Maternal Epilepsy and Long-term Offspring Mortality: A Nationwide Cohort Study

Jakob Christensen, PhD [1,2], Sussie Antonsen, MSci [2], Yuelian Sun, PhD [1,2] and Julie W. Dreier, PhD [2,3]

Objective: We examined how maternal epilepsy and use of antiseizure medications in pregnancy was associated with offspring mortality.
Methods: This population-based cohort study included all live- and stillborn singletons in Denmark between 1981 and 2016. We used nation-wide registers to retrieve information on pregnancy characteristics, epilepsy diagnoses, use of antiseizure medications, and mortality. Adjusted mortality rate ratios (MRR) were estimated using log-linear Poisson regression.
Results: The cohort consisted of 1,862,474 children. In total, 12,026 live-born children died during follow-up, of whom 170 (1.4%) were offspring of mothers with epilepsy. Overall mortality was increased in offspring of mothers with epilepsy compared to offspring of mothers without epilepsy (MRR = 1.46, 95% CI: 1.23–1.71), driven by an excess mortality only in the first year of life. Mortality was increased for natural deaths (MRR = 1.50, 95% CI: 1.25–1.78) but not from unnatural deaths (MRR = 1.38, 95% CI: 0.84–2.14), and only in offspring of women with epilepsy who used antiseizure medications during pregnancy (MRR = 1.51, 95% CI: 1.00–2.17), but not in offspring of women with epilepsy who did not use antiseizure medications while pregnant (MRR = 0.97, 95% CI: 0.69–1.31). When analyses were restricted to children born from 2000 and onwards, the excess mortality that was observed in the first year of life among children of mothers with epilepsy, was no longer evident.
Interpretation: During the 1981 to 1999 epoch, offspring of women with epilepsy were at increased risk of dying in the first year of life. However, this risk did not extend to children born after 2000. Future retrospective studies of the effects of maternal epilepsy on the health of the offspring should take this difference into account.

ANN NEUROL 2022;91:455–465

Increased mortality in individuals with epilepsy is well-documented,[1,2] and pregnancy seems to be a period involving extra high risk.[3–5] Mortality rates in pregnant women with epilepsy are 5 to 12 times higher than rates in pregnant women without epilepsy.[3–5] Inadequate seizure control and antiseizure medication-related factors, such as treatment switch, changes in dose, or pharmacokinetic changes,[3] have been proposed to contribute to maternal mortality in women with epilepsy, but these factors may be harmful to the fetus and offspring as well.[6,7] Indeed, maternal epilepsy and antiseizure medication treatment in pregnancy has been associated with adverse birth outcomes including increased risk of stillbirths.[8,9] Further, a UK study on the outcome of pregnancies in 186 women with epilepsy identified 10 neonatal deaths in the offspring of women with epilepsy – ie, a perinatal mortality rate nearly twice the regional rate.[8] Although these findings are alarming, not all studies report increase in offspring mortality and a Norwegian study identified no association between maternal epilepsy, antiseizure

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.26315

Received May 4, 2021, and in revised form Jan 27, 2022. Accepted for publication Jan 29, 2022.

Address correspondence to Dr Christensen, Department of Neurology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 165, DK-8200 Aarhus N, Denmark. E-mail: jakob@farm.au.dk

From the [1]Department of Neurology, Aarhus University Hospital, Aarhus, Denmark; [2]National Center for Register-Based Research, Aarhus University, Aarhus, Denmark; and [3]Centre for Integrated Register-based Research, CIRRAU, Aarhus University, Aarhus, Denmark

medication exposure and perinatal mortality.[10] Thus, there are conflicting results regarding the perinatal mortality risk in offspring of women with epilepsy and no study has evaluated the long term mortality in the offspring reaching into childhood and adolescence. To address this knowledge gap and apparent inconsistencies, we studied the perinatal and long-term mortality in offspring of women with epilepsy from natural and unnatural causes, and assessed the role of pregnancy-related antiseizure medication treatment on short- and longer-term survival.

Methods

Ethical Approval

The study includes only anonymous data, which by Danish law does not require ethical review board approval. However, the study was approved by the Danish Data Protection Agency

Study Population and Design

We conducted a nation-wide register-based cohort study of all live- and stillborn singletons recorded in the Danish Medical Birth Register[11] between 1 January 1981 and 31 December 2016 (Fig 1). The Danish Medical Birth Register was established in 1973 and allows monitoring of the health of pregnant women and their offspring. The register includes data on all births in Denmark, including home deliveries and stillbirths. The population was restricted to births of mothers born in Denmark to capture the full information on prenatal exposures, including maternal diagnosis of epilepsy and antiseizure medication use in pregnancy. Individual level information was linked between registers using the unique CPR-number from the Civil Registration System.[12]

Mortality, Stillbirths and Causes of Death

Information on overall mortality was derived from the Civil Registration System,[12] which holds continuously updated information on vital status (ie, date of death), place of residence, and emigrations. Cause-specific mortality was based on information from the Danish Register of Causes of Death,[13] which was available up until 31 December 2015 (Fig 1). Causes of death in this register are classified according to the World Health Organization's International Classification of Diseases, 8th revision (ICD-8) until 1993 and the 10th revision (ICD-10) from 1994 and onwards. For this study, we distinguished between unnatural causes (eg, accidental deaths, and deaths due to intentional self-harm or assault; ICD-8: E800-E999; ICD-10: V01-Y89) and natural causes of death (all except unnatural deaths), and considered several more specific causes (accidental deaths (ICD-8: E800-E929, E940-E942; ICD-10: V01-X59), neoplasms (ICD-8: 140-239; ICD-10: C00-D48), diseases of the respiratory system (ICD-8: 460-519; ICD-10: J00-J99), conditions originating in the perinatal period (ICD-8: 760-779; ICD-10: P00-P96), and congenital malformations/chromosomal abnormalities (ICD-8: 740-759; ICD-10: Q00-Q99). Information on stillbirths was based on the Danish Medical Birth Register.[11] Prior to 1 April 2004, stillbirths were defined as fetal deaths with a gestational age of week ≥28, and after 1 April 2004, stillbirths were defined as fetal deaths with a gestational age of week ≥22. Thus, fetal deaths between gestational week 22 and 28 prior to 1 April 2004 were not included in this study. Since 2004, a newborn with any signs of life (breathing, heartbeat, pulsation in the umbilical cord, or movements) is defined as live-born in the Danish Medical Birth Register, regardless of gestational age.[11]

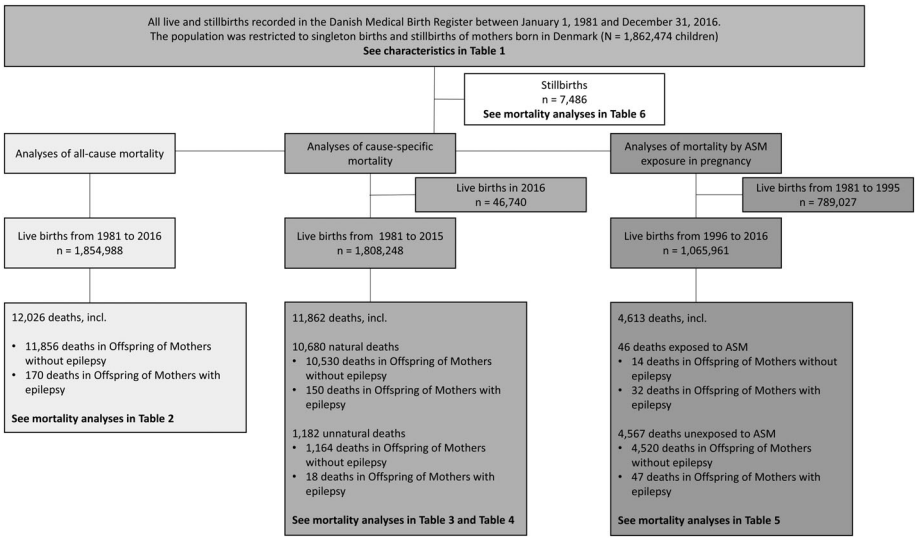

FIGURE 1: Overview of study populations among 1,854,988 live born singletons and 7,486 stillborn in Denmark 1981 to 2016. ASM = Antiseizure medication.

Maternal Epilepsy and the Use of Antiseizure Medications in Pregnancy

Hospital-treated maternal epilepsy was identified via the Danish National Patient Registry[14] as any contact with a diagnosis of epilepsy (ICD-8: 345 excl. 345.29; ICD-10: G40). This register contains information on all admissions to hospitals in Denmark since 1977, including admissions to the only private epilepsy center (Filadelfia Epilepsy Hospital), and outpatient and emergency room contacts since 1995. For identifying mothers with epilepsy, we used both main and secondary diagnoses, but not referral or observation diagnoses. Data were available from 1977 through 2016 (Fig 1). Onset of maternal epilepsy was defined as the date of the first hospital contact with epilepsy, if any. In an effort to identify women with active epilepsy, we performed a sensitivity analysis where we restricted the identification of women with epilepsy to those who had a hospital contact with epilepsy from one year prior to birth and onwards.

We used data from the Danish National Prescription Registry[15] to identify antiseizure medication use during pregnancy defined as any prescription for antiseizure medications (ATC codes N03A and N05BA09) redeemed from 30 days before the estimated date of conception until delivery. Data were available from 1996 through 2016 (Fig 1). For the analyses in this sub-cohort, we categorized the children into four groups, depending on maternal epilepsy status and maternal use of antiseizure medications in pregnancy: (1) no maternal epilepsy and no maternal use of antiseizure medications, which was the reference group, (2) no maternal epilepsy but maternal use of antiseizure medications, (3) maternal epilepsy, but no maternal use of antiseizure medications, and (4) maternal epilepsy and maternal use of antiseizure medications.

Pregnancy and Birth Characteristics

Information on gestational age and birth weight was retrieved from the Medical Birth Register.[11] To estimate the date of conception, we subtracted gestational age from the date of birth and added 14 days. Before 1997, gestational age was available only in completed weeks. During that period, gestational age in days was estimated as gestational age in completed weeks multiplied by 7 and with 4 days added to center the estimate.

Statistical Analyses

The mortality rate ratios (MRRs) in offspring of mothers with epilepsy compared with offspring of mothers without epilepsy were estimated using log-linear Poisson regression. All live born children were followed from birth until death, emigration from Denmark, the day before their 16th birthday, or the end of follow-up (31 December 2016), whichever came first. The basic model was adjusted for sex and calendar year in 5-year bands. Further adjustments were made for potential confounders that were chosen a priori based on the current literature, including maternal psychiatric history (ICD-8: 290-315; ICD-10: F00-F99, yes/no),[16] maternal age (<25 year, 25–29 years, 30–34 years and 35+ years),[12] and maternal educational attainment at the time of birth (primary school, high school/vocational training, and higher education).[17] In order to examine whether any potential association between maternal epilepsy and offspring mortality could be explained by an increased occurrence of epilepsy in the offspring itself (ie, mediation), we further ran all models with additional adjustment for offspring epilepsy to examine this. Calendar year, maternal psychiatric history, and offspring's epilepsy were treated as time-dependent variables, while sex, maternal age, and maternal educational attainment were treated as time-fixed variables. Maternal epilepsy was treated as a time-varying exposure after birth. Analyses for all-cause mortality were stratified by age of the offspring (1–28 days, 29–365 days, 1–4 years, and 5–15 years). MRRs of unnatural and natural deaths were estimated in a restricted cohort consisting of all live born children born in Denmark from 1981 to 2015 with follow-up through 2015 (causes of death were not available for 2016). The analyses for unnatural death were not stratified by offspring age due to limited power.

Although mortality estimates were adjusted for calendar year, the study took place over 40 years where prenatal exposure to teratogenic drugs[18] and folic acid[19] may have changed – factors that could have an impact on offspring mortality. In order to assess whether there were changes in offspring mortality in the study period, we analyzed the mortality in children born to mothers with and without epilepsy in Denmark in 1981 to 1999 and 2000 to 2016, respectively.

Congenital malformations[20] and intrauterine growth restriction[21,22] are associated with excess mortality in the general population. However, these conditions are also associated with maternal use of antiseizure medication during pregnancy.[18,23] To analyze whether these conditions alone accounted for the excess mortality, we performed additional sensitivity analyses excluding children with congenital malformation and children born small for gestational age.

The MRRs in offspring according to maternal epilepsy status and maternal use of antiseizure medication in pregnancy was carried out in a similar way to the above analyses. Analyses were restricted to children born in Denmark between 1996 and 2016, because the Danish National Prescription Registry[15] only had data available from 1995 to 31 December 2016. The analyses were not

stratified by offspring age and type of antiseizure medication due to limited power in these sub-analyses.

The cumulative incidence of all-cause mortality among offspring of mothers with/without epilepsy prior to offspring's date of birth was estimated using competing risk survival analyses, with emigration treated as a competing event.

The risk of stillbirth in offspring of mothers with epilepsy compared to offspring of unaffected mothers was modelled in a log-linear Poisson regression as the number of deaths divided by the number of live and stillbirths. The basic model was adjusted for calendar year (5-year bands) with further adjustment for maternal psychiatric history, maternal age, and maternal educational attainment. All models took siblings into account by using the mother as a cluster.

Confidence intervals at the 95% level were calculated from likelihood ratio tests. All analyses were performed using the SAS 9.4 PROC GENMOD procedure.

Results

The cohort of all live- and stillborn singletons in Denmark from 1981 to 2016 consisted of 1,862,474 children (7,486 stillbirths and 1,854,988 live births), of whom 18,528 (0.99%) had a mother with epilepsy, when assessed at the end of follow-up (Table 1). Of the live-born singletons, 18 (0.001%) were lost to follow-up and 10,194 (0.55%) emigrated from Denmark before 31 December 2016. Overview of the study cohorts and offspring mortality is presented in Figure 1.

Offspring All-Cause Mortality

In total, 12,026 live-born children died during follow-up, of whom 170 (1.4%) were offspring of mothers who were diagnosed with epilepsy before the offspring's date of death (Table 2). The adjusted MRR comparing offspring of mothers with epilepsy to offspring of mothers without epilepsy was 1.46 (95% CI: 1.23–1.71) (Table 2). The mortality associated with maternal epilepsy decreased with the age of the offspring and was not evident after the first year of life (MRR; 1–28 days; 1.75 (95% CI: 1.35–2.23), 29–365 days; 1.42 (95% CI: 1.02–1.92), 1–4 years; 1.25 (95% CI: 0.82–1.80), 5–15 years; 0.72 (95% CI: 0.43–1.11)) (Table 2). When we restricted this analysis to 14,634 offspring of mothers with active epilepsy, an increased mortality was evident in the first 28 days of offspring life (MRR; 1–28 days; 2.20 (95% CI: 1.44–3.19)), but not after the neonatal period (29–365 days; 1.36 (95% CI: 0.77–2.21), 1–4 years; 1.54 (95% CI: 0.90–2.44), 5–15 years; 1.54 (95% CI: 0.90–2.44)).

The cumulative mortality risk at 1 year of age was 0.68% (95% CI: 0.57–0.81) in offspring born to mothers with epilepsy compared to 0.47% (95% CI: 0.46–0.48) in offspring born to mothers without epilepsy (Fig 2). At age 16 years, these numbers had increased to 0.94% (95% CI: 0.81–1.10) in offspring born to mothers with epilepsy compared to 0.69% (95% CI: 0.68–0.70) in offspring born to mothers without epilepsy.

TABLE 1. Overall Cohort Characteristics of 1,862,474 Singleton Births and Stillbirths in Denmark 1981 to 2016

	Children of mothers with epilepsy	Children of mothers without epilepsy
Overall[a]	18,528 (100.0)[b]	1,843,946 (100.0)
Year of birth[c]		
1981 to 1989	2,077 (11.2)	442,116 (24.0)
1990 to 1998	3,839 (20.7)	512,581 (27.8)
1999 to 2007	5,664 (30.6)	471,187 (25.6)
2008 to 2016	6,948 (37.5)	418,062 (22.7)
Maternal age		
<25 yr	4,163 (22.5)	336,941 (18.3)
25 to 29 yr	6,632 (35.8)	684,511 (37.1)
30 to 34 yr	5,437 (29.3)	570,138 (30.9)
35+ yr	2,296 (12.4)	252,356 (13.7)
Maternal psychiatric history prior to birth		
Yes	2,703 (14.6)	90,475 (4.9)
No	15,825 (85.4)	1,753,471 (95.1)
Maternal education		
Primary school	6,712 (36.2)	471,251 (25.6)
High school/ vocational training	6,897 (37.2)	763,785 (41.4)
Higher education	4,919 (26.5)	608,910 (33.0)

[a]Sex was not recorded in stillborn children.
[b]Of 18,528 children of mothers with epilepsy, 14,634 (79%) were born by mothers who had active epilepsy (defined as a hospital contact with epilepsy from one year prior to birth and onwards).
[c]The number of mothers with epilepsy that were identified increased over the calendar period of the study, as more information on the medical history of women giving birth became available (Diagnostic data was available from 1977 and onwards; and outpatient and emergency room visits from 1995).

TABLE 2. Offspring All-Cause Mortality by Age in Singleton Children Born to Mothers With Epilepsy Compared to Singleton Children Born to Mothers Without Epilepsy in 1,854,988 Live Born Singletons in Denmark 1981 to 2016

Offspring age	Offspring of mothers without epilepsy		Offspring of mothers with epilepsy				
	Number of deaths	Mortality rate per 10,000 person years	Number of deaths	Mortality rate per 10,000 person years	Relative risk (basic adjustment)[a]	Relative risk (adjusted)[b]	Relative risk (adjusted + offspring's epilepsy)[c]
<1 yr							
1 to 28 days	5,625	387.13	87	596.82	1.88 (1.45–2.38)	1.76 (1.35–2.24)	1.75 (1.35–2.23)
29 to 365 days	2,872	17.30	39	23.34	1.79 (1.29–2.43)	1.52 (1.09–2.05)	1.42 (1.02–1.92)
1 to 4 yr	1,739	2.57	26	3.75	1.79 (1.19–2.58)	1.62 (1.07–2.34)	1.25 (0.82–1.80)
5 to 15 yr	1,620	1.11	18	1.12	1.12 (0.68–1.73)	1.01 (0.61–1.56)	0.72 (0.43–1.11)
All	11,856	5.13	170	6.86	1.77 (1.50–2.08)	1.67 (1.41–1.96)	1.46 (1.23–1.71)

[a]Adjusted for sex and calendar year.
[b]Adjusted for sex and calendar year, maternal psychiatric history, maternal age, and maternal educational attainment.
[c]Adjusted for sex and calendar year, maternal psychiatric history, maternal age, maternal educational attainment, and offspring's epilepsy.

Offspring Cause-Specific Mortality

In the analyses of cause-specific mortality, the cohort was restricted to live births from 1981 to 2015 (n = 1,808,248) (Fig 1). Cause-specific mortality analyses revealed that while mortality from natural causes was significantly elevated in offspring of mothers with epilepsy compared to offspring of mothers without epilepsy (MRR = 1.50, 95% CI: 1.25–1.78), this could not be demonstrated for unnatural causes (MRR = 1.38, 95% CI: 0.84–2.14) (Table 3). Conditions originating in the perinatal period, and congenital malformations/chromosomal abnormalities were the most common causes of death, regardless of maternal epilepsy status. Just as for overall mortality, we observed an increased mortality risk from natural causes only up to 1 year of age (1–28 days; MRR = 1.79 (95% CI: 1.37–2.28), 29–365 days; MRR = 1.44 (95% CI: 1.02–1.96), 1–4 years; MRR = 0.89 (95% CI: 0.50–1.44), 5–15 years; MRR = 0.79 (95% CI: 0.43–1.31).

(Table 4).

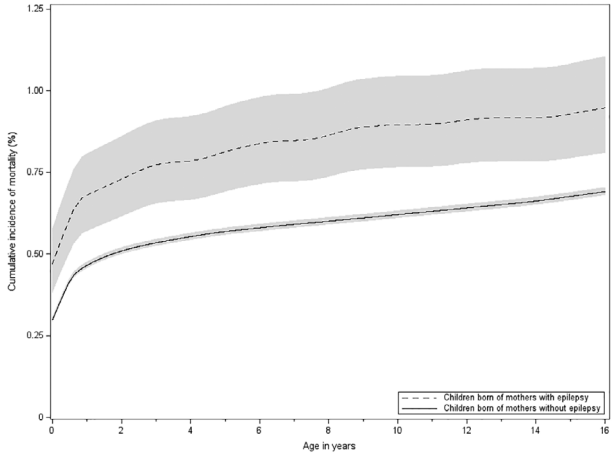

FIGURE 2: Cumulative incidence of mortality in offspring of mothers with and without epilepsy prior to offspring's birth. Shaded areas represent 95% confidence intervals.

Offspring Mortality by Antiseizure Medication Exposure in Pregnancy

To examine the role of maternal use of antiseizure medications during pregnancy, the cohort was restricted to live births from 1996 to 2016 (n = 1,065,961) (Fig 1). In this cohort, 4,613 deaths occurred; 46 (1.0%) of these were offspring of mothers who redeemed one or more prescriptions for antiseizure medications during pregnancy. Table 5 shows MRRs for all-cause mortality when comparing offspring of mothers with epilepsy and/or antiseizure medication use during pregnancy to offspring of women without epilepsy who did not use antiseizure medications during pregnancy. Increased mortality was found

TABLE 3. Unnatural and Natural Causes of Death in Children Born to Mothers With Epilepsy Compared with Children Born to Mothers Without Epilepsy Among 1,808,248 Live Born Singletons in Denmark 1981 to 2015

	Offspring of mothers without epilepsy		Offspring of mothers with epilepsy				
Cause of death	Number of deaths	Mortality rate per 10,000 person years	Number of deaths	Mortality rate per 10,000 person years	Relative risk (basic adjustment)[a]	Relative risk (adjusted)[b]	Relative risk (adjusted + offspring's epilepsy)[c]
Unnatural deaths	1,164	0.52	18	0.77	1.79 (1.08–2.77)	1.44 (0.87–2.23)	1.38 (0.84–2.14)
Accidents	974	0.44	14	0.60	1.67 (0.94–2.72)	1.37 (0.77–2.23)	1.33 (0.75–2.18)
Natural deaths	10,530	4.71	150	6.39	1.80 (1.50–2.13)	1.73 (1.45–2.06)	1.50 (1.25–1.78)
Neoplasms	748	0.33	9	0.38	1.33 (0.64–2.42)	1.37 (0.66–2.49)	1.23 (0.59–2.24)
Respiratory diseases	239	0.11	6	0.26	3.47 (1.37–7.15)	3.01 (1.18–6.23)	2.59 (1.01–5.40)
Perinatal conditions	3,265	1.46	57	2.43	1.97 (1.40–2.69)	1.97 (1.40–2.69)	1.90 (1.34–2.59)
Malformations/ chromosomal abnormalities	3,247	1.45	44	1.87	2.00 (1.44–2.68)	2.02 (1.46–2.71)	1.76 (1.27–2.37)
All	11,694	5.23	168	7.16	1.80 (1.52–2.11)	1.70 (1.43–1.99)	1.48 (1.25–1.74)

[a]Adjusted for sex and calendar year.
[b]Adjusted for sex and calendar year, maternal psychiatric history, maternal age, and maternal educational attainment.
[c]Adjusted for sex and calendar year, maternal psychiatric history, maternal age, maternal educational attainment, and offspring's epilepsy.

TABLE 4. Mortality from Natural Death by Age in Offspring in 1,808,248 Children Born to Mothers With and Without Epilepsy Among Live Born Singletons in Denmark 1981 to 2015

Offspring age	Offspring of mothers without epilepsy		Offspring of mothers with epilepsy				
	Number of deaths	Mortality rate per 10,000 person years	Number of deaths	Mortality rate per 10,000 person years	Relative risk (basic adjustment)[a]	Relative risk (adjusted)[b]	Relative risk (adjusted + offspring's epilepsy)[c]
1 to 28 days	5,516	389.39	86	616.07	1.91 (1.47-2.44)	1.80 (1.38-2.29)	1.79 (1.37-2.28)
29 to 365 days	2,717	16.79	37	23.16	1.82 (1.29-2.48)	1.55 (1.10-2.11)	1.44 (1.02-1.96)
1 to 4 yr	1,304	1.98	14	2.12	1.28 (0.72–2.08)	1.21 (0.68–1.97)	0.89 (0.50–1.44)
5 to 15 yr	993	0.71	13	0.86	1.31 (0.72–2.17)	1.25 (0.69–2.08)	0.79 (0.43–1.31)
All	10,530	4.71	150	6.39	1.80 (1.50–2.13)	1.73 (1.45–2.06)	1.50 (1.25–1.78)

[a]Adjusted for sex and calendar year.
[b]Adjusted for sex and calendar year, maternal psychiatric history, maternal age, and maternal educational attainment.
[c]Adjusted for sex and calendar year, maternal psychiatric history, maternal age, maternal educational attainment, and offspring's epilepsy.

TABLE 5. All-Cause Mortality in Offspring According to Maternal Epilepsy and Maternal Antiseizure Medication Use During Pregnancy Among 1,065,961 Live Born Singletons in Denmark 1996 to 2016

Epilepsy	Antiseizure medications	*n*	Number of deaths	Mortality rate per 10,000 person years	Relative risk (basic adjustment)[a]	Relative risk (adjusted)[b]	Relative risk (adjusted + offspring's epilepsy)[c]
No	No	1,050,095	4,520	4.22	1.00 (ref)	1.00 (ref)	1.00 (ref)
No	Yes	1,818	14	10.27	1.76 (0.85–3.18)	1.55 (0.75–2.81)	1.36 (0.65–2.46)
Yes[d]	No	10,172	47	4.23	1.17 (0.84–1.59)	1.06 (0.76–1.44)	0.97 (0.69–1.31)
Yes[d]	Yes	3,876	32	8.36	2.02 (1.34–2.91)	1.88 (1.24–2.70)	1.51 (1.00–2.17)

Antiseizure medications (monotherapy); Phenobarbital (n = 180 (3.2%)), Primidone (n = 36 (0.6%)), Phenytoin (n = 10 (0.2%)), Ethosuximide (n = <5), Clonazepam (n = 331 (5.8%)), Carbamazepine (n = 474 (8.3%)), Oxcarbazepine (n = 426 (7.5%)), Eslicarbazepine (n <5), Valproic acid (n = 520 (9.1%)), Vigabatrin (n = 19 (0.3%)), Lamotrigine (n = 2,177 (38.2%)), Topiramate (n = 124 (2.2%)), Gabapentin (n = 182 (3.2%)), Levetiracetam (n = 215 (3.8%)), Zonisamide (n <5), Pregabalin (n = 191 (3.4%)), Lacosamide (n < 5), Clobazam (n = 36 (0.6%)), Polytherapy (n = 764 (13.4%)).

[a]Adjusted for sex and calendar year.

[b]Adjusted for sex and calendar year, maternal psychiatric history, maternal age, and maternal educational attainment.

[c]Adjusted for sex and calendar year, maternal psychiatric history, maternal age, maternal educational attainment, and offspring's epilepsy.

[d]Of 14,048 children of mothers with epilepsy, 3,649 (26%) were defined as having active epilepsy during pregnancy. Of 3,649 children of mothers with active epilepsy during pregnancy, 822 (22.5%) were using antiseizure medications during pregnancy.

in offspring of women with epilepsy who used antiseizure medications while pregnant (MRR = 1.51, 95% CI: 1.00–2.17), but this was not found in offspring of women with epilepsy who did not use antiseizure medications while pregnant (MRR = 0.97, 95% CI: 0.69–1.31). When restricting the analyses to 3,649 children of mothers with active epilepsy, the MRRs were somewhat lower (maternal epilepsy with antiseizure medications, MRR = 1.33, 95% CI: 0.82–2.03; maternal epilepsy without antiseizure medications MRR = 0.77, 95% CI: 0.37–1.39).

Excluding children with congenital malformations (n = 130,782) in a sensitivity analysis did not substantially change the results (maternal epilepsy with antiseizure medications, MRR = 1.89, 95% CI: 1.12–2.95; maternal epilepsy without antiseizure medications MRR = 1.15, 95% CI: 0.76–1.66), nor did further exclusion of children born small for gestational age (n = 98,313, maternal epilepsy with antiseizure medications, MRR = 1.86, 95% CI: 1.02–3.08; maternal epilepsy without antiseizure medications MRR = 0.90, 95% CI: 0.53–1.43).

Offspring Mortality in the Study Period 1981 to 1999 versus 2000 to 2016

Examining mortality in the two study periods separately revealed that infant mortality rates have decreased substantially in offspring of mothers with and without epilepsy from the early period (1981–1999) to the late period (2000–2016), but more so in offspring of mothers with epilepsy. Consequently, from this analysis, the excess mortality seen in children of mothers with epilepsy was confined to children born in the early period from 1981 to 1999 (Table 6).

Risk of Stillbirths

To examine the risk of stillbirths, we included the entire cohort of 1,862,474 children including 7,486 stillbirths of whom there were 104 stillbirths in women with epilepsy (Fig 1). The adjusted relative risk of stillbirth was 1.38 (95 % CI: 1.13–1.67) in pregnancies of mothers with epilepsy compared to pregnancies of mothers without epilepsy.

Risk of Stillbirths by Antiseizure Medication Exposure in Pregnancy

To assess the risk of stillbirths by antiseizure medication exposure in pregnancy, we restricted the cohort to 1,069,870 offspring born to mothers from 1996 to 2016 (ie, the time period with information and use of antiseizure medication use in pregnancy). We found that the increased risk of stillbirth in women with epilepsy was restricted to mothers who *did not* use antiseizure medications during pregnancy (MRR = 1.65 (95% CI: 1.27–2.09)), while there was no increased risk of stillbirth in women with epilepsy who used antiseizure medications in pregnancy (MRR = 0.98 (95% CI: 0.56–1.57) (Table 7).

TABLE 6. Offspring All-Cause Mortality by Age in Children Born to Mothers with Epilepsy Compared to Singleton Children Born to Mothers Without Epilepsy in Denmark in 1981 to 1999 versus 2000 to 2016

Offspring age	Offspring of mothers without epilepsy		Offspring of mothers with epilepsy				
	Number of deaths	Mortality rate per 10,000 person years	Number of deaths	Mortality rate per 10,000 person years	Relative risk (basic adjustment)[a]	Relative risk (adjusted)[b]	Relative risk (adjusted + offspring's epilepsy)[c]
Children born 1981 to 1999							
1 to 28 days	3,711	466.95	56	1,102.92	2.61 (1.90–3.48)	2.44 (1.77–3.25)	2.43 (1.77–3.24)
29 to 365 days	2,225	24.20	26	43.60	2.02 (1.34–2.91)	1.69 (1.12–2.44)	1.55 (1.03–2.24)
1 to 4 yr	1,306	3.28	18	6.36	2.11 (1.27–3.25)	1.92 (1.16–2.96)	1.46 (0.88–2.27)
5 to 15 yr	1,375	1.26	13	1.24	1.05 (0.58–1.73)	0.93 (0.51–1.55)	0.66 (0.36–1.10)
All	8,617	5.43	113	8.10	2.03 (1.65–2.45)	1.91 (1.56–2.32)	1.65 (1.34–2.00)
Children born 2000 to 2016							
1 to 28 days	1,914	290.76	31	326.32	1.18 (0.74–1.79)	1.10 (0.68–1.67)	1.10 (0.68–1.66)
29 to 365 days	647	8.73	13	12.10	1.46 (0.80–2.43)	1.23 (0.67–2.05)	1.19 (0.65–1.98)
1 to 4 yr	433	1.56	8	1.95	1.34 (0.61–2.52)	1.19 (0.54–2.25)	0.91 (0.41–1.72)
5 to 15 yr	245	0.67	5	0.90	1.38 (0.53–3.23)	1.28 (0.48–3.01)	0.90 (0.35–2.14)
All	3,239	4.47	57	5.26	1.34 (0.99–1.77)	1.22 (0.89–1.61)	1.08 (0.80–1.43)

[a]Adjusted for sex and calendar year.
[b]Adjusted for sex and calendar year, maternal psychiatric history, maternal age, and maternal educational attainment.
[c]Adjusted for sex and calendar year, maternal psychiatric history, maternal age, maternal educational attainment, and offspring's epilepsy.

TABLE 7. Singleton Stillbirths According to Maternal Antiseizure Medication Use During Pregnancy and Maternal Epilepsy in 1,069,870 Women in Denmark 1996 to 2016

Epilepsy	Antiseizure medications	Number of stillbirths	Stillbirths per 10,000 births	Relative risk (basic adjustment)[a]	Relative risk (adjusted)[b]
No	No	3,818	36.23	1.00 (ref)	1.00 (ref)
No	Yes	12	65.57	1.87 (1.00–3.14)	1.50 (0.80–2.54)
Yes	No	64	62.52	1.78 (1.38–2.26)	1.65 (1.27–2.09)
Yes	Yes	15	38.55	1.07 (0.62–1.71)	0.98 (0.56–1.57)

[a]Adjusted for sex and calendar year.
[b]Adjusted for sex and calendar year, maternal psychiatric history, maternal age, and maternal educational attainment.

Discussion

In this study of almost two million children including more than 18,000 children born to women with epilepsy, the mortality was increased by approximately 40% to 75% in the first year of life in offspring of women with epilepsy compared to offspring of women without epilepsy. However, in long-term follow-up to 16 years of age, there was no increased mortality risk after the first year of life, and this increased mortality in early life was only identified among the offspring born from 1981 to 1999. The cause-specific mortality analyses identified an increased mortality from natural but not unnatural causes; however, the power of the cause-specific analyses was low and the lack of association between maternal epilepsy and unnatural causes of death in the offspring should thus be interpreted with caution. In a subset of the population, it was possible to address the potential impact of antiseizure medication treatment in pregnancy for the long-term mortality in offspring of women with epilepsy. In these analyses, the increased mortality in offspring of women with epilepsy could only be identified among offspring of women with epilepsy who used antiseizure medications during pregnancy. Women with epilepsy, who do not use antiseizure medications in pregnancy may be very different from women with epilepsy who continue using antiseizure medications in pregnancy[24] – thus, continuous use of antiseizure medications in pregnancy likely identifies women more severely affected by their epilepsy. Prenatal exposure to antiseizure medications are associated with increased risk of congenital malformations,[25] and reduced birth weight.[23] However, the increased mortality was also observed in offspring without congenital malformations and who were not born small for gestational age suggesting that the increased mortality is not only caused by congenital malformations or intrauterine growth restriction.

The most common cause of death in offspring of mothers with and without epilepsy were perinatal conditions, which include complications of pregnancy, labor and delivery, disorders related to length of gestation and fetal growth, birth trauma, and infections specific to the perinatal period. Adverse perinatal conditions have been described with increased frequency in offspring of mothers with epilepsy.[8,10] Improved care for women during pregnancy and in early offspring life is the likely reason for reductions in these conditions in the general population in recent years.[26] Focus on adverse perinatal outcomes in offspring of women with epilepsy may account for the reduction in mortality observed in the present study between 1981 to 1999 and 2000 to 2016. Changes in the use of antiseizure medication[18] and folic acid[19] in study period may also account for some of this change in mortality. However, unfortunately we did not have information on prenatal exposure to antiseizure medication in the entire period from 1981 to 1999, where the increased offspring mortality was observed.

In order to fully address the mortality risk associated with maternal epilepsy, the study also addressed the risk of stillbirth and identified an increased risk of stillbirth in offspring of women with epilepsy. However, contrary to the findings for mortality in live-born children, we found that the risk of stillbirth was increased only in mothers with epilepsy who did *not* use antiseizure medications during pregnancy. The finding raises the question whether insufficient antiseizure medication treatment in pregnancy may constitute a risk for pregnant women with epilepsy, although another possible explanation could be that women who continue antiseizure medication treatment during pregnancy are followed more closely for their disorder during pregnancy. We also observed that women using antiseizure medications for other indications than epilepsy experienced elevated rates of stillbirths, but this association was attenuated and no longer statistically significant in the fully adjusted model.

A major strength of this study is the nation-wide nature of the study with nearly complete follow-up of participants, suggesting that selection bias was minimal. The information on maternal epilepsy and use of antiseizure medications was retrieved from registers, reducing the potential impact of recall bias. Further, we were able to adjust for psychiatric comorbidities[27,28] and for time trends that may influence the association between maternal epilepsy and mortality in utero and after birth.[29]

A major weakness of this study is the lack of clinical information such as information on seizure frequency in pregnancy. However, studies based on data from pregnancy registers found that generalized tonic-clonic seizures (that is associated with the highest risk in pregnancy) occurred only in a minor fraction (15.2%) of pregnancies in women with epilepsy.[30] Seizures in pregnancy may therefore only affect a minority of children born to women with epilepsy. With regard to exposure to antiseizure medications, we had no information on whether the pregnant women actually took the antiseizure medications, but compliance with antiseizure medication use identified from prescription databases is high.[31] The cause of death was retrieved from the Danish Register of Causes of Death,[13] and we were unable to verify any direct association with maternal epilepsy, eg, if the offspring death was a direct consequence of maternal seizures. However, since the increased mortality was not present in offspring after the first year of life, and since an increased mortality was only observed from natural causes, maternal seizures (occurring eg, as part of traffic accidents) are unlikely to contribute to mortality in children older than 1 year of life.

Increased perinatal mortality has been described in earlier studies,[32, 33] but no long-term studies have evaluated mortality associated with maternal epilepsy, and most studies have had limited power.[10] Our study enabled us to follow children for a long time and it is reassuring that offspring of women with epilepsy had no increased mortality risk after the first year of life, and it is further reassuring that no increased offspring mortality – short or long term – could be identified in the latter half of the study period from 2000 to 2016.

There are considerable concerns for the wellbeing of the fetus and the offspring of women with epilepsy – in particular the consequences of antiseizure medication exposure in pregnancy and the risk of congenital malformations and adverse neuro-psychiatric development.[9,25,29,34,35] In addition, studies have recently identified pregnancy as a period of high risk of mortality for women with epilepsy.[3–5] Although, the results of the present study show that this mortality risk extends to the unborn child and the offspring during the first year of life it is reassuring that we could not identify this risk in recent years and that we observed no long-term increase in mortality. The results therefore point to the importance of continuous efforts to ensure epilepsy care for pregnant women with epilepsy and for their offspring.[6,36]

The results of the present study raise a number of questions, such as whether any particular antiseizure medication is associated with a high risk of stillbirth. Although, this is the largest study of offspring mortality of women with epilepsy, the study had insufficient power to address this issue. Future research could be based on larger populations with long-term follow-up to further characterize health in offspring of women with epilepsy in order to inform possible preventive measures. More specific assessment of the circumstances surrounding the death of the offspring may also be informative for efforts to ensure optimal health in offspring of women with epilepsy.

In conclusion, offspring of women with epilepsy were at increased risk of dying in the first year of life, but the increased risk did not extend to later in offspring life and no increased mortality could be identified in the offspring born from 2000 and onwards. The results highlight the importance of care of women with epilepsy and their offspring during early offspring life, but also the need for a better understanding of how antiseizure medication treatment may contribute to offspring morbidity and mortality.

Acknowledgements

The study was supported by the Central Denmark Region, the Danish Epilepsy Association, and the Novo Nordisk Foundation (NNF16OC0019126). The founding sources (The Central Denmark Region, the Danish Epilepsy Society, and the Novo Nordisk Foundation) did not influence the study design, the collection, analysis, and interpretation of data, the writing of the report, or the decision to submit the paper for publication.

Author Contributions

JC, SA, YS, and JWD contributed to the conception and design of the study; JC, SA, YS, and JWD contributed to the acquisition and analysis of data; JC, SA, YS, and JWD contributed to drafting the text or preparing the figures

Potential Conflicts of Interest

JC received honoraria for serving on the scientific advisory board and giving lectures for UCB Nordic and Eisai AB, manufacturers of anti-epileptic drugs, and received funding for travel from UCB Nordic.

References

1. Christensen J, Pedersen CB, Sidenius P, et al. Long-term mortality in children and young adults with epilepsy – a population-based cohort study. Epilepsy Res 2015;114:81–88.
2. Thurman DJ, Logroscino G, Beghi E, et al. The burden of premature mortality of epilepsy in high-income countries: a systematic review from the Mortality Task Force of the International League Against Epilepsy. Epilepsia 2017;58:17–26.
3. Edey S, Moran N, Nashef L. SUDEP and epilepsy-related mortality in pregnancy. Epilepsia 2014;55:e72–e74.
4. MacDonald SC, Bateman BT, McElrath TF, Hernandez-Diaz S. Mortality and morbidity during delivery hospitalization among pregnant women with epilepsy in the United States. JAMA Neurol 2015;72:981–988.
5. Christensen J, Vestergaard C, Hammer BB. Maternal death in women with epilepsy: smaller scope studies. Neurology 2018;91:e1716–e1720.
6. Tomson T, Battino D, Bromley R, et al. Management of epilepsy in pregnancy: a report from the International League Against Epilepsy Task Force on Women and Pregnancy. Epileptic Disord 2019;21:497–517.
7. Meador KJ, Baker GA, Finnell RH, et al. In utero antiepileptic drug exposure: fetal death and malformations. Neurology 2006;67:407–412.
8. Razaz N, Tomson T, Wikström AK, Cnattingius S. Association Between Pregnancy and Perinatal Outcomes Among Women With Epilepsy. JAMA Neurol 2017;74:983–991.
9. Bech BH, Kjaersgaard MI, Pedersen HS, et al. Use of antiepileptic drugs during pregnancy and risk of spontaneous abortion and stillbirth: population based cohort study. Bmj 2014;349:g5159.
10. Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Pregnancy, delivery, and outcome for the child in maternal epilepsy. Epilepsia 2009;50:2130–2139.
11. Bliddal M, Broe A, Pottegard A, et al. The Danish Medical Birth Register. Eur J Epidemiol 2018;33:27–36.
12. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014;29:541–549.

13. Helweg-Larsen K. The Danish register of causes of death. Scand J Public Health 2011;39:26–29.

14. Schmidt M, Schmidt SA, Sandegaard JL, et al. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015;7:449–490.

15. Pottegard A, Schmidt SAJ, Wallach-Kildemoes H, et al. Data resource profile: the Danish National prescription registry. Int J Epidemiol 2017;46:798–798f.

16. Mors O, Perto GP, Mortensen PB. The Danish psychiatric central research register. Scand J Public Health 2011;39:54–57.

17. Jensen VM, Rasmussen AW. Danish education registers. Scand J Public Health 2011;39:91–94.

18. Christensen J, Trabjerg BB, Sun Y, et al. Prenatal exposure to valproate and risk of congenital malformations-Could we have known earlier? – A population-based cohort study. Epilepsia 2021;62:2981-2993.

19. Keni RR, Jose M, SR A, et al. Anti-epileptic drug and folic acid usage during pregnancy, seizure and malformation outcomes: changes over two decades in the Kerala Registry of Epilepsy and Pregnancy. Epilepsy Res 2020;159:106250.

20. Boyle B, Addor MC, Arriola L, et al. Estimating global burden of disease due to congenital anomaly: an analysis of European data. Arch Dis Child Fetal Neonatal E 2018;103:F22–f28.

21. Pedersen CB, Sun Y, Vestergaard M, et al. Assessing fetal growth impairments based on family data as a tool for identifying high-risk babies. An example with neonatal mortality. BMC Pregnancy Childbirth 2007;7:28.

22. McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. N Engl J Med 1985;312:82–90.

23. Kilic D, Pedersen H, Kjaersgaard MI, et al. Birth outcomes after prenatal exposure to antiepileptic drugs – a population-based study. Epilepsia 2014;55:1714–1721.

24. Man SL, Petersen I, Thompson M, Nazareth I. Antiepileptic drugs during pregnancy in primary care: a UK population based study. PLoS One 2012;7:e52339.

25. Tomson T, Battino D, Bonizzoni E, et al. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. Lancet Neurol 2018; 17:530–538.

26. Pinstrup Joergensen AS, Bjerregaard-Andersen M, Biering-Sørensen S, et al. Admission and mortality at the main neonatal intensive care unit in Guinea-Bissau. Trans R Soc Trop Med Hyg 2018;112:335–341.

27. Webb RT, Abel KM, Pickles AR, et al. Mortality risk among offspring of psychiatric inpatients: a population-based follow-up to early adulthood. Am J Psychiatry 2006;163:2170–2177.

28. Webb RT, Pickles AR, Appleby L, et al. Death by unnatural causes during childhood and early adulthood in offspring of psychiatric inpatients. Arch Gen Psychiatry 2007;64:345–352.

29. Tomson T, Battino D, Bonizzoni E, et al. Declining malformation rates with changed antiepileptic drug prescribing: an observational study. Neurology 2019;93:e831–e840.

30. Battino D, Tomson T, Bonizzoni E, et al. Seizure control and treatment changes in pregnancy: observations from the EURAP epilepsy pregnancy registry. Epilepsia 2013;54:1621–1627.

31. Olesen C, Sondergaard C, Thrane N, et al. Do pregnant women report use of dispensed medications? Epidemiology 2001;12: 497–501.

32. Speidel BD, Meadow SR. Maternal epilepsy and abnormalities of the fetus and newborn. Lancet 1972;2:839–843.

33. Meador K, Reynolds MW, Crean S, et al. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res 2008;81:1–13.

34. Meador KJ, Baker GA, Browning N, et al. Effects of fetal antiepileptic drug exposure: outcomes at age 4.5 years. Neurology 2012;78: 1207–1214.

35. Christensen J, Gronborg TK, Sorensen MJ, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. Jama 2013;309:1696–1703.

36. Leach JP, Smith PE, Craig J, et al. Epilepsy and pregnancy: for healthy pregnancies and happy outcomes. Suggestions for service improvements from the Multispecialty UK Epilepsy Mortality Group. Seizure. 2017;50:67–72.