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PERINATAL EPIDEMIOLOGY

Preconceptional paternal antiepileptic drugs use and risk of congenital anomalies in offspring: a nationwide cohort study

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Abstract
Recent studies have shown that certain pharmacological agents used by fathers before conception may increase the risk of adverse neonatal outcomes in offspring. However, little is known about the effect of paternal use of antiepileptic drugs (AEDs) on congenital anomalies in children. Based on Danish national registers, we conducted a cohort study of 733, 282 singletons born from 1997 to 2008, with follow-up throughout 2013. The children whose fathers used AEDs during the 3 months before conception were categorized as the exposed. Logistic regression model was used to examine association between paternal AEDs use before conception and the risk of congenital anomalies in offspring. Compared with unexposed children, the exposed had a 23% increased risk of congenital anomalies (odds ratios (OR) 1.23, 95% confidence interval [CI] 1.10–1.37) after adjusting for potential confounders. When extending the exposure window to 1 year before conception to the end of pregnancy, except for those using AEDs during 3 months before conception (the susceptible period of exposure), the increased risks were also observed in children whose fathers were former users (i.e., those using AEDs only from 1 year to 3 months before conception) (OR 1.29, 95%CI 1.03–1.61) and later users (i.e., those using AEDs only during pregnancy) (OR 1.35, 95%CI 1.12–1.65). This study suggested that the mildly increased risk of congenital anomalies in the offspring associated with paternal AEDs use before conception may be attributable to the underlying indications related to AEDs use.

Keywords Antiepileptic drugs · Preconceptional paternal drugs use · Congenital anomalies · Nationwide cohort study

Introduction

Epilepsy is a common neurological condition affecting individuals of all ages, with the lifetime prevalence of 7.60 per 1000 persons [1]. Most of those affected, including people of childbearing age, will require long term treatment with antiepileptic drugs (AEDs) to prevent seizures. Since the first reports of AEDs teratogenicity dated from the 1960s [2, 3], the safety of AEDs usage in pregnant women with epilepsy has been studied intensively. Findings from a systematic review published in 2008 which identified 59 register-based or cohort studies suggested higher congenital anomaly rates among children of mothers with epilepsy than expected, and the increased risk could be mainly attributed to AEDs exposure [4]. Additionally, the latest systematic review and network meta-analysis in 2017 demonstrated a consistent pattern that exposure to maternal AEDs use during pregnancy was associated with an increased risk of major congenital anomalies in offspring [5].

As maternal AEDs exposure during pregnancy plays a role in fetal, even in child's, development, extended effects

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of earlier exposure on gamete, particularly human sperm, are highly expected and biologically plausible. Therefore, the potential role of paternal AEDs use in development of congenital anomalies comes to be a concern in perspectives of clinical practice and public health. Epidemiological studies have shown epilepsy to be more common in males [6], and approximately 0.3% of fathers, reported by studies in the Nordic countries, were dispensed AEDs during the last 3 months before conception [7, 8]. Although data on the potential teratogenic effect of paternal prenatal AEDs use is still limited, the hypothesis of increased risks of developmental defects associated with paternal factors is not novel. A number of epidemiological studies have shown that paternal factors such as age, diet, weight, stress, certain pharmacological drugs, and alcohol consumption contribute, independently of maternal factors, to a wide range of health outcomes in offspring including congenital anomalies, behavioral problems, developmental disorders, obesity, diabetes, cardiovascular disease, and cancer [9–13]. As for AEDs, human and animal studies demonstrated that treatment with this medication could induce impaired sperm quality (decreased sperm concentration, lower sperm motility rate and abnormal sperm morphology) and increased sperm DNA damage [14–18], which has been linked to diminished fertility, adverse pregnancy outcomes (such as pregnancy loss), and increased risks of childhood diseases [19].

To date, no large population-based study has investigated the association between preconceptional paternal AEDs use and offspring congenital anomalies. In the present study using data from nationwide healthcare registers in Denmark, we examined the risk of congenital anomalies in children whose fathers used AEDs during the last 3 months before conception.

Methods

We conducted a nationwide cohort study based on linkage of several national registers in Denmark. All residents in Denmark are assigned a unique personal identification number (a 10-digit civil registration system number used in all registries, which enables accurate linkage of national registries at the individual level [20]). Secondary data were retrieved using encrypted identification numbers and all analyses were performed at the secure platform of Statistics Denmark, so that there was no access to the personal identification numbers of the participants. The Danish Data Protection Agency approved this project (Record No. 2013-41-2569).

Study population

We identified all singletons born alive in Denmark from January 1, 1997 to December 31, 2008 in the Danish Medical Birth Registry (DMBR).The DMBR contains records of all deliveries in Denmark since 1973 and includes information on gestational age at birth from 1978 [21]. Among 752, 712 singleton live births identified during the study period, we excluded 18, 690 children of whom we could not identify their fathers, 29 without information on their mothers, 290 without information on parity, and 421 who had missing or extreme values of gestational age (≤ 22 weeks or ≥ 45 weeks). Finally, 733, 282 children were included in the analyses.

Paternal AEDs use before conception

Information on AEDs use was retrieved from the Danish National Prescription Registry which has recorded all redeemed prescriptions since 1995 in Denmark with the following information: civil registration number of the patient, dispensing date, medication code (the WHO Anatomical Therapeutic Chemical (ATC) classification system), number of packages prescribed, and number of dose units in each package [22]. AEDs use was identified based on the ATC code: Barbiturates and derivatives (N03AA), Hydantoin derivatives (N03AB), Oxazolidine derivatives (N03AC), Succinimide derivatives (N03AD), Benzodiazepine derivatives (N03AE), Carboxamide derivatives (N03AF), Fatty acid derivatives (N03AG) and other AEDs (N03AX). The date of conception was estimated by subtracting gestational age at birth from the date of delivery. Spermatogenesis is estimated to take approximately 74 days [12], therefore we defined the time window of exposure as the last 3 months before conception. Accordingly, a child was categorized into the exposed group if the dispensing date for paternal AEDs treatment fell within the specified exposure window (i.e., the last 3 months before conception) or the number of days for which the AEDs was supplied overlapped with the exposure window. Children born to fathers who had no prescriptions for AEDs and no supply overlap during the entire exposure window were categorized as the unexposed. For further analyses, we extracted data on paternal AEDs use during the last 1 year before conception of the index pregnancy. We also retrieved data on parental AEDs use during the index pregnancy.

Congenital anomalies in children

Information on the diagnosis of congenital anomalies was obtained from the Danish National Patient Register (DNPR) which has collected data on all inpatients from all somatic hospitals in Denmark since 1977 and outpatients from 1995 [23]. During the study period, the diagnosis of congenital anomalies was based on the International Classification of Diseases, 10th version (ICD-10) codes of Q00–Q99. Validation studies of the DNPR suggested that the national registrations were correct for 88% of malformation diagnoses overall [24, 25]. Offspring were followed up from birth until the first diagnosis of a congenital anomaly, death, emigration, or December 31, 2013, whichever came first. The main analyses included the diagnosis of all congenital anomalies throughout the entire follow-up period. To evaluate the effect of potential misclassification of outcome, we restricted congenital anomaly cases to those diagnosed before the child reached 1 year of age, as these were expected to be more severe and the diagnoses more valid. More detailed analyses on sub-categories of congenital anomalies were also performed (ICD-10 codes are shown in Table S1 in the Supplement).

Covariates

For each child, we obtained information on calendar year of birth, gender, birth weight, Apgar score at 5 min, gestational age, parity, maternal years of education and smoking status during pregnancy, cohabitation of parents, and parental age at child's birth from the DMBR. Parental history of congenital anomalies before birth of the child was obtained from DNPR by ICD-8 codes 740–759 from 1977 to 1993 and ICD-10 codes Q00–Q99 from 1994 and onward. Furthermore, we identified parents diagnosed with epilepsy (ICD-8 code: 345 before 1994, ICD-10 code: G40 from 1994 to 2008).

Statistical analysis

All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina, USA). Baseline characteristics of children with and without paternal AEDs use before conception were compared. Since most congenital anomalies are supposed to occur during pregnancy, the time of the diagnoses is not a good indicator to the time of events. Therefore, logistic regression model was used to derive odds ratios (OR) and 95% confidence intervals (CIs) as estimates of relative risks for congenital anomalies amongst children following paternal preconceptional AEDs use compared with those without preconceptional AEDs use.

Confounding factors were evaluated on the basis of their hypothesized relationship with children's congenital anomalies and paternal AEDs use. We adjusted for the following potential confounders: calendar year of birth (1997–1999, 2000–2002, 2003–2005, 2006–2008), gender of the child (boy, girl), parity (1, 2, ≥ 3), parental age at child birth (≤ 25, 26–30, 31–35, and > 35 years), maternal smoking status during pregnancy (yes or no), and parental history of congenital anomalies before birth of the child (yes or no) (model 1). We additionally adjusted for paternal history of epilepsy before conception (yes or no) (model 2).

We conducted sub-analyses according to the types of paternal AEDs use before conception. Here we choose four most commonly used antiepileptic drugs-carbamazepine (N03AF01), lamotrigine (N03AX09), oxcarbazepine (N03AF02), and valproic acid (N03AG01). The risks of sub-categories of congenital anomalies among children with paternal AEDs use were also estimated.

To distinguish the direct effect of AEDs from that of the underlying indication (including but not limited to epilepsy), we extended the exposure window to a longer period that was from 1 year before conception to child birth. We thus examined the effects of AEDs use before or after, but not during, the main time window (3-month before conception). The reference group consisted of those children born to fathers who never used AEDs from 1 year before conception to child birth. This so-called negative-control analytic strategy allowed us to identify: (1) the group of children born to fathers who used AEDs only during the period from 1 year to 3 months before conception (former users); (2) the group of children born to fathers who initiated AEDs treatment during the 3 months before conception, and were likely to continue AEDs treatment after the conception date (current users); (3) and the group of children born to fathers who used AEDs only during pregnancy (later users). Considering that spermatogenesis of inseminating sperm happened during the 3 months before conception, the risks of congenital anomalies observed among children of former users might reflect the effect of underlying indication rather than the AEDs use itself. As for later users, these fathers might experience the onset of the underlying condition that needs AEDs treatment during pregnancy, and the risk observed in offspring might indicate the role of paternal underlying conditions that contributed to the occurrence of indication for AED use.

To further disentangle the effect of AEDs medication from that of the main indication (i.e., epilepsy), we performed stratified analyses according to paternal history of epilepsy before birth of the index child.

To control for unmeasured family-related confounding factors (such as genetic liability for congenital anomalies and early postnatal environmental influences), we conducted a sibling-matched analysis including the families with multiple children born in our study period and with at least one child with the exposure to paternal AEDs and one child without the exposure. We then compared exposure- and outcome-discordant siblings to estimate the association between paternal AEDs exposure and congenital anomalies in children using conditional logistic regression model.

We then used the following analytic strategies to assess the robustness of these findings: (1) Stratified analysis was performed to examine the extent to which the association between paternal AEDs use and congenital anomalies in children differed by fetal gender; (2) Considering the teratogenicity of maternal epilepsy and AEDs use during pregnancy, we restricted the analyses to the children whose mothers neither used AEDs nor had an diagnosis of epilepsy during pregnancy; (3) The Danish National Prescription Registry did not have information on AEDs treatment given during hospitalization, therefore, those exposed fathers who were inpatient during the 3 months before conception might be misclassified as unexposed. To control this information bias, we re-conducted the analysis by excluding those fathers whose onset of epilepsy was during the 3 months before conception; and (4) We did a sub-analysis by only including congenital anomalies diagnosed before 1 year of age, which were expected to be more severe with a higher validity of diagnosis.

Considering significant differences in several baseline characteristics between the exposed group and unexposed group, which might not be fully addressed by multivariate analyses, we further created a propensity score matched (PSM) sub-cohort to reduce potential selection bias. The propensity scores were estimated using logistic regression as the probability of paternal AEDs exposure given some of the baseline factors. The independent variables included in propensity score model were birth weight of the child, parity, preterm birth, parental age at child birth, maternal smoking and AEDs use during pregnancy, maternal history of epilepsy, and parental history of congenital anomalies. We then used greedy match algorithms to match exposed group to unexposed group. After the matched pairs were identified, standardized differences of the variables between matched pairs were evaluated. In the PSM sub-cohort, the risk of congenital anomalies amongst children with paternal AEDs use before conception was calculated with additional adjustment for the calendar year of birth, gender of the child, and paternal history of epilepsy before conception.

The 3-month susceptible period that we defined was based on theory of the so-called 70–90 day-long spermatogenesis, whereas it may also be possible that AEDs induce adverse effects (including sperm damage) at the very primitive stage. Hence, we defined another exposure period as 6 months before conception and repeated all the above analyses.

Results

Characteristics of the study cohort

Among all singletons included in the study, 3086 children (0.42%) were born to fathers who used AEDs during the 3 months before conception. During the study period, 73, 445(10.0%) children were diagnosed with congenital anomalies. The median age at diagnosis of congenital anomalies was 0.60 years (interquartile range: 0.03 to 2.91 years). Characteristics of the study population are shown in Table 1. Compared with the unexposed group (i.e., those children whose fathers had no AEDs use during the 3 months before conception), a higher proportion of exposed children (i.e., those children whose fathers used AEDs during the 3 months before conception) were born in later calendar years. Not surprisingly, fathers with history of epilepsy in the exposed group (64.3%) were far more frequent than those in unexposed group (0.9%). In addition, fathers of exposed children were more likely to have a history of congenital anomalies before birth of the child. Mothers of exposed children were characterized as being more likely to smoke and have lower educational attainment during pregnancy. Besides, the percentage of mothers who have history of epilepsy in the exposed group was slightly higher than that in the unexposed group.

Risk of congenital anomalies

The association between paternal AEDs use and congenital anomalies in children was shown in Table 2. Overall, we identified 73,073 cases of congenital anomalies in unexposed children (100.1 per 1000 children), as compared with 372 cases who were exposed (120.5 per 1000 children), corresponding to an OR of 1.23(95%CI 1.11–1.37). The adjusted OR (aOR) of congenital anomalies did not change after adjusting for potential confounders included in model 1. Additional adjustment for parental history of epilepsy in model 2 attenuated the estimate slightly (aOR 1.19, 95%CI 1.05–1.34). In the sub-analysis when extending the exposure window to 1 year before conception to child birth, the children born to current users had an elevated risk of congenital anomalies (aOR 1.56, 95%CI 1.16–2.10). The increased risk was also observed in children born to former users (aOR 1.29, 95%CI 1.03–1.61) as well as later users (aOR 1.35, 95%CI 1.12–1.65).

When we looked into the effect of the four most commonly used AEDs, only lamotrigine and oxcarbazepine used by fathers before conception were associated with higher risk of congenital anomalies (Table S2).

In Table 3, results are shown for specific groups of congenital anomalies among the children with paternal AEDs exposure compared with those unexposed group. Elevated risks were found for congenital anomalies of circulatory system (aOR 1.32, 95%CI 1.03–1.69) and musculoskeletal system (aOR 1.24, 95%CI 1.04–1.48).

Among children of fathers with epilepsy, the risk of congenital anomalies caused by AEDs use was attenuated to a non-statistically significant level (aOR = 1.08, 95%CI

Table 1 Baseline characteristics of the study population

Characteristic	Paternal AEDs use before conception (N = 3086) N (%)	No paternal AEDs use before conception (N = 730,196) N (%)
Calendar year of birth		
1997–1999	664 (21.5)	186,710 (25.6)
2000–2002	677 (22.0)	182,943 (25.1)
2003–2005	812 (26.3)	179,840 (24.6)
2006–2008	933 (30.2)	180,703 (24.7)
Gender		
Boy	1605 (52.0)	374,659 (51.3)
Girl	1481 (48.0)	355,537 (48.7)
Birth weight (g)		
< 2500	123 (4.0)	24,587 (3.4)
2500–3249	749 (24.2)	170,356 (23.3)
3250–3999	1540 (49.9)	383,590 (52.5)
4000–8000	644 (20.9)	145,422 (19.9)
Unknown	30 (1.0)	6241 (0.9)
Parity		
1	1303 (42.2)	310,880 (42.6)
2	1099 (35.6)	276,158 (37.8)
≥ 3	684 (22.2)	143,158 (19.6)
Preterm birth (< 37 weeks)		
No	2901 (94.0)	695,055 (95.2)
Yes	185 (6.0)	35,141 (4.8)
Apgar score at 5 min		
0–7	41 (1.3)	9116 (1.2)
8–9	209 (6.8)	43,879 (6.0)
10	2796 (90.6)	667,936 (91.5)
Unknown	40 (1.3)	9265 (1.3)
Maternal age at child birth (years)		
≤ 25	489 (15.9)	112,204 (15.4)
26–30	1072 (34.7)	270,100 (37.0)
31–35	1030 (33.4)	246,617 (33.8)
> 35	495 (16.0)	101,275 (13.8)
Paternal age at child birth (years)		
≤ 25	229 (7.4)	53,566 (7.3)
26–30	771 (25.0)	200,922 (27.5)
31–35	1088 (35.3)	266,644 (36.5)
> 35	998 (32.3)	209,064 (28.7)
Maternal years of education (years)		
≤ 9	824 (26.7)	142,578 (19.5)
10–14	1408 (45.6)	350,993 (48.1)
> 14	776 (25.2)	216,675 (29.7)
Unknown	78 (2.5)	19,950 (2.7)
Maternal smoking status[a]		
No	2053 (66.5)	524,581 (71.8)
Yes	612 (19.8)	120,498 (16.5)
Unknown	421 (13.7)	85,117 (11.7)
Cohabitation		
No	1485 (48.1)	352,038 (48.2)
Yes	1579 (51.2)	371,593 (50.9)

Table 1 (continued)

Characteristic	Paternal AEDs use before conception (N = 3086) N (%)	No paternal AEDs use before conception (N = 730,196) N (%)
Unknown	22 (0.7)	6565 (0.9)
Maternal antiepileptic drugs use during pregnancy		
No	3047 (98.7)	727,334 (99.6)
Yes	39 (1.3)	2862 (0.4)
Maternal history of epilepsy		
No	3005 (97.4)	719,570 (98.5)
Yes	81 (2.6)	10,626 (1.5)
Paternal history of epilepsy		
No	1101 (35.7)	723,503 (99.1)
Yes	1985 (64.3)	6693 (0.9)
Maternal history of congenital anomalies		
No	2911 (94.3)	693,573 (95.0)
Yes	175 (5.7)	36,623 (5.0)
Paternal history of congenital anomalies		
No	2791 (90.4)	690,302 (94.5)
Yes	295 (9.6)	39,894 (5.5)

[a]Maternal smoking information was missing among those children born from 2007 to 2008

Table 2 Association between paternal AEDs use before conception and congenital anomalies in offspring

Paternal AEDs use before conception	Offspring with congenital anomalies no.	Risk no./1000 children	Odds ratio (95%CI)		
			Crude	Model 1[a]	Model 2[b]
No use during 3 months before conception	73,073	100.1	Ref.	Ref.	Ref.
Use during 3 months before conception	372	120.5	1.23 (1.11–1.37)	1.23 (1.10–1.37)	1.19 (1.05–1.34)
Sub-analysis: paternal AEDs use from 1 year before conception to birth					
Never users	72,858	100.0	Ref.	Ref.	Ref.
Former users	87	125.4	1.29 (1.03–1.62)	1.30 (1.04–1.63)	1.29 (1.03–1.61)
Current users	52	147.3	1.56 (1.16–2.09)	1.59 (1.18–2.14)	1.56 (1.16–2.10)
Later users	118	128.8	1.33 (1.10–1.62)	1.36 (1.12–1.66)	1.35 (1.12–1.65)

[a]Model1: adjusted for calendar year of birth, gender, parity, mother age, father age, maternal smoking during pregnancy, parental history of congenital anomalies before birth of the child

[b]Model2: further adjusted for paternal history of epilepsy before conception

0.92–1.27). Among children of fathers without a history of epilepsy, the patterns of associations were generally comparable to the main analyses, though the risk estimate was greater for AEDs users (aOR = 1.38, 95%CI 1.15–1.64) (Table 4).

In the sibling-matched analysis, we did not find that paternal AEDs use before conception increased the risk of congenital anomalies (aOR = 1.01, 95%CI 0.99–1.02) (Table 5).

When stratified by child gender, the risk of congenital anomalies attenuated slightly and lost significance among boys (aOR = 1.14, 95%CI 0.97–1.33), while a slightly elevated risk was observed among girls (aOR = 1.26, 95%CI 1.05–1.52) (Table S3). Restriction to children whose mothers neither used AEDs during pregnancy nor had epilepsy history did not change the estimates essentially (Table S4). The relative risk of congenital anomalies did not deviate quantitatively or qualitatively from the main findings after excluding those children whose fathers experienced onset of epilepsy during the 3 months before conception (Table S5). Restriction to congenital anomalies diagnosed in the first year of age also yields the same pattern with slightly higher risk among AEDs users (Table S6).

In the PSM sub-cohort, the exposed children (N = 3086) and unexposed children (N = 3086) were well balanced on baseline characteristics (Table S7). The results from this analysis remained similar as the main analysis (Table S8).

Table 3 Risk of congenital anomaly groupings in children according to paternal AEDs use before conception

Congenital anomaly groupings	Paternal AEDs use before conception	Offspring with congenital anomalies no.	Risk no./1000 children	Odds ratio (95%CI)		
				Crude	Model 1[a]	Model 2[b]
Nervous system	No	1719	2.4	Ref.	Ref.	Ref.
	Yes	7	2.3	0.96 (0.46–2.03)	0.96 (0.46–2.02)	0.88 (0.40–1.95)
Eye, ear or nose	No	6695	9.2	Ref.	Ref.	Ref.
	Yes	30	9.7	1.06 (0.74–1.52)	1.10 (0.77–1.58)	1.02 (0.69–1.51)
Circulatory system	No	13,310	18.2	Ref.	Ref.	Ref.
	Yes	78	25.3	1.40 (1.12–1.75)	1.39 (1.11–1.74)	1.32 (1.03–1.69)
Respiratory system	No	1664	2.3	Ref.	Ref.	Ref.
	Yes	9	2.9	1.28 (0.67–2.47)	1.24 (0.65–2.40)	1.38 (0.67–2.82)
Orofacial clefts	No	1653	2.3	Ref.	Ref.	Ref.
	Yes	9	2.9	1.29 (0.67–2.49)	1.29 (0.67–2.48)	1.51 (0.73–3.11)
Digestive system	No	4012	5.5	Ref.	Ref.	Ref.
	Yes	21	6.8	1.24 (0.81–1.91)	1.22 (0.79–1.87)	1.01 (0.63–1.60)
Genital organs	No	14,641	20.1	Ref.	Ref.	Ref.
	Yes	69	22.4	1.18 (0.88–1.42)	1.09 (0.86–1.39)	1.08 (0.83–1.40)
Urinary system	No	3046	4.2	Ref.	Ref.	Ref.
	Yes	13	4.2	1.01 (0.59–1.74)	0.99 (0.57–1.70)	0.81 (0.45–1.46)
Musculoskeletal system	No	29,941	41.0	Ref.	Ref.	Ref.
	Yes	158	51.2	1.26 (1.08–1.48)	1.26 (1.08–1.48)	1.24 (1.04–1.48)
Others and chromosomal abnormalities	No	6800	9.3	Ref.	Ref.	Ref.
	Yes	38	12.3	1.33 (0.96–1.83)	1.33 (0.97–1.84)	1.16 (0.82–1.66)

[a]Model1: adjusted for calendar year of birth, gender, parity, mother age, father age, maternal smoking during pregnancy, parental history of congenital anomalies before birth of the child

[b]Model2: further adjusted for paternal history of epilepsy before conception

Table 4 Association between paternal AEDs use before conception and congenital anomalies in offspring born to fathers diagnosed with epilepsy or not

Paternal AEDs use before conception	Offspring with congenital anomalies no.	Risk no./1000 children	Odds ratio (95%CI)	
			Crude	Model 1[a]
Fathers with epilepsy				
No use during 3 months before conception	728	108.8	Ref.	Ref.
Use during 3 months before conception	229	115.4	1.07 (0.91–1.25)	1.08 (0.92–1.27)
Sub-analysis: Paternal AEDs use from 1 year before conception to birth				
Never users	697	107.8	Ref.	Ref.
Former users	16	136.8	1.31 (0.77–2.23)	1.29 (0.76–2.21)
Current users	14	160.9	1.59 (0.89–2.83)	1.56 (0.87–2.78)
Later users	9	103.4	0.96 (0.48–1.91)	0.98 (0.49–1.97)
Fathers without epilepsy				
No use during 3 months before conception	72,345	100.0	Ref.	Ref.
Use during 3 months before conception	143	129.9	1.34 (1.13–1.60)	1.38 (1.15–1.64)
Sub-analysis: Paternal AEDs use from 1 year before conception to birth				
Never users	72,161	99.9	Ref.	Ref.
Former users	71	123.1	1.26 (0.99–1.62)	1.29 (1.01–1.65)
Current users	38	142.9	1.50 (1.07–2.12)	1.56 (1.11–2.21)
Later users	109	131.5	1.36 (1.12–1.67)	1.40 (1.14–1.71)

[a]Model 1:adjusted for calendar year of birth, gender, parity, mother age, father age, maternal smoking during pregnancy, parental history of congenital anomalies before birth of the child

Table 5 Paternal AED use before conception and congenital anomalies in exposed and unexposed siblings from 1444 families

Paternal AED use before conception	Offspring with congenital anomalies no.	Risk no./1000 children	Odds ratio (95%CI)	
			Crude	Model 1[a]
No use during 3 months before conception	89	112.6	Ref.	Ref.
Use during 3 months before conception	79	121.5	1.01 (0.99–1.02)	1.01 (0.99–1.02)

[a]Model1: adjusted for gender, parity, mother age, father age, maternal smoking during pregnancy

When extending the exposure period to 6 months before conception and repeated all above analyses, patterns of association were essentially unchanged (Table S9).

Discussion

Principal findings

In this large population-based study, we found that children whose fathers used AEDs during 3 months before conception had a higher risk of congenital anomalies, especially the congenital anomalies of circulatory system and musculoskeletal system. Higher risk of congenital anomalies in exposed children observed in propensity score matched sub-cohort seemed to corroborate the main finding. However, further analyses showed that the observed association might be attributed to the underlying indication, instead of the effect of AEDs: (1) Similar to that in children of current users, the associations were also observed among children of former users and later users, among whom the AEDs exposure did not occur in the etiologically relevant time window; (2) the association was not observed in children with paternal epilepsy, as well as in sibling analysis.

Comparison with other studies

Previous studies have mainly focused on the role of maternal epilepsy as well as AEDs use during pregnancy with inconsistent findings [4, 5, 26]. Only one study focusing on the teratogenic effect of anticonvulsants (one of the AEDs) used by parents [27] noted a significant increase of minor congenital anomalies among the children of treated fathers. Another study on maternal prenatal AEDs exposure and child development included epileptic fathers as a control group, and found that AEDs treatment of fathers was not associated with the risk of major malformation in children [28]. But the above two studies were limited by small samples, lack of prospective data, and the insufficient data on potential confounders.

To our knowledge, this is the first large cohort to investigate the link between paternal preconception AEDs use and the risk of congenital anomalies in offspring. Confounding by epilepsy and other underlying indications posed the main challenge in this study because they might contribute to higher risk of congenital anomalies independent of AEDs use. To disentangle the effect of paternal AEDs use from the effect of indication, we performed several analytic strategies: (1) regression adjustment for paternal epilepsy history; (2) negative controls (i.e., former- and later- user analyses); (3) stratified analyses according to paternal epilepsy history; and (4) sibling analysis. Although children whose fathers used AEDs during the 3 months before conception did have a higher risk of congenital anomalies, the decreased odds ratio after adjustment for paternal epilepsy history, the associations observed in former users, and the non-association among those exposed children with paternal epilepsy history as well as those exposed siblings all suggested the effects of underlying conditions. A stronger association among children of current user (those starting to use AEDs during the susceptible period) might be attributed to the physiological changes accompanied with the epilepsy (or other indications) onset. Besides, the observed increased risk in children of later users further supported the role of underlying conditions instead of AEDs use in congenital anomalies. It was worth noting that, in the subgroup of children of fathers without epilepsy, there was an increased risk associated with AEDs use. One possible interpretation was that a large number of fathers might receive AEDs treatment from their general practitioners and were therefore not registered with a diagnosis of epilepsy in the hospital system. Therefore, it was possible that the increased risk observed was partly confounded by paternal epilepsy diagnosed outside a hospital department for which we were not able to identify. In addition, other underlying diseases related to AEDs such as neuropathic psychiatric disorders, pain syndromes, and essential tremor might also, to some extent, contribute to the observed association.

Strengths and limitations

Our study has several methodological strengths. The linkage of several nationwide health registries in Denmark enabled us to conduct a large cohort study with virtually complete follow-up. The information on exposure to parental AEDs use was based on a national registry, which eliminated the risk of recall bias. The information on congenital anomalies with a high validity [24] in children was obtained independently of exposure measurement, which could also mitigate the information bias. Furthermore, the availability of fruitful covariates enabled us to adjust for a number of potential confounders including socio-demographic factors and parental congenital anomalies history.

However, our findings should be interpreted with caution in the light of some limitations. First, we were unable to distinguish between major and minor congenital anomalies in our data. Therefore, completeness would be expected to be poorer for minor congenital anomalies, especially if they are not visible. Restricting the analysis to congenital anomalies diagnosed in the first year of life would most likely limit the analysis to more major anomalies. Second, the study included live births only, and those severe congenital anomalies that resulted in spontaneous abortion, stillbirth, or termination of the pregnancy would therefore be missed. However, the actual risk of congenital anomalies would be undermined if pregnancy losses or prenatal screening for congenital anomalies were more common among fathers with AEDs use before conception. Third, we did not have information on maternal folic acid use during pregnancy that be recommended to prevent neutral tube defects [29], which may have caused confounding, if the maternal pregnancy-related use of folic acid supplementation differed between the exposed group and unexposed group. However, only 2% of the congenital malformations identified in our study were neural tube defects, and such confounding might not affect our results remarkably. Fourth, we were unable to validate actual use of AEDs by fathers before conception because we relied on medical records of prescriptions. This may lead to misclassification of exposure if patients did not take the medication. Nevertheless, the misclassification was most likely non-differential, which was expected to bias the estimates towards null. Besides, we did not have information on AEDs treatment given at admission. We expect this problem to be minor since most epileptic people most likely continue AEDs treatment after discharge. In addition, to further control this information bias, we did sensitivity analysis excluding those fathers whose first onset of epilepsy happened within the 3 months before conception and found similar results. Fifth, fathers receiving AEDs treatment might have other risk factors that would be associated with the risk of congenital anomalies in children, and this selection bias would distort the actual causal inference. To minimize this selection bias, we created a PSM sub-cohort to balance potential baseline characteristics and the patterns of association did not change remarkably. Finally, a regression technique like the proportional hazard Cox model is the first choice when examining an endpoint with various follow-up time. However, most of the congenital anomalies are supposed to occur during pregnancy, therefore, the time of diagnoses is not a good indicator to the time of events. Despite this, we also tried the Cox regression models to estimate the hazard ratios (HRs) of congenital anomalies in children following exposure to paternal AEDs use, and materially unchanged results emerged.

Implications and future directions

Caution is required before making a causal assumption or clinical decisions based on this observational study. Considering the limited number of congenital anomalies cases and the challenges posed by potential confounding, further studies are needed to corroborate our findings.

Conclusion

The modestly increased risk of congenital anomalies observed in the children of fathers using AEDs before conception might be explained by the underlying indications, although a causal relationship could not be ruled out.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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