Randorn, 92 0.04 (0.00, 0.64 (0.15, 0.93 (0.57, 0.94 (0.79, 0.71 (0.40, 0.93 (0.5, 0.94 (0.17) 0.93 (0.5, 0.94 (0.17) 0.93 (0.5, 0.94 (0.7) 0.93 (0.7)	0.01 5% CI 0.30] ← 2.86] 1.50] 1.12] 1.12] 9.5% CI 9.5% CI 9. 1.12] 9. 1.10] 9. 1.10] 5% CI 0.73]	1 0.	1 Contro IV, Rand	Is Ratio	10 % CI	
nderson et al (1964) tal (95% CI) tal events terogeneity. Tau <sup>2</sup> = 0.0 st for overall effect. Z = <b>idy or Subgroup</b> owdhury et al (2020) ng*ala-Odera et al (2000) itehead et al (2006) tal (95% CI) tal events terogeneity. Tau <sup>2</sup> = 0.18 st for overall effect. Z = 1 <b>idy or Subgroup</b> enneth et al (1996) intehead et al (2006) tal (95% CI) tal events terogeneity. Tau <sup>2</sup> = 0.0 st for overall effect. Z = Study or Subgroup	31 0; Chi <sup>p</sup> = Fi Eve 8) 1; Chi <sup>p</sup> = 9 (; Chi <sup>p</sup> = 9 Eve 50 0; Chi <sup>p</sup> = Eve 12 ( <i>P</i> = 1 Eve 1 12 ( <i>P</i> = 1 Eve 1	0.47, df pilepsy pilepsy 1 2 2 4 1 172 6 8 8 199 .47, df - .24 172 2 4 172 2 4 172 2 2 4 172 198 0.24, df 172 2 4 172 198 0.24, df 199 199 199 199 199 199 199 199 199 19	$\begin{array}{c} 4\\ r=1 \ (P= \\ \hline \\ c\\ r= \\ r= \\ r= \\ r= \\ r= \\ r= \\ r= \\$	3 3 3 3 3 3 3 3 3 3 3 3 3 3	i = 0%         We           otal         We           408         1           408         1           816         1           88%         1           408         100           68%         1           408         100           68%         1           408         816           418         11           = 0%         1           56         36.           534         54	ight IV, .0% .9% .9% .0% Veight I 1.2% 1.5% 37.3% 00.0% ight IV, .2%	Odds Ratio Randorn, 99 0.04 (0.00, 0.84 (0.15, 0.93 (0.57, 0.94 (0.78, 0.71 (0.40, V. Randorn, 0.84 (0.1 0.93 (0.6 0.93 (0.6 0.94 (0.7) 0.93 (0.7) 0.93 (0.7)	0.01 5% Cl 0.30] ← 2.86] 1.150] 1.12] 1.29] 5,2.86] 7,1.50] 9,1.12] 9,1.12] 9,1.10] 6,2.86] 7,1.50] 9,1.12] 9,1.10] 5,2.83]	1 0.	1 Contro IV, Rand	Is Ratio	10 % CI	
Inderson et al (1964) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.0 st for overall effect: Z = <b>idy or Subgroup</b> owdhury et al (2020) owdhury et al (2020) itchead et al (2006) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.16 st for overall effect Z = 1 <b>idy or Subgroup</b> enneth et al (1996) ong'ala-Odera et al (2001) itchead et al (2006) tal events terogeneity: Tau <sup>2</sup> = 0.0 st for overall effect Z = 1 <b>idy or Subgroup</b> enneth et al (1996) ong'ala-Odera et al (2001) itchead et al (2005) tal events terogeneity: Tau <sup>2</sup> = 0.0 st for overall effect Z = <b>Study or Subgroup</b> Dhowdhury et al (2020) Venderson et al (1964)	31 0; Chi <sup>p</sup> = Fi Eve 8) 1; Chi <sup>p</sup> = 9 (; Chi <sup>p</sup> = 9 Eve 50 0; Chi <sup>p</sup> = Eve 12 ( <i>P</i> = 1 Eve 1 12 ( <i>P</i> = 1 Eve 1	0.47, dti 0.74, dti 0.74, dti 1 2 24 1 1 2 24 1 172 6 8 9 9.47, dti 0.26, dti 172 198 0.24, dti 0.24, dti 0.23, dti 198 198 198 198 198 198 198 198	4 F = 1 (P = C T = 1 (P = 10 10 11 10 11 148 148 148 148 148 148 148	3 Control Its T 18 18 89 71 124 125 94 125 94 125 94 125 94 125 94 125 94 125 94 125 94 125 94 125 94 125 94 125 94 125 124 125 124 125 124 125 125 124 125 124 125 124 125 125 124 125 124 125 125 124 125 125 125 125 125 125 125 125	i = 0%         i = 0%           total         We           dots         11           H1816         35           2007         45           68%         100           68%         100           68%         101           207         45           816         1           408         816           916         1           4225431         11           4205         55           555         55           555         54           810         1           910         1           910         1	ight         IV,           .0%         .0%           .7%         .4%           .0.0%         .1.2%           .0%         .0%           .0% </td <td>Odds Ratio Randorn, 92 0.04 (0 00, 0.64 (0 15, 0.93 (0 57, 0.94 (0 78, 0.93 (0 57, 0.94 (0 78, 0.93 (0 56, 0.94 (0 78, 0.93 (0 56, 0.94 (0 79, 0.93 (0 57, 0.93 (0 79, 0.93 (</td> <td>0.01 5% CI 0.30) ← 2.86] 1.12] 1.29] 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.</td> <td>1 0.</td> <td>1 Contro IV, Rand</td> <td>Is Ratio</td> <td>10 % CI</td> <td></td>	Odds Ratio Randorn, 92 0.04 (0 00, 0.64 (0 15, 0.93 (0 57, 0.94 (0 78, 0.93 (0 57, 0.94 (0 78, 0.93 (0 56, 0.94 (0 78, 0.93 (0 56, 0.94 (0 79, 0.93 (0 57, 0.93 (0 79, 0.93 (	0.01 5% CI 0.30) ← 2.86] 1.12] 1.29] 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.	1 0.	1 Contro IV, Rand	Is Ratio	10 % CI	
Inderson et al (1964) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.0 st for overall effect: Z = <b>idy or Subgroup</b> owdhury et al (2020) owdhury et al (2020) itchead et al (2006) tal (95% CI) tal events terogeneity: Tau <sup>2</sup> = 0.16 st for overall effect Z = 1 <b>idy or Subgroup</b> enneth et al (1996) ong'ala-Odera et al (2006) tal events terogeneity: Tau <sup>2</sup> = 0.0 st for overall effect Z = 2 st or overall effect Z = 2 st or overall effect Z = 2 terogeneity: Tau <sup>2</sup> = 0.0 st for overall effect Z = 2 Study or Subgroup Chowdhury et al (2020)	31 31 1.47 (P = Eve 8) (; Chi <sup>P</sup> = 9 1.12 (P = Even 1.12 (P = Even 0.05 (P = Epile Epile 1.12 (P = 1.12 (P	0.47, dit = 0.74) pilepsy nts To 2 2 4 1 1 2 2 4 1 5 3 3 3 3 2 8 8 7 8 8 7 8 8 7 1 1 5 3 3 3 8 8 8 7 8 8 7 8 8 8 7 8 8 7 8 8 7 8 8 7 8 8 8 7 8 8 8 8 7 8 8 8 8 8 8 8 8 8 8 8 8 8	4 4 1 (P = 1 (P =	3 0.49);   <sup>2</sup> Control tts T 18 89 91 16 18 92 92 12 12 12 12 12 12 12 12 12 1	i=0%           otal         Wee           55         7           408         1816           207         455           208         100           68%         100           408         816           410         816           410         11           =0%         10           td1         Wei           td2         10           302         100	ight         IV,           .0%         .0%           .7%         .4%           .0.0%         .1.2%           .0%         .0%           .0% </td <td>Odds Ratio Randorn, 92 0.04 (0 00, 0.64 (0 15, 0.93 (0.57, 0.94 (0.79, 0.71 (0.40, 0.64 (0.11, 0.93 (0.57, 0.93 (0.65, 0.94 (0.72, 0.93 (</td> <td>0.01 5% CI 0.30) ← 2.86] 1.12] 1.29] 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.</td> <td>1 0.</td> <td>1 Contro IV, Rand</td> <td>Is Ratio</td> <td>10 % CI</td> <td></td>	Odds Ratio Randorn, 92 0.04 (0 00, 0.64 (0 15, 0.93 (0.57, 0.94 (0.79, 0.71 (0.40, 0.64 (0.11, 0.93 (0.57, 0.93 (0.65, 0.94 (0.72, 0.93 (	0.01 5% CI 0.30) ← 2.86] 1.12] 1.29] 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.	1 0.	1 Contro IV, Rand	Is Ratio	10 % CI	
	Coemott et al (2010) un et al (a) (2008) un et al (a) (2008) hitshead et al (2006) Mai events eterogeneity: Tau" = 0.00 Mai events eterogeneity: Tau" = 0.00 to verail effect Z = 5 dy or Subgroup maili et al (2011) worknuy et al (2020) worknuy et al (2020) to verail effect: Z = 1 udy or Subgroup urmaili et al (2011) al events eterogeneity: Tau" = 0.00 tro overail effect: Z = 1 udy or Subgroup urmaili et al (2017) nowdhury et al (2020) enderson et al (1964) tal (95% CI) at levents eterogeneity: Tau" = 0.01 tat (95% CI) tat (95% CI) tat (2011) tenderson et al (1964) tat (2011) tenderson et al (1964) tat (2011) tenderson et al (1964) terogeneity: Tau" = 0.01 tat (95% CI) tat (95% CI) tat (95% CI) tat (95% CI) tat (95% CI)	clement et al (2010) 966 un et al (0) (2009) 119 hitchead et al (2006) 119 hitchead et al (2006) 111 stal sevents 1421 eterogeneity: Tau" = 0.00; Ch" = 0 <b>ty or Subgroup</b> Events mail et al (2011) 5 widhury et al (2020) 6 diversion et al (1964) 1 tehead et al (2006) 19 al (95% CI) al events 31 erogeneity: Tau" = 0.00; Ch" = 1 Epipe toty or Subgroup Event umail et al (2017) 8 nowdhury et al (2020) 1 events 31 erogeneity: Tau" = 0.00; Ch" = 1 Epipe toty or Subgroup Event umail et al (2017) 8 nowdhury et al (2020) 1 events 11 tet (2007) 8 nowdhury et al (2020) 1 tat events 11 tet (2007) 8 nowdhury et al (2020) 1 tat events 11 tet (2017) tat events 11 tet (2017) tet (2017) tat events 11 tet (2017) tet (2017) tat events 11 tet (2017) tet	cDermott et al (2010)         966         2165           nu et al (a) (2008)         113         664           nu et al (a) (2008)         137         643           hitshead et al (2006)         111         648           hitshead et al (2006)         111         648           hitshead et al (2006)         111         648           hitshead et al (2010)         5428         1421           elerogeneily Tau" = 0.01; Chi" = 8.64, df =         devents         Total           mall effect Z = 5.26 (P=0.0007)         Events         Total           mall effect (1964)         1         283           debrond et al (2011)         6         82           widhury et al (2020)         1         648           at (95% CI)         1068         al (95% CI)         1068           at (95% CI)         1021         800         000// Chi" = 3.0, df           tail events         0.01; Chi" = 0.71; Chi" = 14.32, st         800         000// 13         61           nowdruny et al (2007)         83         800         000// 13         62           staf events         117         2400 ergeneity: Tau" = 0.71; Chi" = 14.32, st         7         7           tat events         117         24	Common tet (a) (2006)         196 2165 47654 1           net (a) (2008)         113         643         1232 2           hithehead et al (2006)         111         648         1271 4           Attail events         1421         95242           eternogramely: Tau"= 0.00; Ch7= 8.25, df = 7 (P = 0.2           com           dy or Subgroup         com           Epilepsy         Com           com           a 10, cf = 3 (P = 0.2)           com           com           by or Subgroup         Events         com           tono         com	$\begin{tabular}{ c c c c c c } \hline \begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	$\begin{tabular}{ c c c c c c c } \hline Control (C) (C) (C) (C) (C) (C) (C) (C) (C) (C)$	$\begin{tabular}{ c c c c c c c } \mbox{Commutation} & $$ $$ $$ $$ $$ $$ $$ $$ $$ $$ $$ $$ $$	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $

Fig. 3 (See legend on previous page.)

2.16 times higher in preterm groups [35]. However, postterm birth was not associated with the risk of epilepsy. Several studies have indicated the association between preterm birth and epilepsy onset at a younger age is mediated by white matter gliosis and hypoxic-ischemic brain injury [13, 36]. However, in our study, by excluding cerebral palsy and stroke, we emphasize alternative hypotheses. In fact, hippocampal sclerosis, impaired development of brain structure and a higher risk of infection in preterm groups have been reported to contribute to this association [13]. Given the limited data on the risk of epilepsy occurrence in children and adolescents with preterm, full-term, or post-term births, we were unable to compare the risk of epilepsy between those with preterm and full-term births, and between those with postterm and full-term births.

Our results showed that smoking during pregnancy significantly increased epilepsy occurrence by 28%. Smoking during pregnancy has been identified as the first environmental risk factor for epilepsy worldwide. Furthermore, it doubles the risk of seizures in children [37]. Among the few studies exploring the association of smoking at pregnancy with epilepsy onset at an early age, smoking has been found to induce placental inflammation, placenta damage, decreased blood flow in the placenta, remodeling of the uterine vasculature, low birth weight and fetal growth restriction [38–40], which may underlie the increased risk of epilepsy [38–40]. Additionally, tobacco contains various chemicals with proconvulsant effects such as ammonia, hexane, toluene and arsenic; however, it remains unknown whether these chemicals can cross the placental barrier to induce epileptic seizures in children [40]. Furthermore, some studies have reported brain structural changes associated with maternal smoking, such as cortical thinning in the lateral and perisylvian occipital cortices and a significantly smaller frontal lobe [40, 41]. Moreover, maternal smoking affects the expression of many genes that are related with epilepsy [42]. Further research is required to elucidate the pathophysiology of smoking during pregnancy and the risk of epilepsy in children or adolescents.

In our study, children/adolescents born to epileptic mothers were 2.06 times more likely to have epilepsy. Out of the 6 studies that examined the association of maternal epilepsy with epilepsy onset in children or adolescents, two were cross-sectional and case-control studies [11, 12], three were case-control studies [27, 30, 32] and one was a cohort study [20]. Notably, the two studies that exerted the most significant influence on the overall results were those by Ngugi et al. (2013) and Whitehead et al. (37.5% and 30.6% respectively) [12, 20]. This finding was similar to those reported in various other studies [12, 16, 43]. In fact, maternal epilepsy was associated with an~45% increased risk of epilepsy in the offspring [43]. Additionally, antiepileptic drug use during pregnancy is not an explanation for epilepsy occurrence in children/adolescents [44]. Another hypothesis that can explain this relationship is the genetic origin of epilepsy. In fact, epilepsy can be inherited from the mothers [43]. Additional studies are needed to fully establish the mechanism behind the association between maternal epilepsy and the risk of epilepsy in children and adolescents.

While preeclampsia was not identified as a risk factor for epilepsy, eclampsia was strongly associated with this risk and conferred an OR of 16.9. The variation in study design has been identified as the origin of heterogeneity in this analysis. Specifically, we integrated two cohort studies [19, 20] along with one case-control study [32]. The research conducted by Whitehead et al. carried the greatest significance in the analysis, accounting for 40.1% of the total weight [20]. Eclampsia is a serious complication that can lead to epilepsy in children/ adolescents through various pathways. In fact, mothers can experience hypoxia, which can affect the normal development of the fetal brain and increase the risk of epilepsy. Rocca et al. showed that eclampsia increases the risk of generalized tonic-clonic seizures, partial seizures and absence seizures by 2 folds; however, this relationship is not significant [45]. This association may be explained by placental dysfunction, biological changes during eclampsia, premature birth and low-weight birth. Meanwhile, the exact mechanism remains unknown. As preeclampsia precedes eclampsia, prompt diagnosis and treatment of preeclampsia are needed to prevent eclampsia onset and its associated complications.

In our meta-analysis, we found that maternal infection, regardless of the type or term, is the leading cause of epilepsy in children and adolescents. Sun et al. showed that

<sup>(</sup>See figure on next page.)

Fig. 4 Forest plot of the associations of prolonged labor, cesarean section, forceps use, and breech presentation with the risk of epilepsy. **a** Forest plot of the association between prolonged labor and the epilepsy risk. **b** Forest plot of the association between prolonged labor and the epilepsy risk after sensitivity analysis. **c** Forest plot of the association between cesarean section and the epilepsy risk. **d** Forest plot of the association between forceps use and the epilepsy risk. **f** Forest plot of the association between breech presentation and the epilepsy risk. **g** Forest plot of the association between breech presentation and the epilepsy risk. **g** Forest plot of the association between breech presentation and the epilepsy risk after sensitivity analysis.

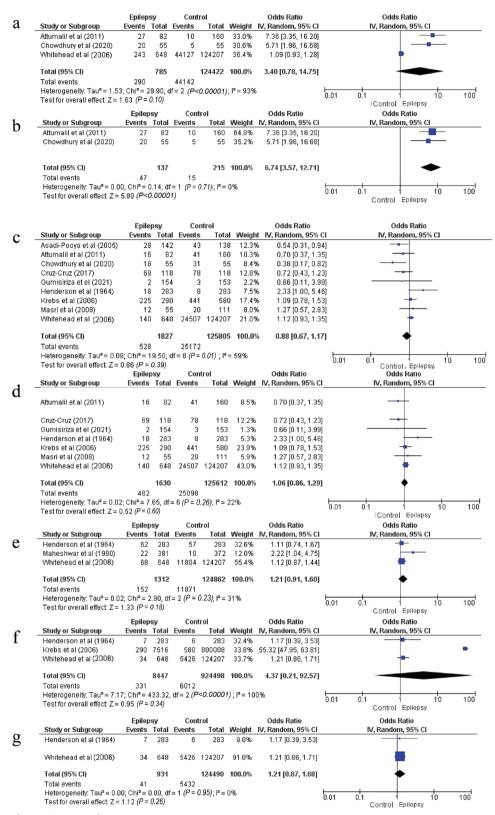


Fig. 4 (See legend on previous page.)

prenatal exposure to maternal cystitis, pyelonephritis, persistent diarrhea, coughing, and vaginal yeast infections is linked to an elevated risk of juvenile epilepsy [13]. Additionally, Casetta et al. found that maternal illness, notably upper respiratory infections, is linked to an elevated incidence of cryptogenic and idiopathic partial epilepsy [46]. While the pathophysiological mechanisms remain unclear, a plausible explanation is that the immune response and cytokines might potentially induce placental abnormalities and fetal brain damage. This finding highlights the importance of antenatal care to prevent infection and other pregnancy-related issues. Other factors related to epilepsy occurrence are prolonged labor and cord prolapse. These results could also be explained by the increased risk of infection. Cord prolapses can also lead to oxygen deprivation inducing brain injury [47]. Glass et al. showed a positive association between cord prolapses and seizure occurrence in children with an OR of 6.9 [95% CI: 5.9–8.1] [47].

The occurrence of epilepsy following head trauma has been extensively studied in both children/adolescents and adults [45, 48]. We found that children/adolescents with a history of head trauma had a 2.31-fold increased risk of epilepsy. This finding aligns with the results of previous studies. In fact, this association can be linked to neuroinflammation, glial scars and brain injuries induced by head trauma.

After sensitivity analysis by excluding the study of McDermott et al. [16], the risk of epilepsy occurrence was shown to be higher in male newborns (56% vs 50.7%, pooled OR=1.18 [95% CI: 1.06-1.32]). We excluded this particular study because it was the primary source of variations of results. Our findings are consistent with those of other studies [49, 50]. Two potential explanations for our findings are as follows: sex differences in cerebral connectivity and in astrocyte structure [51–53]. The male brain typically has a larger amygdala and thalamus, while the female brain features a larger hippocampus, caudate nuclei, regional gray matter, and cortices [54]. Studies have shown that men exhibit stronger rightside connectivity in the amygdala, while women display more prominent left-side connections [54]. These sexrelated distinctions in brain development, influenced by steroid hormones, impact the susceptibility to seizures [54]. Additionally, astrocyte structural variations may contribute to the sex difference in epilepsy, as cultured astrocytes and microglia from male and female rats display distinct functional responses and inflammatory marker expression [52, 53]. Further research is needed to uncover the structural and neuroendocrine factors contributing to the sex differences in epilepsy.

In our study, birth complications including feeding complications, crying, respiratory complications, infection (excluding central nervous system infection) and Apgar < 6, are significantly associated with a higher risk of epilepsy occurrence (pooled OR=3.91 [95% CI: 2.43–6.29]). This discovery aligns with previous research. Indeed, the presence of respiratory complications and an Apgar score below 6 increase the likelihood of neurodevelopmental issues and the risk of epilepsy development [55]. Hypoxia can result in energy depletion, oxidative stress, and inflammation, ultimately causing cellular death, which can contribute to the development of cerebral palsy and epileptic lesions [56]. Additionally, Frederik et al. discovered that the likelihood of an epilepsy diagnosis is elevated not only after central nervous system infections but also after a wide variety of peripheral infections [57]. Some infections can enhance the likelihood of experiencing seizures, particularly in individuals who already have a pre-existing susceptibility to epilepsy [58]. Infections, particularly those linked to inflammation, have the potential to alter the immune responses in the brain and disrupt the equilibrium of neurotransmitters [59], which may potentially elevate the likelihood of epilepsy development [58]. Conversely, adequate nutrition is essential for healthy brain development. Insufficient intake of vital nutrients can have adverse effects on brain growth and development, increasing the vulnerability to various neurological disorders, including epilepsy [59]. Moreover, difficulties with feeding can give rise to metabolic imbalances, such as hypoglycemia or disruptions in electrolytes. These metabolic irregularities can impact brain function and potentially provoke seizures [59].

We assume that multiple factors during the prenatal, delivery and postnatal periods interact synergistically and dynamically, elevating the risk of epilepsy in children or adolescents. For instance, eclampsia can

<sup>(</sup>See figure on next page.)

Fig. 5 Forest plots of the associations of meconium, head trauma, birth complications, low birth weight and male gender with the epilepsy risk. **a** Forest plot of the association between meconium and the epilepsy risk. **b** Forest plot of the association between head trauma and the epilepsy risk. **c** Forest plot of the association between head trauma and the epilepsy risk after sensitivity analysis. **d** Forest plot of the association between birth complications and the epilepsy risk after subgroup analysis. **e** Forest plot of the association between epilepsy risk after subgroup analysis. **e** Forest plot of the association between epilepsy risk and male newborns **g** Forest plot of the association between male gender and the epilepsy risk after sensitivity analysis

a	Study or Subgroup	Epilepsy Events Tot	tal Ev	Contro vents		Weight	Odds Ratio IV, Random, 95% Cl		Odds F IV, Randon		
	Attumalil et al (2011) Whitehead et al (2006)	3	82	4	160 24207	1.7%	1.48 [0.32, 6.78] 0.88 [0.72, 1.08]			<u> </u>	
	Total (95% CI)		30			100.0%	0.89 [0.73, 1.09]		•		
	Total events Heterogeneity: Tau <sup>2</sup> = 0.00;	120 Chi <sup>2</sup> = 0.43		4781 1 (P = 0.	51);  ²=	0%		L			
	Test for overall effect: Z = 1.	13 (P = 0.2 Epileps	26)	Cont			Odds Ratio	0.01	0.1 1 Control Odds	1'0 Epilepsy Patio	100
h	Study or Subgroup	Events	Total	Events	Total		IV, Random, 95% Cl		IV, Randor		
υ	Ae-Ngibise et al (2015) Attumalil et al (2011)	36 17	144 82	32 10	171 160	19.3% 16.0%	1.45 [0.85, 2.48] 3.92 [1.70, 9.03]		T		
	Burton et al (2012) Cansu et al (2007)	7 75	112 805	2 9	113 848	8.9% 17.5%	3.70 [0.75, 18.22] 9.58 [4.76, 19.26]				-
	Daoud et al (2003) Kakoooza-Mwesig (2017)	13 6	200 155	3 1	200 170	11.5% 6.1%	4.57 [1.28, 16.28] 6.81 [0.81, 57.18]		_		·
	Ngugi et al (2013)	66	822	46	1025	20.8%	1.86 [1.26, 2.74]				
	Total (95% CI) Total events	220	2320	103	2687	100.0%	3.39 [1.84, 6.25]			•	
	Heterogeneity: Tau <sup>z</sup> = 0.43; Test for overall effect: Z = 3.			6 (P = 6	0.0007)	I <sup>z</sup> = 74%		0.01	0.1 1 Control	10	100
		Epileps	sy	Cont			Odds Ratio		Odds	Ratio	
c	Study or Subgroup Ae-Ngibise et al (2015)	Events 36	Total 144	Events 32		28.3%	IV, Random, 95% Cl 1.45 [0.85, 2.48]		IV, Rando	n, 95% Cl	
C	Attumalil et al (2011) Burton et al (2012)	17 7	82 112	10		16.8% 5.9%	3.92 [1.70, 9.03] 3.70 [0.75, 18.22]		_	_	_
	Cansu et al (2007) Daoud et al (2003)	75 13	805	9	848	8.7%	Not estimable 4.57 [1.28, 16.28]				_
	Kakoooza-Mwesig (2017)	6	155	1	170	3.4%	6.81 [0.81, 57.18]		-	-	
	Ngugi et al (2013)	66	822	46		37.0%	1.86 [1.26, 2.74]			-	
	Total (95% CI) Total events	145	1515	94		100.0%	2.31 [1.54, 3.48]			₹.	
	Heterogeneity: Tau <sup>2</sup> = 0.08 Test for overall effect: Z = 4			5 (P = 0	. <i>19)</i> ;  ² =	= 33%		0.01	0.1 1 Control	10 Epilensy	100
		Experiment	tal	Contro			Odds Ratio		Odds Ratio		
d	Study or Subgroup 29.2.1 Infection		otal E			Weight	IV, Random, 95% Cl		IV, Random, 95%	CI	
	Masri et al (2008) Subtotal (95% CI)	4	55 55	0	111 111	2.1% 2.1%	19.49 [1.03, 368.71] 19.49 [1.03, 368.71]		_		→
	Total events Heterogeneity: Not applicabl	4 e		0							
	Test for overall effect: Z = 1.9	18 (P = 0.05)									
	29.2.2 Respiratory distress Attumalil et al (2011)	52	82	15	160	9.4%	16.76 [8.35, 33.61]				
	Cruz-Cruz (2017) Thygesen et al (2017)	237 2	118 326		118 92700	9.7% 11.6%	2.16 [1.13, 4.10] 1.59 [1.38, 1.82]		+		
	Whitehead et al (2006) Subtotal (95% CI) Total events	3	174	2	24207 17185	11.5% 42.2%	1.62 [1.30, 2.01] 2.77 [1.57, 4.89]				
	Heterogeneity: Tau <sup>2</sup> = 0.28; 0	417 Chi <sup>2</sup> = 43.22,	df = 3 (	18162 P < 0.000	001);  ² =	93%					
	Test for overall effect: Z = 3.5 29.2.3 Feeding, breathing ar			tion							
	Ae-Ngibise et al (2015) Asadi-Pooya et al (2005)	43	136 142	1 7	164 138	3.8% 7 8.0%	5.37 [10.21, 556.28] 1.89 [0.73, 4.88]				+
	Daoud et al (2003) Kakoooza-Mwesig (2017)	43	200	16 3	200	9.8% 6.1%	3.15 [1.71, 5.81] 3.42 [0.91, 12.88]				
	Ngugi et al (2013) Subtotal (95% CI)	96	794	16	1003	10.2% 38.0%	8.48 [4.95, 14.53] 5.25 [2.27, 12.16]				
	Total events Heterogeneity: Tau <sup>#</sup> = 0.63; 0	204 Chi# = 17.33	df = 4 (	43 P = 0.002	2)· P = 77	7%					
	Test for overall effect: Z = 3.8	7 (P = 0.000	)1)			-					
	29.2.4 Apgar < 6 Cansu et al (2007)		805	12	848	9.8%	7.79 [4.22, 14.41]				
	Krebs et al (2006) Subtotal (95% CI)	1	290 095	10	580 1428	7.9% 17.7%	1.41 [0.53, 3.74] 3.46 [0.65, 18.46]		-		
	Total events Heterogeneity: Tau <sup>2</sup> = 1.29; 0			22 = 0.004)	( I <sup>z</sup> = 889	6					
	Test for overall effect: Z = 1.4 Total (95% CI)		748	2	20395	100.0%	3.91 [2.43, 6.29]				
	Total events Heterogeneity: Tau <sup>2</sup> = 0.50; 0	713		18227							-
	Test for overall effect: Z = 5.6 Test for subgroup difference	i1 (P < 0.000	01)				0.	01 0.1	Control Epile	10 10 psy	10
		Epilepsy		Contro		~	Odds Ratio		Odds Rat	0	
	o: 1 o 1	Events To		vents 13		Weight 5.4%	IV, Random, 95% Cl 2.33 [1.00, 5.46]		IV, Random, 9		
e	Study or Subgroup Masri et al (2008)	13									
e	Masri et al (2008) Whitehead et al (2006)	13 115		3255 1		94.6%	1.81 [1.48, 2.21]				
e	Masri et al (2008) Whitehead et al (2006) Total (95% CI)	115	648 1 703	13255 1	24207	94.6% 100.0%	1.81 [1.48, 2.21] 1.83 [1.50, 2.23]		•		
e	Masri et al (2008) Whitehead et al (2006) Total (95% CI) Total events Heterogeneity: Tau <sup>a</sup> = 0.0	115 i 128 I0; Chi <sup>2</sup> = 0.3	648 703 33, df =	13255 1 1 13268 1 (P = 0.	24207 24318	100.0%	1.81 [1.48, 2.21] 1.83 [1.50, 2.23]	0.01 0	•	l 	100
e	Masri et al (2008) Whitehead et al (2006) Total (95% CI) Total events	115 128 0; Chi <sup>2</sup> = 0.3 6.02 (P < 0.4	648 703 33, df = 00001)	13255 1 1 13268 1 (P = 0.	24207 24318 57); I <sup>2</sup> =	100.0%	1.81 [1.48, 2.21] 1.83 [1.50, 2.23]	0.01 0	Control Ep	10 ilepsy	100
0	Masri et al (2006) Whitehead et al (2006) Total (95% CI) Total events Heterogeneity: Tau <sup>z</sup> = 0.0 Test for overall effect: Z = Study or Subgroup	115 128 0; Chi <sup>2</sup> = 0.3 6.02 (P < 0.) Epileps; Events 1	648 1 703 33, df = <i>00001)</i> y Fotal E	13255 1 13268 1 (P = 0. Contro	24207  24318 57);   <sup>2</sup> =   Total	100.0% 0% Weight IV	1.81 [1.48, 2.21] 1.83 [1.50, 2.23] Odds Ratio Random, 95% Cl		↓ 1 1 Control Ep Odds Ratio Random, 95% CI	10 ilepsy	100
e f	Masri et al (2008) Whilehead et al (2006) Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect Z = <u>Study or Subgroup</u> Button et al (2012) Cansu et al (2007)	115 1 128 0; Chi <sup>2</sup> = 0.3 6.02 ( <i>P</i> < 0. Epileps: Events 1 57 477	648 1 703 33, df = <i>00001)</i> y <u>Fotal E</u> 112 805	13255 1 13268 1 (P = 0. Contro Svents 57 435	24207  24318 57);   <sup>2</sup> =     <u>Total  </u>  113  848	100.0% 0% <u>Weight IV</u> 16.4% 16.8%	1.81 [1.48, 2.21] 1.83 [1.50, 2.23] Odds Ratio <u>Random, 95% C1</u> 1.02 [0.60, 1.72] 1.38 [1.14, 1.68]		Control Ep Odds Ratio	10 10 ilepsy	100
0	Masri et al (2006) Whitehead et al (2006) Total (95% CI) Total events Heterogeneity Tau"= 0.0 Test for overall effect Z = <u>Study or Subgroup</u> Butch et al (2017) Carsu et al (2021) McDemothe al (2020)	115 1 128 0; Chi <sup>z</sup> = 0.3 6.02 ( <i>P</i> < 0. Epileps: Events 1 57 477 93 126 2	648 1 703 33, df = 00001) y 112 805 154 2185	13255 1 13268 1 (P = 0. Contro Svents 57 435 84 63822 1	24207 124318 57); I <sup>2</sup> = 1 113 848 153 25563	100.0% 0% Weight IV 16.4% 16.8% 16.5% 16.8%	1.81 [1.48, 2.21] 1.83 [1.50, 2.23] Odds Ratio Random, 95% CI 1.02 [0.60, 1.72] 1.38 [1.14, 1.66] 1.25 [0.80, 1.37] 0.06 [0.05, 0.07]		Control Ep Odds Ratio	10 ilepsy	100
0	Masri et al (2006) Whitehead et al (2006) Total (95% CI) Total events Heterogeneity: Tau'= 0.0 Test for overall effect. Z = <u>Study or Subgroup</u> Burton et al (2012) Cansu et al (2007) Gurnisinza et al (2014) McDiemot et al (2016) Writishead et al (2016)	115 1 128 128 10; Chi <sup>z</sup> = 0.3 6.02 ( <i>P</i> < 0. Epileps; Events 1 57 477 93 126 54 343	648 703 33, df = 000001) 9 112 805 154 2185 110 648	13255 1 13268 1 1 (P = 0. Contro Vents 57 435 84 63822 1 385 62977 1	24207 24318 57); I <sup>2</sup> = 1 113 848 153 25563 816 24207	100.0% 0% Weight IV 16.4% 16.8% 16.5% 16.8% 16.6% 16.8%	1.81 [1.48, 2.21] 1.83 [1.50, 2.23] Odds Ratio Random, 95% C1 1.02 [0.60, 1.72] 1.38 [114, 1.66] 1.25 [0.80, 1.97] 0.06 [0.05, 0.07] 1.08 [0.72, 1.61] 1.09 [0.94, 1.28]		Control Ep Odds Ratio	10 ilepsy	100
0	Masri et al (2006) Whitehead et al (2006) Total (95% C) Total events Heterogeneity: Tau' = 0.0 Test for overall effect. Z = <u>Study or Subgroup</u> Burton et al (2017) Gurnisitza et al (2021) McDarmot et al (2010) McDarmot et al (2010) McDarmot et al (2010) Total (95% C) Total (95% C)	115 1 ; 128 0; Chi <sup>z</sup> = 0.3 6.02 ( <i>P</i> < 0. Epiteps; Events 1 57 477 93 126 2 ) 54 343 343 4 1150	648 703 83, df = 000001) y Fotal E 112 805 154 2185 154 2185 154 2185 140 648 4014	13255 1 13268 1 1 (P = 0. Contro Svents 57 435 84 63822 1 385 62977 1 227760	24207 24318 57); I <sup>P</sup> =	100.0% 0% Weight IV 16.4% 16.8% 16.8% 16.8% 16.8% 16.8% 16.8%	1.81 [1.48, 2.21] 1.83 [1.50, 2.23] Odds Ratio Random, 95% CI 1.02 (0.60, 1.72] 1.38 [114, 1.68] 1.25 (0.80, 1.97] 0.06 [0.05, 0.07] 1.08 [0.72, 1.81]		Control Ep Odds Ratio	liepsy	100
0	Masri et al (2006) Whitehead et al (2006) Total (95% CI) Total events Heterogenehr, Tau" = 0.0 Test for overall effect Z = <u>Brutha et al (2017)</u> Granu et al (2017) Granu et al (2017) McDemorth et al (2010) Mung'ala-Odera et al (2006) Total (95% CI)	115 1 128 128 10; Chi <sup>2</sup> = 0.3 6.02 (P < 0. Epileps; Events 1 6.7 477 93 128 2 128 2 4 4 150 2 Chi <sup>2</sup> = 777 52 Chi <sup>2</sup> = 175 2 150 2	648 703 83, df = 000001) y Fotal E 112 805 154 2185 154 2185 154 2185 140 648 4014	13255 1 13268 1 1 (P = 0. Contro Svents 57 435 84 63822 1 385 62977 1 227760	24207 24318 57); I <sup>P</sup> =	100.0% 0% Weight IV 16.4% 16.8% 16.8% 16.8% 16.8% 16.8% 16.8%	1.81 [1.48, 2.21] 1.83 [1.50, 2.23] Odds Ratio Random, 95% C1 1.02 [0.60, 1.72] 1.38 [114, 1.66] 1.25 [0.80, 1.97] 0.06 [0.05, 0.07] 1.08 [0.72, 1.61] 1.09 [0.94, 1.28]	IV.	Control Ep Odds Ratio Random, 95% CI	10 ilepsy 0 100	100
	Masri et al (2006) Whitehead et al (2006) Total (95% C) Total events Heterogeneity Tau <sup>2</sup> = 0.0 Test for overall effect Z = <u>Study or Subgroup</u> Burton et al (2012) Carau et al (2007) Ourniseriza et ol (2021) Morg also 26% et al (2006) Whitehead et al (2006) Whitehead et al (2006) Total events Heterogeneity: Tau <sup>2</sup> = 2,41;	115 1 128 0; ChP = 0.3 0; ChP = 0.3 Events 1 57 477 93 126 2 54 343 1150 ChP = 777.52 56 (P = 0.58)	648 703 83, df = 000001) y Fotal E 112 805 154 2185 154 2185 154 2185 140 648 4014	13255 1 13268 1 (P = 0. Contro Contro Contro Contro Second 1 (P = 0. Contro Second 1 (P = 0.00) (P < 0.00) (P < 0.00) Contro Second Co	24207 24318 57); I <sup>P</sup> =	100.0% 0% 16.4% 16.8% 16.3% 16.8% 16.8% 16.8% 16.8% 18.8% 100.0% 99%	1.81 [1.48, 2.21] 1.83 [1.50, 2.23] Odds Ratio <u>Randem, 95% C1</u> 1.30 [1.41, 1.80] 1.30 [1.41, 1.80] 1.30 [1.41, 1.80] 1.30 [1.41, 1.80] 1.30 [1.41, 1.80] 0.01 [0.94, 1.28] 0.01	N.	Control Ep Odds Ratio Random, 95% Cl	ilepsy	100
0	Masri et al (2006) Whitehead et al (2006) Total (95% CI) Total events Heterogeneity Tau" = 0.0 Test for overall effect Z = <u>Study or Subgroup</u> Burdon et al (2017) Gurnis et al (2007) Gurnisitza et al (2021) McDamothe al (2010) Mungriab-Odera et al (2006) Total (95% CI) Total events Heterogeneity: Tau" = 2.41; Test for overall effect Z = 0.5 Study or Subgroup	115 1 128 0; Chi <sup>2</sup> = 0.3 0; Chi <sup>2</sup> = 0.3 Epileps; Events 1 57 477 93 128 : 150 Chi <sup>2</sup> = 777 52 55 (P = 0.58) Epilepsy Events 1 Epilepsy	703 703 33, df = 112 805 154 2185 110 848 110 848 110 848 110 848 110 848 110 848 110 848 848 110 848 110 848 110 848 848 110 848 848 110 848 848 848 848 848 848 848 848 848 84	13255 1 13268 1 (P = 0. Control Vents 57 435 84 385 62977 1 2 27760 (P < 0.000 Control ents	24207 24318 57);  * = 113 848 153 25563 816 24207 51700 001);  * = Total W	100.0% 0% Weight IV 16.4% 16.5% 16.5% 16.8% 16.8% 16.8% 16.8% 99% Veight IV,	1.81 [1.48, 2.21] 1.83 [1.50, 2.23] Odds Ratio (Randem, 95% Cl 1.28 [1.41, 1.80] 1.29 [1.00, 1.72] 1.30 [1.41, 1.80] 1.29 [1.00, 1.97] 0.09 [1.02, 1.51] 0.09 [1.02, 1.52] 0.01 Odds Ratio 0.01 Odds Ratio	IV.	Control Ep Odds Ratio Random, 95% CI	ilepsy	100
0	Masri et al (2006) Whitehead et al (2006) Total (95% CI) Total events Heterogeneity Tau <sup>2</sup> = 0.0 Test for overall effect Z = Study or Subgroup Button et al (2017) Genue tet al (2007) Genue tet al (2007) MuCpernot et al (2010) MuCpernot et al (2010) Mucperson et al (2010) Mucperson et al (2010) Total events Heterogeneity: Tau <sup>2</sup> = 2.41; Test for overall effect Z = 0.5 Study or Subgroup Button et al (2017) Cansu et al (2007)	115 1 128 128 10; Chi <sup>2</sup> = 0.2 Epileps; Events 1 477 93 126 54 343 145 Chi <sup>2</sup> = 777 52 55 ( <i>P</i> = 0.58) Epilepsy Events To 57 1 477 8	648         1           703         ,           33, df =         ,           900001)         ,           y         r           112         ,           905         154           154         110           848         110           848         110           4014         1           4, df = 5         ,           905         ,           112         ,           303, df = 5         ,	13255 1 13268 1 (P = 0. Control Vents 57 435 84 63822 1 385 62977 1 2 27760 (P < 0.000 Control ents 57 435 62977 1 2 27760 (P < 0.000 Control 57 435 62977 1 2 27760 (P < 0.000 Control 57 435 62977 1 2 27760 (P < 0.000 Control 57 435 62977 1 2 27760 (P < 0.000 Control 435 62977 1 2 27760 (P < 0.000 Control 435 62977 1 2 27760 (P < 0.000 Control 435 62977 1 2 27760 (P < 0.000 Control 435 62977 1 2 27760 57 435 62977 1 2 27760 57 435 57 435 62977 1 2 27760 57 435 57 435 62977 1 2 27760 57 435 57 435 57 435 57 435 57 435 57 435 57 435 57 435 57 435 57 435 57 57 435 57 435 57 57 435 57 57 57 57	24207 24318 57);   <sup>#</sup> = 1 113 848 816 24207 51700 51700 5070;   <sup>#</sup> = 113 848 846 24207 51700 113 848 848 848 848 848 848 848 84	100.0% 0% Weight IV 16.4% 16.8% 16.8% 16.8% 16.8% 16.8% 99% Veight IV. 18.8%	1 81 [1 48, 2.21] 1.83 [1.50, 2.23] Odds Ratio Random, 95% CI 1.36 [14, 1.68] 1.59 [0.24, 1.28] 0.06 [0.05, 0.07] 1.36 [14, 1.68] 0.70 [0.20, 2.45] 0.70 [0.20, 2.45] 0.71 [0.20, 0.72] 1.28 [1.4], 1.68] 0.71 [0.20, 0.72] 1.28 [1.4], 1.68]	IV.	Control Ep Odds Ratio Random, 95% Cl	ilepsy	100
0	Masri et al (2006)           Whitehead et al (2006)           Violal events           Heterogeneity: Tau" = 0.0           Test for overall effect Z =           Study or Subgroup           Burton et al (2012)           Carsia et al (2007)           Carsia et al (2017)           Carsia et al (2017)           Mung also-Gerra et al (2006)           Total event et al (2017)           Mung also-Gerra et al (2006)           Total event et al (2017)           Total event et al (2016)           Total event et al (2017)           Burton et al (2012)           Burton et al (2012)           Gurmisute at et (2021)	115           128           0; Chi² = 0; Si 20; (P < 0;	Addition	$\begin{array}{c} 13255 & 1 \\ 13268 \\ 1 & (P = 0. \\ \hline \\ $	24207 24318 57);  * = 1 113 840 816 25563 816 24207 51700 0001);  * = Total W 113 848 316 24207	100.0% 0% 16.4% 16.3% 16.5% 16.8% 16.8% 16.8% 16.8% 16.8% 16.8% 18.8% 18.8% 18.8% 18.8% 18.8% 18.8% 19.6% 10.4% 10.5% 10.5% 10.4% 10.8	1.81 [1.48, 2.21] 1.83 [1.50, 2.23] Odds Ratio <u>Random, 95% C1</u> 1.36 [1.41, 1.60] 1.25 [0.00, 1.72] 1.36 [1.41, 1.60] 1.06 [10.55, 0.07] 1.08 [10.54, 1.78] 0.01 0.040 Ratio 0.01 0.	IV.	Control Ep Odds Ratio Random, 95% Cl	ilepsy	100
0	Masri et al (2006) Whitehead et al (2006) Total (95% CI) Total events Heterogeneity Tau <sup>2</sup> = 0.0 Test for overall effect Z = <u>Study or Subgroup</u> Burton et al (2017) Cansu et al (2007) Gurnisitza et el (2021) McDaronto et al (2010) McDaronto et al (2010) Total (95% CI) Total events Heterogoneity, Tau <sup>2</sup> = 2.41; Test for overall effect Z = 0.5 <u>Study or Subgroup</u> Burton et al (2017) Cansu et al (2007) Gurnisitza et el (2021) Cansu et al (2007) Gurnisitza et el (2021) Cansu et al (2007) Gurnisitza et el (2021) Comenta et al (2007) Study or Subgroup	115 128 128 10; Chi <sup>≠</sup> = 0.3 6.02 (P < 0. Epilepsy Events 1 54 77 93 128 54 1150 Chi <sup>≠</sup> = 777 52 55 (P = 0.56) Epilepsy Events Te 57 T 1 477 83 14 15 54 57 57 57 53 54 57 57 53 54 57 57 57 57 57 57 57 57 57 57	visit         visit <thvisit< th="">         visit         <thv< td=""><td>13255 1 13268 1 (P = 0. Control Vents 57 435 84 63822 1 385 62977 1 2 27760 (P &lt; 0.000 Control ents 57 435 62977 1 2 27760 (P &lt; 0.000 Control 57 435 62977 1 2 27760 (P &lt; 0.000 Control 57 435 62977 1 2 27760 (P &lt; 0.000 Control 57 435 62977 1 2 27760 (P &lt; 0.000 Control 435 62977 1 2 27760 (P &lt; 0.000 Control 435 62977 1 2 27760 (P &lt; 0.000 Control 435 62977 1 2 27760 (P &lt; 0.000 Control 435 62977 1 2 27760 57 435 62977 1 2 27760 57 435 57 435 62977 1 2 27760 57 435 57 435 62977 1 2 27760 57 435 57 435 57 435 57 435 57 435 57 435 57 435 57 435 57 435 57 435 57 57 435 57 435 57 57 435 57 57 57 57</td><td>24207 24318 57);  <sup>a</sup> = 1 113 848 153 825563 816 24207 51700 0001);  <sup>a</sup> = 113 848 153 816</td><td>100.0% 0% Weight IV 16.4% 16.8% 16.8% 16.8% 100.0% 99% Weight IV, 1.8% 5.9% 7.6% 10.4%</td><td>1.81 [1.48, 2.21] 1.83 [1.50, 2.23] Odds Ratio (Randem, 95% Cl 1.30 [1.41, 1.80] 1.30 [1.41, 1.80] 1.30 [1.41, 1.80] 1.30 [1.41, 1.80] 0.70 [0.20, 2.45] 0.01 Odds Ratio Random, 95% Cl 1.30 [1.41, 1.60] 1.30 [1.41, 1.40] 1.30 [1.41, 1.40] 1.30 [1.41, 1.40] 1.30 [1</td><td>IV.</td><td>Control Ep Odds Ratio Random, 95% Cl</td><td>ilepsy</td><td>100</td></thv<></thvisit<>	13255 1 13268 1 (P = 0. Control Vents 57 435 84 63822 1 385 62977 1 2 27760 (P < 0.000 Control ents 57 435 62977 1 2 27760 (P < 0.000 Control 57 435 62977 1 2 27760 (P < 0.000 Control 57 435 62977 1 2 27760 (P < 0.000 Control 57 435 62977 1 2 27760 (P < 0.000 Control 435 62977 1 2 27760 (P < 0.000 Control 435 62977 1 2 27760 (P < 0.000 Control 435 62977 1 2 27760 (P < 0.000 Control 435 62977 1 2 27760 57 435 62977 1 2 27760 57 435 57 435 62977 1 2 27760 57 435 57 435 62977 1 2 27760 57 435 57 435 57 435 57 435 57 435 57 435 57 435 57 435 57 435 57 435 57 57 435 57 435 57 57 435 57 57 57 57	24207 24318 57);   <sup>a</sup> = 1 113 848 153 825563 816 24207 51700 0001);   <sup>a</sup> = 113 848 153 816	100.0% 0% Weight IV 16.4% 16.8% 16.8% 16.8% 100.0% 99% Weight IV, 1.8% 5.9% 7.6% 10.4%	1.81 [1.48, 2.21] 1.83 [1.50, 2.23] Odds Ratio (Randem, 95% Cl 1.30 [1.41, 1.80] 1.30 [1.41, 1.80] 1.30 [1.41, 1.80] 1.30 [1.41, 1.80] 0.70 [0.20, 2.45] 0.01 Odds Ratio Random, 95% Cl 1.30 [1.41, 1.60] 1.30 [1.41, 1.40] 1.30 [1.41, 1.40] 1.30 [1.41, 1.40] 1.30 [1	IV.	Control Ep Odds Ratio Random, 95% Cl	ilepsy	100
0	Masri et al (2006) Whitehead et al (2006) Total (95% CI) Total events Heterogeneity: Tau" = 0.0 Test for overall effect. Z = <u>Study or Subgroup</u> Burton et al (2017) Cansu et al (2007) Gumisitza et el (2021) Mul grain-Odera et al (2010) Total events Heterogeneits: Tau" = 2.41; Test for overall effect. Z = 0.5 <u>Study or Subgroup</u> Burton et al (2010) Cansu et al (2007) Cansu et al (2007)	$\begin{array}{c} 115 \\ 128 \\ 0; Chl^{2} = 0.3 \\ 6.02 \ (P < 0. \\ \hline \\ $	off         off <thoff< th=""> <thoff< th=""> <thoff< th=""></thoff<></thoff<></thoff<>	13255         1           1         1           1         1           1         1           1         1           2         1           1         1           1         1           1         1           2         1           57         1           58         2           84         385           82977         1           2         2           2         7           2         2           385         2           395         2           395         3           395         3           395         3           395         3           395         3           395         3           395         3           395         3           393         3           393         3           393         3           393         3           393         3           393         3           393         3           393         3	24207 24318 57);   <sup>2</sup> = 1 113 848 25563 816 24207 51700 0001);   <sup>2</sup> = 7 7 7 7 7 7 8 8 8 8 8 8 8 8 8 8 8 8 8	100.0% 0% Weight IV 16.4% 16.8% 16.8% 16.8% 100.0% 99% Weight IV, 1.8% 5.9% 7.6% 10.4%	1.81 [1.48, 2.21] 1.83 [1.50, 2.23] Odds Ratio Random, 95%C1 1.30 [1.41, 1.60] 1.30 [1.41, 1.60] 1.30 [1.41, 1.60] 1.30 [1.41, 1.60] 1.30 [1.41, 1.60] 1.30 [1.41, 1.60] 0.61 [0.50, 0.77] 1.08 [0.27, 1.61] 0.70 [0.20, 2.45] 0.71 1.23 [0.20, 1.57] 1.25 [0.80, 1.57] 1.25 [0.80, 1.57]	IV.	Control Ep Odds Ratio Random, 95% Cl	ilepsy	100

Fig. 5 (See legend on previous page.)

Table 2 Summary	related and non-related variables for epilepsy onset in childhood and adolescen	nce

Prenatal conditions			
Variables	Related	Non-related	Pooled OR [95% CI]
Preterm birth	×		4.36 [95% Cl: 1.26-15.09]
Post-term birth		×	0.52 [95% Cl: 0.16-1.77]
Smoking during pregnancy	×		1.28 [95% Cl:1.1-1.49],
Maternal epilepsy	×		2.06 [95% Cl:1.26-3.36]
Eclampsia	×		16.9 [95% Cl: 2.05–139.53]
Pregnancy metrorrhagia	×		2.24 [95% Cl: 1.36-3.71]
Maternal infection	X		1.28 [95% Cl: 1.17-1.41]
Gestational diabetes		×	1.29 [95% Cl: 0.86-1.96]
Hypertension		×	1.17 [95% Cl: 0.64–2.14]
Preeclampsia		×	0.69 [95% Cl: 0.42-1.13]
Maternal age		×	0.93 [95% Cl: 0.79–1.10]
Newborn delivery conditions			
Variables	Related	Non-related	Pooled OR [95% CI]
Cord prolapses	×		2.58 [95% Cl: 1.25-5.32]
Prolonged labor >6 h	×		6.74 [95% Cl: 3.57-12.71]
Cesarean section		×	1.06 [95% Cl: 0.86-1.29]
Forceps		×	1.06 [95% Cl: 0.86-1.29]
Breech presentation		×	1.21 [95% Cl: 0.87-1.68]
Meconium		×	0.89 [95% Cl: 0.73-1.09]
Postnatal factors			
Variables	Related	Non-related	Pooled OR [95% CI]
Head trauma	×		2.31 [95% Cl: 1.54–3.48]
Birth complications	×		3.91 [95% Cl: 2.43-6.29]
Low birth weight (< 2.5 kg)	×		1.83 [95% Cl: 1.5-2.23]
Gender	×		1.18 [95% Cl: 1.06-1.32]

OR odds ratio, Cl confidence interval

contribute to premature birth and low-weight birth, which, in turn, can lead to frequent newborn infections and complications. Additionally, maternal infection can be linked to cord prolapse and prolonged labor. A better understanding of these factors is critical for advancing effective preventive and treatment measures to reduce the likelihood of epilepsy.

While our study is novel and represents the first meta-analysis on prenatal, delivery and postnatal factors, it has some limitations. First, our research included 25 studies with various study designs. Second, some data were unavailable, such as the exact term and the quantity or severity of pregnancy metrorrhagia, which prevented us from establishing a stronger relationship between these factors and epilepsy onset. Furthermore, the inclusion and exclusion criteria varied across the studies. The age of children/adolescents included in different studies ranged from 0 to 20 years, potentially introducing bias. Third, our study only examined children and adolescents, excluding adults. It is essential to acknowledge that the factors we examined may have implications for epilepsy in adult-hood [60, 61].

# Conclusions

Epilepsy onset in children or adolescents is related to multiple and complex factors, according to the pregnancy and postnatal characteristics. Among these factors, eclampsia is the strongest prenatal risk factor, prolonged labor is the strongest delivery factor and child infection is the most influential postnatal factor. These findings call for improved awareness about these factors. Further studies are required to understand the physiological mechanisms underlying each of these factors.

## Abbreviations

NOS Newcastle-Ottawa quality assessment scale

OR Odds ratio

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

# **Supplementary Information**

The online version contains supplementary material available at https://doi. org/10.1186/s42494-023-00143-2.

#### Additional file 1.

#### Acknowledgements

Not applicable.

#### Authors' contributions

Imen Ketata: study design, methodology, literature search, data extraction, statistical analysis and interpretation, quality assessment, draft writing, and final approval of manuscript. Emna Ellouz: methodology, literature search, reevaluation of the article if there are different opinions, quality assessment, draft review and editing, supervision and validation, and final approval of manuscript. Rahil Mizouri: literature search, quality assessment, draft writing, final approval of manuscript, and screening for eligibility.

#### Funding

No funding was received to assist with the preparation of this manuscript.

#### Availability of data and materials

Data are available from the corresponding author upon reasonable request.

#### Declarations

**Ethics approval and consent to participate** Not applicable.

#### Consent for publication

Not applicable.

#### **Competing interests**

All authors declare that they have no conflict of interest.

Received: 19 September 2023 Accepted: 28 November 2023 Published online: 02 January 2024

#### References

- Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55:475–82.
- 2. Beghi E. The epidemiology of epilepsy. Neuroepidemiology. 2020;54:185–91.
- Miller N, Ehrenstein V, Nielsen RB, Bakketeig LS, Sørensen HT. Maternal use of antibiotics, hospitalisation for infection during pregnancy, and risk of childhood epilepsy: a population-based cohort study. PLoS ONE. 2012;7:e30850.
- Christensen J, Vestergaard M, Pedersen MG, Pedersen CB, Olsen J, Sidenius P. Incidence and prevalence of epilepsy in Denmark. Epilepsy Res. 2007;76:60–5.
- Daoud AS, Batieha A, Bashtawi M, El-Shanti H. Risk factors for childhood epilepsy: a case-control study from Irbid. Jordan Seizure. 2003;12:171–4.
- Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. Epilepsia. 1993;34:453–68.
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372: n71.
- Sidik K, Jonkman JN. Robust variance estimation for random effects metaanalysis. Comput Stat Data Anal. 2006;50(12):3681–701.
- van Aert RCM, Wicherts JM, van Assen MALM. Publication bias examined in meta-analyses from psychology and medicine: a meta-meta-analysis. PLoS ONE. 2019;14(4):e0215052.

- Sterne JAC, Harbord RM, Sutton AJ, Jones DR, Ioannidis JP, Terrin N, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;343(7818):1–8.
- Ae-Ngibise KA, Akpalu B, Ngugi A, Akpalu A, Agbokey F, Adjei P, et al. Prevalence and risk factors for active convulsive epilepsy in kintampo. Ghana Pan Afr Med J. 2015;21:29.
- Ngugi AK, Bottomley C, Kleinschmidt I, Wagner RG, Kakooza-Mwesige A, Ae-Ngibise K, et al. Prevalence of active convulsive epilepsy in sub-Saharan Africa and associated risk factors: cross-sectional and case-control studies. Lancet Neurol. 2013;12:253–63.
- Sun Y, Vestergaard M, Christensen J, Nahmias AJ, Olsen J. Prenatal exposure to maternal infections and epilepsy in childhood: a populationbased cohort study. Pediatrics. 2008;121:e1100–7.
- 14. Asadi-Pooya AA, Hojabri K. Risk factors for childhood epilepsy: a casecontrol study. Epilepsy Behav. 2005;6:203–6.
- Malmqvist O, Ohlin A, Ågren J, Jonsson M. Seizures in newborn infants without hypoxic ischemic encephalopathy - antenatal and laborrelated risk factors: a case-control study. J Matern Fetal Neonatal Med. 2020;33:799–805.
- McDermott S, Mann JR, Wu J. Maternal genitourinary infection appears to synergistically increase the risk of epilepsy in children of women with epilepsy. Neuroepidemiology. 2010;34:117–22.
- Krebs L, Langhoff-Roos J. The relation of breech presentation at term to epilepsy in childhood. Eur J Obstet Gynecol Reprod Biol. 2006;127:26–8.
- Hirvonen M, Ojala R, Korhonen P, Haataja P, Eriksson K, Gissler M, et al. The incidence and risk factors of epilepsy in children born preterm: a nationwide register study. Epilepsy Res. 2017;138:32–8.
- Odd D, Glover Williams A, Winter C, Draycott T. Associations between early term and late/post term infants and development of epilepsy: a cohort study. PLoS ONE. 2018;13:e0210181.
- Whitehead E, Dodds L, Joseph KS, Gordon KE, Wood E, Allen AC, et al. Relation of pregnancy and neonatal factors to subsequent development of childhood epilepsy: a population-based cohort study. Pediatrics. 2006;117:1298–306.
- Chou IC, Sung FC, Hong SY. Incidence of epilepsy in children born prematurely and small for gestational age at term gestation: A populationbased cohort study. J Paediatr Child Health. 2020;56:324–9.
- Burton KJ, Rogathe J, Whittaker R, Mankad K, Hunter E, Burton MJ, et al. Epilepsy in Tanzanian children: association with perinatal events and other risk factors. Epilepsia. 2012;53(4):752–60.
- 23. Cansu A, Serdaroğlu A, Yüksel D, Doğan V, Ozkan S, Hirfanoğlu T, et al. Prevalence of some risk factors in children with epilepsy compared to their controls. Seizure. 2007;16:338–44.
- Cruz-Cruz MDR, Gallardo-Elías J, Paredes-Solís S, Legorreta-Soberanis J, Flores-Moreno M, Andersson N. Factores asociados a epilepsia en niños en México: un estudio caso-control [Factors associated with epilepsy in children in Mexico: a case-control study]. Bol Med Hosp Infant Mex. 2017;74(5):334–40.
- Attumalil TV, Sundaram A, Varghese VO, Vijayakumar K, Kunju PA. Risk factors of childhood epilepsy in Kerala. Ann Indian Acad Neurol. 2011;14:283–6.
- Chowdhury SH, Tabassum R, Tarannum R, Kabir S. Pregnancy related factors associated with epileptic & NonEpileptic children. IOSR J Dent Med Sci. 2020;19:19–25.
- 27. Kakooza-Mwesige A, Ndyomugyenyi D, Pariyo G, Peterson SS, Waiswa PM, Galiwango E, et al. Adverse perinatal events, treatment gap, and positive family history linked to the high burden of active convulsive epilepsy in Uganda: a population-based study. Epilepsia Open. 2017;2:188–98.
- Masri A, Badran E, Hamamy H, Assaf A, Al-Qudah AA. Etiologies, outcomes, and risk factors for epilepsy in infants: a case-control study. Clin Neurol Neurosurg. 2008;110(4):352–6.
- Mung'ala-Odera V, White S, Meehan R, Otieno GO, Njuguna P, Mturi N, et al. Prevalence, incidence and risk factors of epilepsy in older children in rural Kenya. Seizure. 2008;17(5):396–404.
- Kuenneth CA, Boyle C, Murphy CC, Yeargin-Allsopp M. Reproductive risk factors for epilepsy among ten-year-old children in metropolitan Atlanta. Paediatr Perinat Epidemiol. 1996;10:186–96.
- Maheshwari MC. Forceps delivery as a risk factor in epilepsy: a comparative prospective cohort survey. Acta Neurol Scand. 1990;81:522–3.

- Henderson M, Goldstein H, Rogot E, Goldberg ID, Entwisle G. Perinatal factors associated with epilepsy in Negro children. Public Health Rep. 1964;79:501–9.
- Gumisiriza N, Kugler M, Brusselaers N, Mubiru F, Anguzu R, Ningwa A, et al. Risk factors for nodding syndrome and other forms of epilepsy in Northern Uganda: a case-control study. Pathogens. 2021;10(11):1451.
- Thygesen SK, Olsen M, Pedersen L, Henderson VW, Østergaard JR, Sørensen HT. Respiratory distress syndrome in preterm infants and risk of epilepsy in a Danish cohort. Eur J Epidemiol. 2018;33:313–21.
- Li W, Peng A, Deng S, Lai W, Qiu X, Zhang L, et al. Do premature and postterm birth increase the risk of epilepsy? An updated meta-analysis. Epilepsy Behav. 2019;97:83–91.
- Berger R, Garnier Y, Jensen A. Perinatal brain damage: underlying mechanisms and neuroprotective strategies. J Soc Gynecol Investig. 2002;9:319–28.
- Berg A, Nickels K, Wirrell E, Geerts A, Callenbach P, Arts F, et al. Mortality risks in new-onset childhood epilepsy. Pediatrics. 2013;132:124–31.
- Guan H, Zhou P, Qi Y, Huang H, Wang J, Liu X. Cigarette smoke-induced trophoblast cell ferroptosis in rat placenta and the effects of L-arginine intervention. Ecotoxicol Environ Saf. 2022;243:114015.
- Zdravkovic T, Genbacev O, McMaster MT, Fisher SJ. The adverse effects of maternal smoking on the human placenta: a review. Placenta. 2005;26:S81–6.
- Rong L, Frontera AT Jr, Benbadis SR. Tobacco smoking, epilepsy, and seizures. Epilepsy Behav. 2014;31:210–8.
- Ekblad M, Korkeila J, Parkkola R, Lapinleimu H, Haataja L, Lehtonen L, et al. Maternal smoking during pregnancy and regional brain volumes in preterm infants. J Pediatr. 2010;156(2):185–90.
- 42. Falk L, Nordberg A, Seiger A, Kjaeldgaard A, Hellstrom-Lindahl E. Smoking during early pregnancy affects the expression pattern of both nicotinic and muscarinic acetylcholine receptors in human first trimester brainstem and cerebellum. Neuroscience. 2005;132:389–97.
- Dreier JW, Ellis CA, Berkovic SF, Cotsapas C, Ottman R, Christensen J. Epilepsy risk in offspring of affected parents; a cohort study of the "maternal effect" in epilepsy. Ann Clin Transl Neurol. 2021;8(1):153–62.
- 44. Berkovic SF, Scheffer IE. Genetics of the epilepsies. Epilepsia. 2001;42:16–23.
- Rocca WA, Sharbrough FW, Hauser WA, Annegers JF, Schoenberg BS. Risk factors for absence seizures: a population-based case-control study in Rochester. Minnesota Neurology. 1987;37(8):1309–14.
- Casetta I, Monetti VC, Malagù S, Paolino E, Govoni V, Fainardi E, et al. Risk factors for cryptogenic and idiopathic partial epilepsy: a community-based case-control study in Copparo. Italy Neuroepidemiology. 2002;21(5):251–4.
- Glass HC, Pham TN, Danielsen B, Towner D, Glidden D, Wu YW. Antenatal and intrapartum risk factors for seizures in term newborns: a populationbased study, California 1998–2002. J Pediatr. 2009;154(1):24–8.
- Kieslich M, Jacobi G. Incidence and risk factors of posttraumatic epilepsy in childhood. Lancet. 1995;345(21):187.
- Serdaroğlu A, Ozkan S, Aydin K, Gücüyener K, Tezcan S, Aycan S. Prevalence of epilepsy in Turkish children between the ages of 0 and 16 years. J Child Neurol. 2004;19(4):271–4.
- Reddy DS, Thompson W, Calderara G. Molecular mechanisms of sex differences in epilepsy and seizure susceptibility in chemical, genetic and acquired epileptogenesis. Neurosci Lett. 2021;750:135753.
- 51. Savic I, Engel J Jr. Structural and functional correlates of epileptogenesis does gender matter? Neurobiol Dis. 2014;70:69–73.
- 52. Lenz KM, McCarthy MM. A starring role for microglia in brain sex differences. Neuroscientist. 2015;21(3):306–21.
- Morizawa Y, Sato K, Takaki J, Kawasaki A, Shibata K, Suzuki T, et al. Cellautonomous enhancement of glutamate-uptake by female astrocytes. Cell Mol Neurobiol. 2012;32(6):953–6.
- Luders E, Gaser C, Narr KL, Toga AW. Why sex matters: brain size independent differences in gray matter distributions between men and women. J Neurosci. 2009;29(45):14265–70.
- McGrath MM, Sullivan MC, Lester BM, Oh W. Longitudinal neurologic follow-up in neonatal intensive care unit survivors with various neonatal morbidities. Pediatrics. 2000;106(6):1397–405.
- 56. Graham HK, Rosenbaum P, Paneth N, Dan B, Lin JP, Damiano DL, et al. Cerebral palsy. Nat Rev Dis Primers. 2016;2:15082.

- Ahlers FS, Benros ME, Dreier JW, Christensen J. Infections and risk of epilepsy in children and young adults: a nationwide study. Epilepsia. 2019;60(2):275–83.
- Vezzani A, Fujinami RS, White HS, Preux PM, Blümcke I, Sander JW, et al. Infections, inflammation and epilepsy. Acta Neuropathol. 2016;131(2):211–34.
- Yang G, Zou LP, Wang J, Shi X, Tian S, Yang X, et al. Neonatal hypoglycemic brain injury is a cause of infantile spasms. Exp Ther Med. 2016;11(5):2066–70.
- 60. Scher MS. Prenatal contributions to epilepsy: lessons from the bedside. Epileptic Disord. 2003;5(2):77–91.
- Watila MM, Balarabe SA, Komolafe MA, Igwe SC, Fawale MB, Otte WM, et al. Epidemiology of epilepsy in nigeria: a community-based study from 3 sites. Neurology. 2021;97(7):e728–38.

#### Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

#### At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

