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RESEARCH ARTICLE

Epilepsy risk in offspring of affected parents; a cohort study of the "maternal effect" in epilepsy

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Abstract

Objective: To assess whether the risk of epilepsy is higher in offspring of mothers with epilepsy than in offspring of fathers with epilepsy. **Methods**: In a prospective population-based register study, we considered all singletons born in Denmark between 1981 and 2016 (N = 1,754,742). From the Danish National Patient Register since 1977, we identified epilepsy diagnoses in all study participants and their family members. Cox regression models were used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CI), adjusted for relevant confounders. **Results**: We included 1,754,742 individuals contributing > 30 million person-years of follow-up. The incidence rate of epilepsy in offspring of unaffected parents was 78.8 (95% CI: 77.8–79.8) per 100,000 person-years, while the corresponding rate in offspring with an affected father was 172 per 100,000 person-years (95% CI: 156–187) and in offspring with an affected mother was 260 per 100,000 person-years (95% CI: 243–277). Having an affected mother was associated with a 1.45-fold (95% CI: 1.30–1.63) higher risk of epilepsy in the offspring, compared to having an affected father. This maternal effect was found both in male (HR = 1.39, 95% CI: 1.19–1.62) and female offspring (HR = 1.53, 95% CI: 1.30–1.80), and across various ages at onset in the offspring. The maternal effect was also found in familial epilepsies (i.e. where the affected parent had an affected sibling; HR = 1.50, 95% CI: 1.04−2.16). **Interpretation**: We found a clear maternal effect on offspring risk of epilepsy in this nationwide cohort study.

Introduction

Offspring of parents with epilepsy are 2- to 10 times more likely to have epilepsy than offspring of unaffected parents, depending on the type of epilepsy.[1-5] Studies dating back as early as 1880 have shown that this increased risk is higher when the affected parent is the mother rather than the father,[6-8] suggesting the presence of a so-called "maternal effect." Although many of the early studies were based on highly selected samples and were subject to methodological limitations,[8] the maternal effect has also been demonstrated in a series of population-based studies from the Rochester Epidemiology Project.[3-5] In those studies, the risk of unprovoked seizures in the offspring was approximately twofold higher if the affected parent was the mother than if the affected parent was the father.[5] However, two recent studies restricted to familial epilepsies did not replicate the finding.[9,10] In attempts to

resolve this apparent inconsistency, we assessed the association between parental and offspring epilepsy in a study of all children born in Denmark over a 35-year period.

Methods

Study design and study population

Previous studies of the maternal effect in epilepsy have commonly applied either a "downward-looking" or an "upward-looking" analysis strategy.[9] The downward-looking analysis examines the risk of epilepsy in offspring of affected mothers compared to offspring of affected fathers, while the upward-looking analysis examines the risk of having an affected mother compared to having an affected father among affected children. This register-based study was designed to carry out downward-looking analyses, in a prospective population-based setup.

The cohort was established using the Danish Civil Registration System,[11] which has complete coverage of all persons living in Denmark since 1968. To define the population of all parents and their offspring, we considered all singletons (i.e. excluding twin or higher-order multiple births) born in Denmark between 1 January 1981 and 31 December 2016 whose parents were also born in Denmark (N = 1,754,742 offspring). The Civil Registration System is continuously updated with regard to information on vital status, place of residence and emigration. Each person in the register is assigned a unique identification number, which is used for all official and personal registrations. Using the identification number, we were able to accurately link each individual to his or her legal parents and other family members, along with a range of nation-wide social and medical registries.

Epilepsy

Information on epilepsy diagnoses in all study participants and their family members was retrieved from the Danish National Patient Register.[12] The register contains information on all admissions to hospitals in Denmark since 1977, including those at the only private epilepsy center in Denmark (the Epilepsy Hospital, Filadelfia).[13] From 1995 and onwards, all outpatient and emergency room contacts are included as well. In this register, epilepsy diagnoses are classified according to the World Health Organization's International Classification of Diseases. Initially, the 8th revision (ICD-8) was used, but in 1994 the system was replaced by the 10th revision (ICD-10), which remained until the end of the study period in 2016 (ICD9 was never implemented in Denmark). Individuals were considered to have epilepsy if they received an epilepsy diagnosis (IDC-8: 345 [excl. status epilepticus: 345.29] or ICD-10: G40). The onset of epilepsy was defined as the first day of the first hospital contact. Information was also retrieved on the type of epilepsy (focal (ICD-8: 345.3, ICD-10: G40.0-G40.2) and generalized (ICD-8: 345.09-345.11, ICD-10: G40.3)). Using information on both maternal and paternal epilepsy status, we created four exposure categories; both parents unaffected, only father affected, only mother affected, and both parents affected. For this study, we were mainly interested in the comparison of risk of epilepsy in offspring with only an affected mother versus only an affected father. For the analyses of family history, we used information on whether or not the parent had an affected sibling and grouped the offspring into the following categories: offspring with (1) unaffected parents with unaffected siblings, (2) unaffected parents with affected siblings, (3) affected father with unaffected siblings, (4) affected mother with unaffected siblings, (5) affected father with affected sibling, (6) affected mother with affected sibling, (7) both parents affected, (8) affected mother but no maternal siblings, (9) affected father but no paternal siblings, (10) unaffected parents but no parental siblings. We defined the epilepsies as being "familial" if the affected parent had an affected sibling, and as "non-familial" if the affected parent had no affected siblings.

Statistical analyses

The cohort members in the offspring generation were followed from birth until onset of epilepsy, death, emigration or the end of the study period on 31 December 2016, whichever came first. We estimated the incidence rate (IR) of epilepsy in offspring according to parental epilepsy status, which was treated as a time-varying exposure, and used Cox regression models to examine the association between parental and offspring epilepsy. In all analyses, age of the child was used as the underlying time scale and we allowed for separate baseline diagnostic rates of epilepsy (stratum) in males and females. Control for the lack of independence of children within the same family was obtained using a robust (Huber-White) variance estimator. We examined whether the association between parental- and offspring epilepsy varied according to offspring sex and age, by considering the interaction between parental epilepsy and offspring sex and follow-up time (0–4, 5–9, 10–14, 15–19, 20–24, and 25–29 years), respectively. Next, to examine whether the maternal effect was present for both focal and generalized epilepsies, we estimated the offspring risk of (any) epilepsy in a model with an interaction between parental epilepsy status and parental epilepsy subtype (no epilepsy, focal, generalized, or other). The role of family history of epilepsy among the parents was evaluated using three different models; in

model 1, we compared the risk of epilepsy in offspring with various combinations of affected family members to the risk of epilepsy in the offspring with two unaffected parents with unaffected siblings (i.e. the group expected to be at lowest risk). In model 2, we aimed to assess the maternal effect in non-familial epilepsies, and thus compared the epilepsy risk in offspring of affected mothers with that of affected fathers in families where the affected parents did not have any other affected siblings. Finally, in model 3, we aimed to assess the maternal effect in familial epilepsies, and thus compared the risk of epilepsy in the offspring of affected mothers with the risk of epilepsy in the offspring of affected fathers, in families where the affected parent also had an affected sibling. All analyses were adjusted for a range of perinatal and sociodemographic characteristics that were selected a priori, based on the current literature. Information on potential confounders was extracted from various registries[14-16] and included: maternal parity (1, 2, ≥3), the highest level of completed maternal and paternal education at the time of birth (primary, secondary, undergraduate, graduate education), and parental income in the year the child was born (quintiles by year). All estimates were additionally adjusted for psychiatric disorders in the parents, which was treated as a time-varying covariate. Calendar time (cut points: 1981, 1986, 1990, 1994, 1998, 2002, 2006, 2010) was also treated as a time-varying covariate to account for calendar period effects. This was important given the more extensive registration methods post 1995. Proportionality of hazards was assessed using Schoenfeld's scaled residuals, and the assumption was satisfied for all main exposures. Competing risk regression was used to estimate the cumulative incidence of epilepsy in the offspring, while taking into account the risk of dying. We used a nonparametric approach based on the subdistribution hazards for this purpose.[17] In these models, age of the offspring was used as the underlying time scale, and separate risk estimates were estimated according to parental epilepsy status (two unaffected parents, affected mother, and affected father) at the time of birth.

Sensitivity analyses

To examine whether a maternal effect in epilepsy extended to offspring risk of other seizure disorders, we compared the risk of febrile seizures (ICD-8: 780.21; ICD-10: R56.0) [18] in offspring of mothers and fathers with epilepsy. Furthermore, to examine whether a maternal effect was also observed in other brain disorders, we considered risk in offspring of affected parents for migraine (ICD-8: 346; ICD-10: G43),[12] schizophrenia and related disorders (ICD-8: 295.x9, 296.89, 297.x9, 298.29-298.99, 299.04, 299.05, 299.09, 301.83; ICD-10: F20-F29),[19] cerebral palsy (IDC-8: 343.99, 344.99, ICD-10: G80),[12] and concussions (ICD-8: 850.99; ICD-10: S06.0).[12]

For this study, we considered parental epilepsy status as a time-varying exposure, meaning that the offspring were considered as having an unaffected parent up until the date of the parents' first hospital contact with epilepsy, if any. However, if the association between offspring risk of epilepsy and parental epilepsy is entirely genetic, it could be argued that the offspring should be considered as exposed from birth, regardless of when the parent's first hospital contact for epilepsy occurred (i.e. even if the parent had onset of epilepsy after birth of the child). To assess the potential impact of treating parental epilepsy as a time varying covariate, we therefore carried out a sensitivity analysis where parental epilepsy status was defined by their diagnosis at any time up to the end of the study period on 31 December 2016. Finally, since parental epilepsy diagnoses were only available from 1977 and onwards, we carried out a sensitivity analysis restricted to offspring of parents born after 1967 (n = 793,252), where we had full diagnostic information in all parents from at least 10 years of age. The analysis included an interaction with offspring age (0-4, 5-9, 10-14, and ≥ 15 years), to account for the different age-structure of the full- and restricted cohort. We were unable to restrict the cohort further (i.e. to offspring of parents born after 1977) because of the very short remaining follow-up period in the offspring (median age at end of follow-up in this cohort was only 4.5 years).

All analyses were conducted using Stata, version 15.[20]

Results

We included 1,754,742 individuals in the offspring generation contributing 31,601,243 person-years of follow-up. Follow-up was stopped before the end of the study period for 35,568 offspring (2.0%) due to either emigration (1.3%) or death (0.8%). The median offspring age at the end of follow-up was 18.3 years (interquartile range = 9.5–26.4 years). When parents' epilepsy status was assessed at the end of follow-up, a total of 1,698,959 (96.8%) individuals had two unaffected parents, 27,079 (1.5%) had an affected father, 28,039 (1.6%) had an affected mother, and 665 (0.04%) had two affected parents (Figure 1). The IR of epilepsy in offspring of two unaffected parents was 78.8 (95% CI: 77.8–79.8) per 100,000 person-years, while the corresponding rate was higher in offspring with an affected father (IR = 172 per 100,000 person-years, 95% CI: 158–187), an affected mother (IR = 260 per 100,000 person-years, 95% CI: 243–277) or two affected parents (IR = 622 per 100,000 person-years, 95% CI: 456–848). After adjustment for

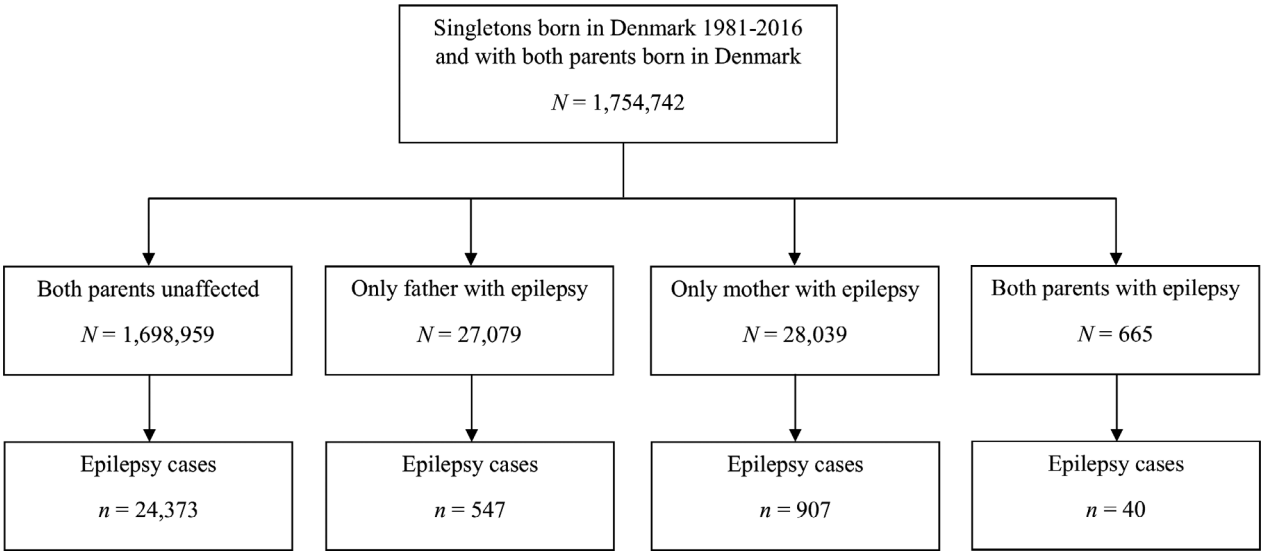

Figure 1. Flowchart of the study population, with parental epilepsy status assessed at the end of follow-up 31 December 2016

potential confounders, the risk of epilepsy was 1.45 (95% CI: 1.30–1.63) times higher in offspring of affected mothers than in offspring of affected fathers (Table 1). This did not differ between male (HR = 1.39, 95% CI: 1.19–1.62) and female (HR = 1.53, 95% CI: 1.30–1.80) offspring (*P*-value for interaction = 0.378). The 30-year cumulative risk of epilepsy was 2.1% (95% CI: 2.1–2.2%) in offspring of two unaffected parents, 5.3% (95% CI: 4.7–6.0%) in offspring of affected fathers and 8.1% (95% CI: 7.4–8.9%) in offspring of affected mothers (Figure 2). The cumulative incidence curves in Figure 2, furthermore suggested that the maternal-paternal difference became particularly evident during adolescence and early adulthood.

The higher risk of epilepsy in offspring of affected mothers compared to offspring of affected fathers was evident

Table 1. Cox regression analyses showing the relative risk of epilepsy in offspring born to mothers with epilepsy, compared to offspring born to fathers with epilepsy, in a cohort of 1,754,742 children born in Denmark from 1981 to 2016

Parental epilepsy[1]	Person-years of follow-up	Number of offspring with epilepsy	Incidence rate per 100,000 person-years (95% CI)	Basic adjustment Hazard ratio[2](95% CI)	Fully adjusted hazard ratio[3](95% CI)
All, *n* = 1,754,742					
No parent with epilepsy	30,926,254	24,373	78.8 (77.8-79.8)	0.42 (0.39-0.46)	0.47 (0.43-0.52)
Only father with epilepsy	318,972	547	172 (158-187)	1.00 (ref)	1.00 (ref)
Only mother with epilepsy	349,585	907	260 (243-277)	1.46 (1.31-1.63)	1.45 (1.30-1.63)
Both parents with epilepsy	6,435	40	622 (456-848)	3.70 (2.65-5.17)	3.27 (2.31-4.62)
Male offspring, n = 901,255					
No parent with epilepsy	15,857,683	12,671	79.9 (78.5-81.3)	0.41 (0.37-0.46)	0.46 (0.40-0.52)
Only father with epilepsy	164,507	292	178 (158-199)	1.00 (ref)	1.00 (ref)
Only mother with epilepsy	179,160	458	256 (233-280)	1.39 (1.19-1.61)	1.39 (1.19-1.62)[4]
Both parents with epilepsy	3,383	22	650 (428-988)	3.70 (2.42-5.67)	3.24 (2.09-5.02)
Female offspring, n = 853,487					
No parent with epilepsy	15,068,571	11,702	77.7 (76.3-79.1)	0.44 (0.39-0.50)	0.49 (0.43-0.56)
Only father with epilepsy	154,465	255	165 (146-187)	1.00 (ref)	1.00 (ref)
Only mother with epilepsy	170,425	449	263 (240-289)	1.55 (1.32-1.81)	1.53 (1.30-1.80)[4]
Both parents with epilepsy	3,052	18	590 (372-936)	3.69 (2.30-5.93)	3.29 (2.02-5.37)

[1]Parental epilepsy is treated as a time-varying exposure.
[2]Estimates are adjusted for offspring sex, and calendar year.
[3]Estimates are additionally adjusted for parity, maternal and paternal education, parental income, and parental psychiatric disorders.
[4]*P*-value for interaction: 0.378

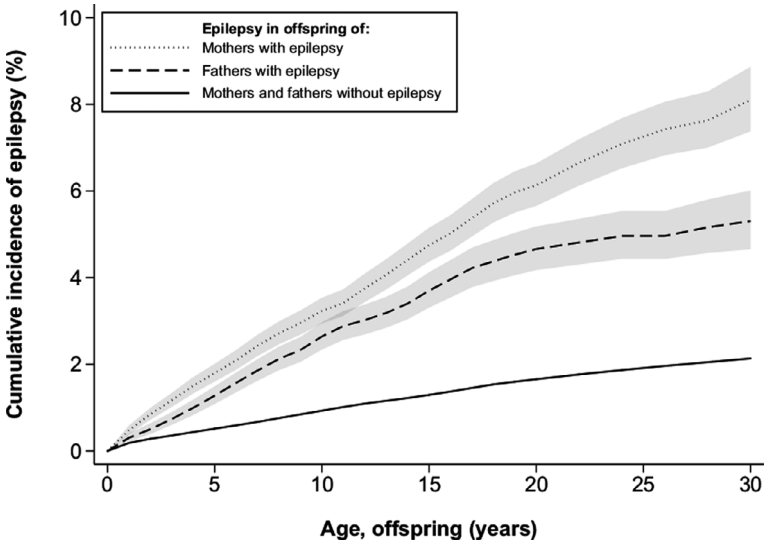

Figure 2. Cumulative incidence of epilepsy in offspring according to parental epilepsy at the time of birth, in a cohort of 1,754,742 children born in Denmark from 1981 to 2016

across all age at onset categories in the offspring (Table 2). The maternal effect on offspring risk of epilepsy was least pronounced between ages 5–9 years (HR = 1.29, 95% CI: 1.03–1.63) and most pronounced between ages 25 and 29 years (HR = 2.01, 95% CI = 1.13–3.56).

When considering the risk of epilepsy in offspring of affected parents with focal versus generalized epilepsy, we found that having a parent with generalized epilepsy, regardless of the sex of the affected parent, was associated with higher rates of epilepsy in the offspring than was focal epilepsy (Table 3). However, the maternal effect was similar for generalized (HR = 1.43, 95% CI: 1.19–1.72) and focal epilepsies (HR = 1.36, 95% CI: 1.06–1.74), *P*-value for interaction = 0.751.

We then examined whether the maternal effect was influenced by family history of epilepsy in the affected parent (Table 4). To do this, we ran a set of models using different reference groups (*model 1*: unaffected parents with unaffected siblings; model 2: affected father with unaffected siblings; model 3: affected father with affected sibling). We found that having an affected mother without an affected sibling was associated with a 1.47-fold (95% CI: 1.28–1.69) higher risk of epilepsy in the offspring, compared with having an affected father without an affected sibling (model 2). Similarly, having an affected mother with an affected sibling was associated with a 1.50-fold (95% CI: 1.04–2.16) higher risk of epilepsy in the offspring, compared with having an affected father with an affected sibling (model 3). Thus, the maternal effect was seen in both familial and non-familial epilepsies.

The risk of febrile seizures was not higher in offspring of mothers with epilepsy than in offspring of fathers with epilepsy (HR = 1.08, 95% CI: 0.98–1.20). When considering other neurological and psychiatric disorders, we found that having a mother vs. a father with the disorder, generally conferred a slightly higher risk for the same disorder in the offspring, although the maternal effect was less pronounced than what we found for epilepsy (maternal effect in migraine HR = 1.15, 95% CI: 1.01-1.31; schizophrenia HR = 1.19, 95% CI: 1.04–1.37; cerebral palsy HR = 1.20, 95% CI: 0.39-3.63; concussion HR = 1.13, 95% CI: 1.10–1.17). These findings suggest that potential methodological issues related to ascertainment or nonpaternity (which should not be specific to epilepsy) cannot fully explain the maternal effect seen in epilepsy.

Finally, the estimate of the maternal effect was very similar when based on the parent's epilepsy status at the end of the study period (HR = 1.47, 95% CI: 1.33–1.62), rather than treating parent's epilepsy as a time-varying covariate. In the restricted cohort of offspring of parents born after 1967, the estimates of the maternal effect were similar to those in the overall analysis (presented in Table 2), although several estimates did not reach statistical significance (maternal effect in offspring aged 0–4 years: 1.18, 95% CI: 0.92–1.51; age 5-9 years: 1.29, 95% CI: 0.93–1.79; age 10–14 years: 1.74, 95% CI: 1.06–2.84; and age ≥ 15 years: 1.50, 95% CI: 0.86–2.62).

Discussion

In this large population-based study of children born in Denmark, we found robust evidence of a maternal effect in epilepsy. Having an affected mother with epilepsy was

Table 2. Cox regression analyses[1] showing the risk of epilepsy in offspring at various ages, depending on parental epilepsy status in a cohort of 1,754,742 children born in Denmark from 1981 to 2016

	Risk of being diagnosed with epilepsy at ages:											
	0–4 years		5–9 years		10–14 years		15–19 years		20–24 years		25–29 years	
Parental epilepsy[1]	*N*[2]	HR (95% CI)[3]	*N*[2]	HR (95% CI)[3]	*N*[2]	HR (95% CI)[3]	*N*[2]	HR (95% CI)[3]	*N*[2]	HR (95% CI)[3]	*N*[2]	HR (95% CI)[3]
No parent with epilepsy	8,423	0.49 (0.41–0.58)	5,781	0.43 (0.36–0.51)	4,188	0.40 (0.33–0.49)	3,246	0.46 (0.37–0.57)	1,666	0.59 (0.43–0.80)	825	0.78 (0.49–1.24)
Only father with epilepsy	149	1.00 (ref)	130	1.00 (ref)	109	1.00 (ref)	87	1.00 (ref)	44	1.00 (ref)	19	1.00 (ref)
Only mother with epilepsy	283	1.47 (1.19–1.81)	198	1.29 (1.03–1.63)	176	1.43 (1.12–1.82)	142	1.53 (1.17–2.02)	66	1.62 (1.09–2.40)	35	2.01 (1.13–3.56)
Both parents with epilepsy	-	-	-	-	-	-	-	-	-	-	-	-

[1]Parental epilepsy is treated as a time-varying exposure.
[2]Number of offspring with onset of epilepsy
[3]Estimates are adjusted for offspring sex, calendar year, parity, parental education, parental income, and parental psychiatric disorders.

associated with approximately ~ 45% greater risk of epilepsy in the offspring, compared with having an affected father with epilepsy. This finding was very consistent, and was present both in male and female offspring and for onset of epilepsy from birth until 30 years of age. The maternal effect was present in both focal and generalized epilepsies, and in both familial and nonfamilial epilepsies.

In this study, we found a 30-year cumulative incidence of epilepsy of 2.1% (95% CI: 2.1–2.2%) in offspring of two unaffected parents, 5.3% (95% CI: 4.7–6.0%) in offspring of affected fathers and 8.1% (95% CI: 7.4–8.9%) in offspring of affected mothers. These findings are partially consistent with previous population-based estimates from Rochester, Minnesota, where the 25-year cumulative incidence of unprovoked seizures was 1.6% in the general population, 2.4% in offspring of affected fathers and 8.7% in offspring of affected mothers.[5] However, unlike the Rochester study, where numbers were much smaller, we found that epilepsy risk in offspring of affected fathers was significantly higher than in the general population (approximately 2-fold). Correspondingly, our estimate of the maternal effect (HR = 1.45, 95% CI: 1.30–1.63) was somewhat lower than the estimate reported in Rochester (relative risk = 2.1, after adjustment for potential confounders).[5] Our findings are, however, in line with previous clinic-based studies reporting estimates of the maternal effect in the ranges between 1.5 and 1.7.[21,22]

When considering the offspring's risk of epilepsy across age, we found that the excess risk of epilepsy associated with having an affected father seemed to wear off in late adolescence and early adulthood (Figure 2). This was contrary to what we found for offspring of affected mothers, where the increase persisted throughout the period of observation (i.e. at least until age 30). This may indicate that the maternal-paternal difference over the life-course may be even more pronounced than what we and others have found so far. Future studies with long-term follow-up are however needed to corroborate this finding.

In this study, the maternal effect was observed in offspring of parents with both generalized and focal epilepsies. While these findings must be interpreted with caution due to a relatively low diagnostic validity of the registered epilepsy subtypes,[13] it is interesting to note that the incidence of epilepsy in offspring of parents with focal epilepsy was lower than the incidence of epilepsy in offspring of parents with generalized epilepsy, providing some indirect support for the validity of the registered epilepsy subtypes. For focal as well as for generalized epilepsy, we identified a maternal effect, that is, the risk of epilepsy associated with having an affected mother was increased by approximately 40%, compared with the risk associated with having an affected father. In the most recent study based on the Rochester data,[3] the maternal

Table 3. Cox regression analyses showing the risk of epilepsy in offspring according to parental focal and generalized epilepsy in a cohort of 1,754,742 children born in Denmark from 1981 to 2016

Parental epilepsy, subtype[1]	Person-years of follow-up	Number of offspring with epilepsy	Incidence rate of epilepsy (any) in offspring per 100,000 person-years (95% CI)	Basic adjustment Hazard ratio[2] (95% CI)	Fully adjusted hazard ratio[3](95% CI)
Focal epilepsy					
No parent with epilepsy	30,926,254	24,373	78.8 (77.8-79.8)	0.50 (0.42-0.61)	0.54 (0.45-0.66)
Only father with focal epilepsy	75,256	104	138 (114-167)	1.00 (ref)	1.00 (ref)
Only mother with focal epilepsy	85,716	167	194 (167-227)	1.36 (1.07-1.74)	1.36 (1.06-1.74)[4]
Both parents with focal epilepsy	NA	NA	NA	-	-
Generalized epilepsy					
No parent with epilepsy	30,926,254	24,373	78.8 (77.8-79.8)	0.31 (0.27-0.36)	0.35 (0.30-0.41)
Only father with generalized epilepsy	73,373	181	247 (213-285)	1.00 (ref)	1.00 (ref)
Only mother with generalized epilepsy	94,390	342	362 (326-403)	1.45 (1.21-1.74)	1.43 (1.19-1.72)[4]
Both parents with generalized epilepsy	NA	NA	NA	-	-

[1]Parental epilepsy is treated as a time-varying exposure. If a parent was registered with both focal and generalized epilepsy, we classified them according to the first occurrence.
[2]Estimates are adjusted for offspring sex, and calendar year.
[3]Estimates are additionally adjusted for parity, maternal and paternal education, parental income, and parental psychiatric disorders.
[4]*P*-value for interaction: 0.751

Table 4. Cox regression analyses showing the risk of epilepsy in offspring according to family history of epilepsy, in a cohort of 1,754,742 children born in Denmark from 1981 to 2016, and presented for three different comparison groups (Models 1-3).

Family history of epilepsy[4]	Person-years of follow-up	Number of offspring with epilepsy	Incidence rate per 100,000 person-years (95% CI)	Model 1[1] Fully adjusted hazard ratio[5] (95% CI)	Model 2[2] Fully adjusted hazard ratio[5] (95% CI)	Model 3[3] Fully adjusted hazard ratio[5] (95% CI)
Unaffected parents with unaffected sibling	25,017,150	19,642	78.5 (77.4-79.6)	1.00 (ref)	0.48 (0.43–0.54)	0.29 (0.22–0.39)
Unaffected parents with affected sibling	1,539,162	1,583	103 (98–108)	1.25 (1.19–1.32)	0.60 (0.53–0.68)	0.37 (0.27–0.49)
Affected father with unaffected sibling	200,542	336	168 (151–186)	2.09 (1.87–2.34)	1.00 (ref)	0.61 (0.44–0.84)
Affected mother with unaffected sibling	235,582	601	255 (236–276)	3.07 (2.82–3.35)	1.47 (1.28–1.69)	0.90 (0.66–1.22)
Affected father with affected sibling	17,377	50	288 (218–380)	3.43 (2.55–4.62)	1.64 (1.20–2.25)	1.00 (ref)
Affected mother with affected sibling	20,763	95	458 (374–559)	5.15 (4.17–6.36)	2.47 (1.94–3.13)	1.50 (1.04–2.16)
Affected mother and affected father	6435	40	622 (456–847)	7.07 (5.06–9.89)	3.38 (2.38–4.82)	2.06 (1.32–3.22)
Affected father but no paternal siblings	101,053	161	159 (137–186)	2.06 (1.74–2.44)	0.99 (0.81–1.21)	0.60 (0.43–0.84)
Affected mother but no maternal siblings	93,240	211	226 (198–259)	2.82 (2.43–3.27)	1.35 (1.12–1.62)	0.82 (0.59–1.15)
Unaffected parents but no parental siblings	4,369,942	3,148	72.0 (69.6–74.6)	1.04 (1.00–1.08)	0.50 (0.44–0.56)	0.30 (0.22–0.41)

[1]Model 1: reference group is offspring with two unaffected parents with unaffected siblings (i.e. the group with the lowest risk).
[2]Model 2: reference group is offspring of affected fathers with no affected siblings (non-familial epilepsy)
[3]Model 3: reference group is offspring of affected fathers with affected sibling (familial epilepsy)
[4]Parental epilepsy is treated as a time-varying exposure, while family history of epilepsy is treated as time-fixed.
[5]Estimates are adjusted for offspring sex, calendar year, parity, parental education, parental income, and parental psychiatric disorders.

effect was only seen in offspring of parents with focal epilepsy, while other studies report a maternal effect in various types of generalized epilepsies (including juvenile myoclonic epilepsy),[23-25] although findings are not entirely consistent in the literature.[26] In the present study, we were limited by the lack of clinical information available in the registers, and were consequently unable to examine individual epilepsy syndromes specifically.

In two recent studies of multiplex families,[9,10] there was no evidence of a maternal effect, suggesting that the distribution of causal genetic and non-genetic factors may differ between sporadic and familial epilepsies. However, these studies were based on highly selected populations. In the present population-based study, we found that the maternal effect was also seen in familial epilepsy defined as epilepsy in the siblings of affected parents. However, our definition of familial epilepsy did not include other configurations such as epilepsy in siblings of the offspring. In subsequent analyses, it would be of interest to extend the definition to include siblings of the at-risk offspring, which will require additional adjustment for ascertainment bias.

Possible explanations for the maternal effect have been discussed extensively over the past few decades,[8,9,24] but none of them fully explains the finding. We found maternal effects in other brain disorders, such as migraine, schizophrenia and cerebral palsy, but in none of these disorders was the effect as pronounced as in epilepsy. A slight maternal effect was also seen for concussions – a condition that is otherwise thought to have little or no genetic contribution. These findings suggest that potential issues related to ascertainment or non-paternity cannot fully explain the maternal effect seen in epilepsy, which is in line with conclusions from previous reports.[3,8] Other explanations include perinatal or pregnancy factors, such as seizure occurrence or use of antiepileptic drugs (AEDs).[5] For instance, maternal use of valproate in pregnancy is known to adversely influence fetal development and increase offspring risk of neurodevelopmental disorders.[27,28] However in the studies from Rochester, the maternal effect was found both in women using and not using AEDs during pregnancy,[4] and currently there is no robust evidence to suggest that AEDs used in pregnancy contributes to offspring epilepsy risk. Furthermore there is no evidence of mitochondrial inheritance in most common forms of epilepsy, which could otherwise explain a maternal effect.[29] A maternal effect would, however, arise if the proportion with generalized epilepsy is higher among mothers with epilepsy than among fathers with epilepsy, because generalized epilepsies are associated with higher rates of offspring epilepsy than are focal epilepsies. Although the commonest form of heritable epilepsy, genetic generalized epilepsy, is more common in women than in men,[30] this does not explain the maternal effect since the magnitude of the maternal effect was similar when restricted to parents with either focal or generalized epilepsy.

Perhaps most plausible, is the hypothesis of selective fertility; that is, that men with genetic forms of epilepsy are less likely to reproduce than are women with genetic forms. This would result in a higher proportion of affected children (of either sex) born to mothers with epilepsy compared to fathers with epilepsy as found in this study. Future research utilizing genetic information could clarify whether the "genetic load" for epilepsy is higher in women with epilepsy who reproduce than in men with epilepsy who reproduce.

Strengths and limitations

This was a population-based study of all singleton children born in Denmark during a 35-year period and included more than 31 million person-years of follow-up. In view of this large population size and extended follow-up period, we were able to robustly estimate the risk of epilepsy in offspring of affected mothers and fathers, and examine the influence of family history of epilepsy in a population-based setting. The study was based entirely on information from nationwide registries, and owing to the virtually complete coverage of the population registers, bias arising from sampling and attrition was low. In total, only 2.0% were lost to follow-up due to either death or emigration before the study ended. Furthermore, a validation study of the epilepsy diagnoses in the Danish National Patient Register has shown that the overall epilepsy diagnosis has a good positive predictive value (81%, 95% CI: 75%–87%) when validated against the International League Against Epilepsy classification.[13]

Our ascertainment of epilepsy in the parents and parental siblings was limited by the coverage of the Danish National Patient Registry, which does not hold information about epilepsy contacts prior to 1977. This suggest that our ascertainment of parental epilepsies with onset in early life was incomplete. Age at onset distributions in epilepsy differ somewhat between males and females, with males having higher rates of epilepsy than females in early childhood.[31] Thus, misclassification of parental epilepsy status may have been more pronounced in males, if the epilepsy did not persist into the period of coverage for the register. In addition, previous studies have shown that early age at onset among affected parents is associated with higher transmission risk to the offspring.[5] To address this issue, we carried out a sensitivity analysis, where the study population was restricted to offspring with parents born after 1967, and where we had full information on parental epilepsy contacts from at least 10 years of age.

The estimates of the maternal effect were generally in line with the findings from the main analyses, although there was some indication of attenuation of the maternal effect in offspring below the age of 5 years. The reason for the weaker maternal effect for early onset epilepsies is unclear, but could possibly be due to the fact that many epilepsies in young children have other causes (e.g. severe perinatal complications, *de novo* mutations in specific genes), than do epilepsies with onset later in life.

Conclusion

The findings from this large population-based study showed a clear maternal effect in epilepsy, thereby confirming the results of previous population-based studies. This study also provides the first evidence that the maternal effect may extend to familial epilepsies, but the paradox of the absence of a maternal effect in selected high density families[9] remains unexplained.

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Author contributions

JWD, CAE, SFB, CC, RO, and JC contributed to the conception and design of the study. The analytical approach was prepared by all authors, while data management and analysis was performed by JWD. JWD drafted the manuscript and all authors critically reviewed the manuscript and approved the final version.

Conflicts of Interest

Nothing to report.

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