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Perinatal adversities and risk of epilepsy after traumatic brain injury: A Danish nationwide cohort study

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Objectives: Traumatic brain injury (TBI) and perinatal adversities such as low gestational age at birth, low birth weight, low Apgar, and being born small for gestational age are well-established risk factors for epilepsy. We examined whether perinatal adversities modified the risk of epilepsy after TBI in a nationwide cohort study of Danish singletons born from 1982 to 2011.

Materials and Methods: We categorized perinatal adversities as a composite measure of preterm delivery, low birth weight, low Apgar score, or being born small for gestational age. Cox regression and competing risk regression were used to estimate the risk of epilepsy after TBI according to such perinatal adversities. The study included 1,715,095 singletons (51.1% males). The mean age at end of follow-up was 19.3 years (Interquartile range [IQR] = 12.1–26.3). During follow-up, 85,636 persons (58.2% males) sustained a TBI and 18,064 developed epilepsy (50.7% males), of whom 1329 persons had a preceding TBI.

Results: The hazard ratio (HR) of epilepsy in persons with perinatal adversities was 1.19 (95% confidence interval [CI] 1.15–1.24), compared to persons without. The HR of epilepsy in persons with TBI was 2.31 (95% CI 2.18–2.45) compared to persons without TBI, but this risk was not modified by perinatal adversities ($p = 0.2460$).

Conclusions: Perinatal adversities and TBI both increased the risk of epilepsy, but the risk of epilepsy after TBI was not modified by these perinatal adversities.

KEYWORDS
epilepsy, head injury, neuroepidemiology, seizures

1 | INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of acquired epilepsy.[1–3] Injury severity,[3] type, and location of the injury[4,5] are critical risk factors for epilepsy after TBI, but other characteristics and conditions, such as sex, age, genetics,[2] psychiatric co-morbidity, and preceding TBI[6] are all likely to influence the epileptogenic processes as well. Far from all contributions of personal traits are well understood. Perinatal adversities such as low birth weight, low gestational age at birth, low Apgar score, and being born small for gestational age are well-known risk factors for the development of epilepsy,[7–15] but the impact of these factors on the risk of epilepsy and other neurological conditions among persons who have suffered TBI has not previously been studied. Related studies on the cognitive sequelae following TBI suggested that recovery following TBI was attenuated in low birth weight children compared with normal birth weight children[16] and that children with underlying neurodevelopmental disorders experienced prolonged trajectories of mild TBI with respect to the severity of symptoms.[17] This suggests that such perinatal adversities may increase the brain's vulnerability to subsequent neurologic

insults, and in particular TBI. However, it remains unknown whether such perinatal adversities and TBI act independently of each other on the risk of epilepsy, or if adverse perinatal outcomes modify the risk of epilepsy after TBI.

In this nationwide register-based cohort study, we explored whether the risk of epilepsy after TBI was modified by perinatal adversities including low birth weight, short gestational age, low Apgar score, and being born small for gestational age. This association was further examined according to severity of and age at TBI.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

We identified 1,794,360 singletons born in Denmark between January 1, 1982 and December 31, 2011 with a known mother who were alive and residing in Denmark on their 5th birthday. Personal identification numbers of focal persons and their parents were identified using the Danish Civil Registration System.[18,19] These individual numbers were used for inter-register linkage. Persons diagnosed with either epilepsy (N = 9907) or TBI (N = 39,092) before the age of five years were excluded. Furthermore, we excluded persons with missing information of either birth weight, gestational age at birth or Apgar score five minutes after birth (N = 29,683), with a registered gestational age at birth lower than 22 weeks (N = 75) and higher than 45 weeks (N = 133), and children with an improbably high birth weight (more than three standard deviations) according to their gestational age in weeks 22–33 (N = 375).[20] The final population included 1,715,095 persons (51.1% males).

2.2 | Birth weight, gestational age, and Apgar score

Information on gestational age at birth, birth weight, and Apgar score at five minutes after birth was obtained from the Danish Medical Birth Registry, which contains records on all Danish births since 1973.[21] Persons were characterized with *preterm birth* if they were born before gestational week 37, with *low birth weight* if they were born lighter than 2500 *g*, with *low Apgar score* if the Apgar score was lower than 7, and *small for gestational age* based on the distribution of sex- and gestational age-specific z-scores in the full sample, if their z-score was below the 10th percentile.[9,22] We defined a composite measure of *any adverse perinatal outcome* if persons were either born preterm, with a low birth weight, with a low Apgar score, or small for gestational age.

2.3 | Traumatic brain injury

TBI diagnoses were identified from the Danish National Patient Registry, which holds information on all inpatient hospitalizations from 1977 and all outpatient and emergency room contacts from 1995.[23] Prior to January 1, 1994, diagnoses were registered according to the International Classification of Diseases, eighth revision (ICD-8), and subsequently according to the tenth revision (ICD-10). Similar to our previous studies,[2,6] subjects were classified with mild TBI (ICD-8:850.99; ICD-10:S060), skull fracture (ICD-8: 800, 801, and 803; ICD-10: S020, S021, S027, and S029), and severe TBI (ICD-8: 851-854; ICD-10: S061-S069) based on hospital diagnoses of TBI. TBI onset was defined as the first day of the first hospital contact with a TBI diagnosis. Persons with multiple diagnoses on the same hospital contact were characterized with the most severe diagnosis with regard to the risk of epilepsy.

2.4 | Epilepsy

The Danish National Patient Registry was used to classify subjects with epilepsy based on hospital diagnoses of epilepsy (ICD-8: 345, excluding 345.29; ICD-10: G40). Epilepsy onset was defined as the first day of the first hospital contact with an epilepsy diagnosis. Epilepsy diagnoses within two weeks of a TBI were ignored, because seizures occurring within the first two weeks after a TBI are considered the result of acute injury and by definition not epilepsy.[24]

2.5 | Statistical methods

Children were followed from their 5th birthday until onset of epilepsy, death, emigration from Denmark, or December 31, 2016, whichever came first. Cox regression models were used to estimate the hazard ratios (HR) of epilepsy after TBI according to the composite measure of adverse perinatal outcomes along with the corresponding 95% confidence intervals (CIs). HRs of epilepsy after TBI were further estimated according to any adverse perinatal outcome by strata of TBI severity and age at TBI. TBI was treated as a time-varying exposure. We used the *coxph* function in R with robust standard errors.[25] Age was used as the underlying time scale. Effect modification was evaluated on a multiplicative scale using Wald tests and on an additive scale using the relative excess risk of interaction (RERI).[26] Confidence intervals of the latter were calculated using the delta method.[27] Regression models were adjusted for calendar year, maternal age at delivery (continuous), maternal education at birth (lower, medium, higher, and missing), maternal civil status at birth (married, unmarried, divorced, and widowed), psychiatric comorbidity (ICD-8:290-315.99; ICD-10: F00-F99), parental epilepsy, maternal hypertension (ICD-8: 637.00; ICD-10: O13, O16), and preeclampsia during pregnancy (ICD-8: 637.03, 637.04, 637.09; ICD-10: O141-O143, O149, O15), congenital malformations of the nervous system (ICD-8: 740-743; ICD-10: Q00-Q07), cerebral palsy (ICD-8: 343, ICD-10: G80-G83), and were stratified by sex. Maternal covariates and sex were treated as time-invariant, whereas the remaining covariates were treated as time-varying.

The 20-year cumulative incidence of epilepsy after TBI was estimated according to adverse perinatal outcomes by means of

competing risk regression with death and emigration as competing events and time since TBI as the underlying time scale. In order to estimate the cumulative incidence of epilepsy among persons without TBI, we used exposure density sampling[28] to sample controls (5:1) who did not have a TBI at the date of TBI in the index person, but had a similar distribution of sex and age (year of birth).

2.6 | Sensitivity analyses

The risk of epilepsy after TBI may differ according to the individual adverse perinatal risk factors, and we estimated this risk according to preterm delivery, low birth weight, low Apgar score, and being born small for gestational age, respectively.

The risk of epilepsy is inversely associated with gestational age at birth, birth weight, and Apgar score. We examined if the risk of epilepsy after TBI was modified by different levels of gestational age at birth (weeks <33, 33–36, 37–38, 39–41, and ≥42), birth weight (<2000 g, 2000–2499 g, 2500–2,999 g, 3000–3999 g, and ≥4000 g), and Apgar scores (<7, 7–8, 9, and10). Wald tests were performed to test for equality of the risk of epilepsy after TBI according to levels of each risk factor.

3 | RESULTS

The study population was followed for a total of 24,797,809 person years. The median age at the end of follow-up was 19.3 years (Interquartile range [IQR] = 12.1–26.3). During follow-up, 85,636 persons (58.4% males) sustained a TBI and 18,064 developed epilepsy (50.7% males). At end of follow-up, 1329 persons had developed epilepsy after a TBI. Adverse perinatal outcomes were associated with both TBI and epilepsy; the differences were subtle with respect to TBI status and more pronounced with respect to epilepsy (Table 1). Other characteristics of the study population are shown in Table S1.

3.1 | Main results

The relative risk of epilepsy was higher in persons with adverse perinatal outcomes, than in persons without such perinatal adversities (HR 1.19, 95% CI 1.15–1.24, not presented in tables). Compared with persons without TBI, the relative risk of epilepsy was doubled in persons after a TBI (HR 2.31, 95% CI 2.18 to 2.45, not presented in tables). The risk of epilepsy after TBI was not modified by the composite measure of any adverse perinatal outcome neither on a multiplicative ($p = .2460$) nor additive (RERI 0.05, 95% CI −0.32 to 0.42) scale (Table 2). The 20-year cumulative risk of epilepsy after TBI was higher in persons with both TBI and adverse perinatal outcomes, compared to persons with either or none of the conditions (Table 2).

The risk of epilepsy was higher after TBI in accord with the severity of said TBI (Table 3), but was not modified by the composite measure of any adverse perinatal outcome for either mild TBI ($p = .3381$, RERI 0.05, 95% CI −0.32 to 0.42), skull fracture ($p = 0.6608$, RERI −0.16, 95% CI −2.81 to 2.49), or severe TBI ($p = .5948$, RERI 0.23, 95% CI −1.93 to 2.38).

TABLE 1 Perinatal characteristics of the study population with respect to traumatic brain injury (TBI) and epilepsy in a population of 1,715,095 singletons born in Denmark (1982–2011)

	TBI		Epilepsy	
	No (N = 1,629,459)	Yes (N = 85,636)	No (N = 1,697,031)	Yes (N = 18,064)
Any adverse perinatal outcome				
Yes	235,831 (14.47%)	14,506 (16.94%)	246,760 (14.54%)	3,547(19.64%)
No	1,393,628 (85.53%)	71,130 (83.06%)	1,450,241 (85.46%)	14,517 (80.36%)
Preterm birth				
Yes	73,619 (4.52%)	3961 (4.63%)	76,494 (4.51%)	1086 (6.01%)
No	1,555,840 (95.48%)	81,675 (95.37%)	1,620,537 (95.49%)	16,978 (93.99%)
Low birth weight				
Yes	57,641 (3.54%)	3496 (4.08%)	60,116 (3.54%)	1021 (5.65%)
No	1,571,818 (96.46%)	82,140 (95.92%)	1,636,915 (96.46%)	17,043 (94.35%)
Low Apgar score				
Yes	10,691 (0.66%)	627 (0.73%)	11,067 (0.65%)	251 (1.39%)
No	1,618,768 (99.34%)	85,009 (99.27%)	1,685,964 (99.35%)	17,813 (98.61%)
Small for gestational age				
Yes	161,106 (9.89%)	10,524 (12.29%)	169,185 (9.97%)	2445 (13.54%)
No	1,468,353 (90.11%)	75,112 (87.71%)	1,527,846 (90.03%)	15,619 (86.46%)

Note: Tests for group level differences between exposure (TBI vs. no TBI) and outcome (epilepsy vs. no epilepsy) were significant for all perinatal characteristics ($p < .0001$)

TABLE 2 Risk of epilepsy after traumatic brain injury (TBI) according to the composite measure of any adverse perinatal outcome in a population of 1,715,095 singletons born in Denmark (1982–2011)

Any adverse perinatal outcome	Any TBI	IR (95% CI)	20-year cumulative incidence (95% CI)	Unadjusted HR (95% CI)[a]	Adjusted HR (95% CI)[b]	*p*-value[c]
No	No	0.67 (0.66–0.68)	1.16 (1.10–1.21)	Ref	Ref	–
	Yes	1.41 (1.33–1.50)	2.26 (2.09–2.42)	2.59 (2.43–2.76)	2.35 (2.20–2.51)	–
Yes	No	0.88 (0.85–0.91)	1.62 (1.46–1.77)	Ref	Ref	–
	Yes	1.75 (1.56–1.97)	2.80 (2.42–3.17)	2.45 (2.17–2.78)	2.17 (1.92–2.45)	.2460

Note: The relative excess risk of interaction (RERI) was 0.05 (95% CI −0.32 to 0.42).

Abbreviations: CI, Confidence interval; HR, Hazard ratio; IR, Incidence rate per 1000 person years; TBI, Traumatic brain injury.

[a]Models were adjusted for calendar year and stratified by sex.

[b]Models were further adjusted for parental epilepsy, maternal education and marital status at focal persons' birth, maternal age at birth, maternal hypertension and pre-eclampsia during pregnancy, cerebral palsy, congenital malformations of the nervous system, and psychiatric co-morbidity.

[c]Wald test for the interaction between any TBI and any adverse perinatal outcome.

TABLE 3 Risk of epilepsy after traumatic brain injury (TBI) according to the composite measure of any adverse perinatal outcome and TBI severity in a population of 1,715,095 singletons born in Denmark (1982–2011)

Any adverse perinatal outcome	TBI Severity	IR (95% CI)	20-year cumulative incidence (95% CI)	Unadjusted HR (95% CI)[a]	Adjusted HR (95% CI)[b]	*p*-value[c]
No	No TBI	0.67 (0.66–0.68)	1.16 (1.10–1.21)	Ref	Ref	–
	Mild TBI	1.28 (1.20–1.37)	2.07 (1.91–2.24)	2.34 (2.19–2.51)	2.15 (2.01–2.31)	–
	Skull fracture	1.93 (1.39–2.69)	2.67 (1.72–3.61)	3.69 (2.65–5.15)	3.40 (2.44–4.74)	–
	Severe TBI	3.64 (3.07–4.32)	5.33 (4.15–6.52)	6.96 (5.86–8.27)	5.17 (4.35–6.14)	–
Yes	No TBI	0.88 (0.85–0.91)	1.62 (1.46–1.77)	Ref	Ref	–
	Mild TBI	1.62 (1.42–1.83)	2.63 (2.24–3.02)	2.26 (1.98–2.58)	2.00 (1.75–2.28)	.3381
	Skull fracture	2.06 (1.03–4.12)	2.29 (0.58–3.99)	2.95 (1.47–5.90)	2.86 (1.43–5.73)	.6608
	Severe TBI	4.03 (2.88–5.64)	5.65 (3.58–7.71)	5.84 (4.16–8.19)	4.66 (3.32–6.54)	.5948

Note: The relative excess risk of interaction (RERI) with adverse perinatal outcomes was 0.05 (95% CI −0.32 to 0.42) for mild TBI, −0.16 (95% CI −2.81 to 2.49) for skull fracture, and 0.23 (95% CI −1.93 to 2.38) for severe TBI.

Abbreviations: CI, Confidence interval; HR, Hazard ratio; IR, Incidence rate per 1000 person years; TBI, Traumatic brain injury.

[a]Models were adjusted for calendar year and stratified by sex.

[b]Models were further adjusted for parental epilepsy, maternal education and marital status at focal persons' birth, maternal age at birth, maternal hypertension and pre-eclampsia during pregnancy, cerebral palsy, congenital malformations of the nervous system, and psychiatric co-morbidity.

[c]Wald test for the interaction between severity of TBI and any adverse perinatal outcome.

Table 4 depicts the risk of epilepsy after TBI according to age at TBI and adverse perinatal outcomes. For persons who sustained their first TBI between age 10 and 19, the relative risk of epilepsy after TBI was lower for persons with perinatal adversities than for persons without such adversities (p = 0.0465, RERI −0.25, 95% CI −0.75 to 0.25). There was no significant difference in the risk of epilepsy after TBI among the other age groups irrespective of any adverse perinatal outcomes.

3.2 | Sensitivity analyses

When examined individually for each of the included perinatal risk factors, the risk of epilepsy after TBI was lower for persons born preterm (p = .0224, RERI −0.45, 95% CI −0.99 to 0.09) and with low Apgar score (p = .0121, RERI −1.22, 95% CI −2.28 to −0.15), but not for persons with low birth weight (p = .5554, RERI 0.14, 95% CI −0.52 to 0.79) or born small for gestational age (p = .8199, RERI 0.16,

TABLE 4 Risk of epilepsy after traumatic brain injury (TBI) according to the composite measure of any adverse perinatal outcome and age at TBI in a population of 1,715,095 singletons born in Denmark (1982–2011)

Any adverse perinatal outcome	Age at TBI	IR (95% CI)	20-year cumulative incidence (95% CI)	Unadjusted HR (95% CI)[a]	Adjusted HR (95% CI)[b]	*p*-value[c]
No	No TBI	0.67 (0.66–0.68)	1.16 (1.10–1.21)	Ref	Ref	–
	5–9	1.27 (1.14–1.40)	2.28 (2.03–2.52)	2.00 (1.80–2.21)	1.85 (1.67–2.06)	–
	10–19	1.42 (1.30–1.54)	2.21 (1.96–2.47)	2.82 (2.58–3.08)	2.53 (2.32–2.77)	–
	20–39	1.97 (1.68–2.32)	NA	5.49 (4.64–6.50)	4.63 (3.91–5.48)	–
Yes	No TBI	0.88 (0.85–0.91)	1.62 (1.46–1.77)	Ref	Ref	–
	5–9	1.96 (1.64–2.34)	3.38 (2.76–4.01)	2.34 (1.95–2.81)	2.08 (1.74–2.50)	.2778
	10–19	1.54 (1.29–1.83)	2.58 (2.01–3.15)	2.33 (1.95–2.79)	2.07 (1.73–2.48)	.0465
	20–39	2.05 (1.47–2.86)	NA	4.32 (3.09–6.05)	3.55 (2.54–4.97)	.1623

Note: The relative excess risk of interaction (RERI) between TBI and adverse perinatal outcomes was 0.44 (95% CI −0.10 to 0.99) for persons age 5 – 9 at TBI, −0.25 (95% CI −0.75 to 0.25) for persons age 10 – 19 at TBI, and −0.57 (95% CI −2.58 – 1.01) for persons age 20 – 39 at TBI.

Abbreviations: CI, Confidence interval; HR, Hazard ratio; IR, Incidence rate per 1000 person years; TBI, Traumatic brain injury.

[a]Models were adjusted for calendar year and stratified by sex.

[b]Models were further adjusted for parental epilepsy, maternal education and marital status at focal persons' birth, maternal age at birth, maternal hypertension and pre-eclampsia during pregnancy, cerebral palsy, congenital malformations of the nervous system, and psychiatric co-morbidity.

[c]Wald test for the interaction between age at TBI and any adverse perinatal outcome.

95% CI −0.27 to 0.59), contrasted to their comparable counterparts without the respective perinatal adversity (Table 5).

The relative risk of epilepsy after TBI did not differ between the chosen levels of either gestational age at birth ($p = .2356$, Table S2), birth weight ($p = .8402$, Table S3), or Apgar score ($p = .0941$, Table S4). However, the relative risk was lower for persons with a gestational age lower than 37, with a birth weight lower than 2000 g, and an Apgar score below 7, than for persons with other levels of the respective perinatal risk factors. These results were robust with respect to mutual adjustment for other perinatal characteristics (data not shown).

4 | DISCUSSION

In this nationwide cohort study, we showed that the risk of epilepsy following TBI was not modified by the composite measure of adverse perinatal outcomes, irrespective of the severity of TBI.

This is the first study to address the role of adverse perinatal outcomes for the risk of epilepsy after TBI. We suspected that the brain of persons with adverse birth outcomes might be more vulnerable to subsequent insults, and thereby potentiate the risk of epilepsy following TBI. For instance, in a study of cognitive sequelae following TBI, the results indicated impaired cognitive recovery from TBI among children with low birth weight compared with normal birth weight children.[16] This raises concern that persons who are already at a higher risk of epilepsy may suffer a more detrimental impact of TBI. However, results from our study suggest that although adverse perinatal outcomes and TBI are both associated with increased risk of epilepsy, the relative risk of epilepsy after TBI was not modified by adverse perinatal outcomes. Thus, persons with perinatal adversities did not face a greater relative risk of epilepsy after TBI than persons without such adversities.

In fact, opposite to our hypothesis, the relative risk of epilepsy after TBI tended to be slightly lower in persons with adverse perinatal outcomes than in persons without these outcomes. This was especially pronounced in some sub-group analyses when the perinatal risk factors were considered individually (e.g., children born preterm and with low Apgar). However, caution is warranted when interpreting these findings and there may be other explanations, including selection mechanisms and confounding. For instance, TBI may have a weaker bearing on the relative risk of epilepsy in conjunction with perinatal risk factors, as has been proposed for a familial predisposition to epilepsy after repeated[6] and penetrating head injury.[5]

Further, we started follow-up at age 5, and the lower risk could result from early death and a depletion of susceptibles; first, preterm birth complications are a leading cause of child death in children under 5 years[29] and are inversely associated with gestational age at birth.[30] Thus, children who survive perinatal adversities are possibly more resilient than children in general and thus less prone to developing epilepsy; second, perinatal adversities are associated with an early spike in the epilepsy incidence, which may deplete the

TABLE 5 Risk of epilepsy after traumatic brain injury (TBI) according to individual measures of adverse perinatal outcomes in a population of 1,715,095 singletons born in Denmark (1982-2011)

Adverse perinatal outcomes	Any TBI	IR (95% CI)	20-year cumulative incidence (95% CI)	Unadjusted HR (95% CI)[a]	Adjusted HR (95% CI)[b]	*p*-value[c]
Preterm birth						
No	No	0.69 (0.68–0.70)	1.21 (1.15–1.26)	Ref	Ref	–
	Yes	1.47 (1.39–1.55)	2.33 (2.18–2.49)	2.61 (2.46–2.76)	2.35 (2.22–2.49)	–
Yes	No	0.98 (0.93–1.05)	1.83 (1.52–2.14)	Ref	Ref	–
	Yes	1.63 (1.28–2.06)	2.74 (1.90–3.57)	2.01 (1.57–2.57)	1.75 (1.37–2.24)	0.0224
Low birth weight						
No	No	0.69 (0.68–0.70)	1.20 (1.15–1.26)	Ref	Ref	–
	Yes	1.44 (1.37–1.53)	2.31 (2.15–2.46)	2.57 (2.42–2.73)	2.32 (2.19–2.46)	–
Yes	No	1.06 (1.00–1.13)	2.00 (1.63–2.37)	Ref	Ref	–
	Yes	2.14 (1.72–2.67)	3.36 (2.48–4.24)	2.45 (1.96–3.08)	2.16 (1.72–2.72)	0.5554
Low Apgar score						
No	No	0.69 (0.68–0.71)	1.23 (1.17–1.28)	Ref	Ref	–
	Yes	1.47 (1.39–1.55)	2.35 (2.20–2.50)	2.59 (2.44–2.74)	2.33 (2.20–2.47)	–
Yes	No	1.50 (1.32–1.70)	2.43 (1.40–3.46)	Ref	Ref	–
	Yes	1.71 (0.95–3.09)	2.11 (0.86–3.37)	1.38 (0.76–2.53)	1.07 (0.59–1.97)	0.0121
Born small for gestational age						
No	No	0.68 (0.67–0.69)	1.19 (1.14–1.25)	Ref	Ref	–
	Yes	1.43 (1.35–1.52)	2.29 (2.13–2.45)	2.56 (2.41–2.72)	2.32 (2.18–2.46)	–
Yes	No	0.84 (0.80–0.87)	1.53 (1.36–1.71)	Ref	Ref	–
	Yes	1.74 (1.52–2.00)	2.77 (2.35–3.19)	2.56 (2.22–2.96)	2.27 (1.97–2.62)	0.8199

Note: The relative excess risk of interaction (RERI) was −0.45 (95% CI −0.99 to 0.09) for preterm birth and TBI, 0.14 (95% CI −0.52 to 0.79) for low birth weight and TBI, −1.22 (95% CI −2.28 to −0.15) for low Apgar score and TBI, and 0.16 (95% CI −0.27 to 0.59) for small for gestational age and TBI.

Abbreviations: CI, Confidence interval; HR, Hazard ratio; IR, Incidence rate per 1000 person years; TBI, Traumatic brain injury.

[a]Models were adjusted for calendar year and stratified by sex.

[b]Models were further adjusted for parental epilepsy, maternal education and marital status at focal persons' birth, maternal age at birth, maternal hypertension and pre-eclampsia during pregnancy, cerebral palsy, congenital malformations of the nervous system, and psychiatric co-morbidity.

[c]Wald test for the interaction between TBI and individual adverse perinatal outcomes.

population at risk of high-risk persons, leaving fewer persons predisposed to developing epilepsy over the remainder of the follow-up. Also, prophylactic antiseizure medication after TBI may lower the detection rate of epilepsy after TBI; if such treatment is more often administered to persons with unfavorable birth outcomes than to persons without, our results may underestimate the risk of epilepsy after TBI in persons with such outcomes. However, such prophylactic treatment with antiseizure medication after TBI is rare in Denmark.

We cannot exclude the possibility that our findings are confounded by unobserved factors or suffer from residual confounding. We included a wide range of covariates to lessen this risk, but we do not believe that unmeasured or residual confounding

is a major concern because of the similarity between the crude and adjusted risk estimates (see Tables 2-5). However, the risk of epilepsy after a TBI is highly associated with TBI severity,[1,2] and the association between TBI and epilepsy according to perinatal outcomes may differ for persons according to the severity of the trauma. While this was not apparent from our results when examined for the composite measure of adverse perinatal outcomes, we cannot exclude that this holds for the individual measures, and in particular for persons born preterm or with low Apgar score. However, we did not have sufficient observations to address this matter. Similarly, as in previous studies,[2,6] TBIs sustained at younger ages were associated with a lower relative epilepsy risk, and our results might be confounded by a younger age at TBI in persons with perinatal adversities than without. We studied the risk of epilepsy taking into account the age at TBI, and there were only minor differences according to the composite measure of perinatal adversities. Thus, age at TBI do not seem to interact with perinatal adversities more generally, but we cannot rule out the possibility that it does for the individual measures. Also, the age groups may have been defined to broad leaving intra-interval variation in the age at TBI that result in residual confounding.

Some confounders were jointly proxied by more than one covariate. For instance, we adjusted for socioeconomic status by maternal marital status and educational attainment, and for hypertensive disorders by diagnosed hypertension as well as pre-eclampsia (where diagnostic criteria also include maternal hypertension). When two correlated covariates are adjusted for simultaneously, it may lead to less reliable results. However, marital status does not generalize across the full socioeconomic spectrum, and we believe that different mechanistic pathways are involved in pre-eclampsia and other types of disorders including hypertension, for example, essential hypertension, and therefore estimates should be adjusted independently for these covariates.

Brain development is at a critical stage in children and youth, and TBI may result in serious consequences. Further, low birth weight and gestational age are associated with perinatal brain injuries and adverse brain development including anatomical changes such as reduction in brain volume and altered brain function.[31–33] It is noteworthy that, albeit insignificant, the risk of epilepsy after TBI was higher in children under age 10 if they had any adverse perinatal outcome, compared to not having any perinatal adversities. This contrasts the general tendency of a slightly lower relative risk and may indicate that the developing brain in children with preexisting brain anomalies is more vulnerable to succeeding neurologic insults.

We had limited clinical information, and TBI and epilepsy categorizations were based solely on diagnostic information from the Danish National Patient Registry. A positive predictive value of 81% has previously been demonstrated for the first epilepsy diagnosis and 89% for isolated seizures.[34] However, the validity of an epilepsy diagnosis increases with the number of registrations, and a positive predictive value of 88% was found for two or more registrations of epilepsy.[35] We have previously shown that having two or more epilepsy diagnoses only has limited impact on the association between TBI and epilepsy.[6]

The study included only TBIs treated in Danish hospitals. Persons with milder TBIs are often treated or seen in primary care settings, and so may be misclassified without TBI in our study. Thus, results may not be extrapolated to TBIs treated outside the hospitals.

Excluding persons with missing information on perinatal outcomes were unlikely to bias our results. However, if birth registrations were more likely to be missing for children with the most critical birth complications such as with very premature delivery and very low Apgar scores, the incidence rates of epilepsy may be underestimated for persons with adverse perinatal outcomes.

We followed persons from their 5th birthday, because inclusion of children who are likely to die at an early age may lead to a downward selection bias between the association of TBI and epilepsy. Further, whereas epilepsy after TBI may occur in individuals at all ages, the most common single-gene epilepsies have a high incidence in young children with onset in the first years of life.[36] Other seizure disorders that may be misclassified as epilepsy, for example, febrile seizures, have an onset before five years of age.[37] The results of the present study are therefore not generalizable to children who sustained a TBI under five years of age, but the risk of epilepsy after TBI is low in this group.

5 | CONCLUSION

The results from this large population-based cohort study indicate that perinatal adversities and TBI both increased the risk of epilepsy independently and that the relative risk of epilepsy after TBI was not modified by perinatal adversities. It is encouraging that persons who are already in a more disadvantaged position with regard to developing epilepsy, do not also suffer a more detrimental impact of TBI.

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CONFLICT OF INTEREST

Jakob Christensen received honoraria from serving on the scientific advisory board of UCB Nordic and Eisai AB, received honoraria from giving lectures from UCB Nordic and Eisai AB, and received funding for a trip from UCB Nordic. The remaining authors have no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ETHICS STATEMENT

This study is based on anonymized data, which by Danish law does not require ethical review board approval. The study was approved by the Danish Data Protection Agency.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ane.13605.

DATA AVAILABILITY STATEMENT

Information was retrieved solely from Danish national registers and did not require consent from participants. Individual level data may not be shared, but summary statistics, additional results, and Supplementary material may be provided on request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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