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Fertility and marital status in adults with childhood-onset epilepsy: a population-based cohort study

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Abstract

Objective: Our objective was to explore the association of childhood-onset epilepsy (COE) and clinical factors on marital status and fertility in adulthood.

Methods: We identified a population-based cohort of 307 individuals with COE treated in the Tampere University Hospital district with inception date 31th December 1992. A matched reference cohort of 1,244 individuals without COE was established as a random sample of the population in the study area through the Population Register Center (PRC). The PRC also provided data on marriages and offspring up to 2018. Fertility and marriage analysis was done by calculating the time till first child and marriage. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated with Cox regression for follow-up spanning up to January 2018.

Results: Patients with COE had lower fertility rates (32.2% vs. 57.3% any offspring, HR 0.47 95% CI 0.38-0.58) and fewer marriages (28.3% vs. 49.7% ever married, HR 0.49 95% CI 0.39-0.61) than the referents without COE during 25-year follow-up. The largest impact was in patients with COE who had any disability (10.1% any offspring, HR 0.20, 95% CI 0.10 – 0.41, and ever married 6.5%, HR 0.11, 95% CI 0.06 – 0.21), symptomatic etiology of epilepsy (13.1%, HR 0.18 95% CI 0.11-0.31, and 12.1%, HR 0.21 CI 0.12-0.36), onset of epilepsy before 2 years of age (HR 0.20, 95% CI 0.12-0.31, HR 0.29, 95% CI 0.18-0.46) and high seizure frequency after start of treatment (HR 0.13 CI 0.06-0.28, HR 0.20 CI 0.10-0.41). Patients with COE without any disabilities had only slightly lowered fertility (HR 0.76, 95% CI 0.61 – 0.95) and non-significant reduction in marriages (HR 0.80, 95% CI 0.64 – 1.02).

Significance: COE associated with lower chance of finding a partner at adulthood and having less children. The extent of such effect varied between patient subgroups.

Key point box:
COE associated with poorer social outcomes in terms of marriage and fertility rates.
Clinical factors such as symptomatic etiology, young age of onset and high seizure rate predicted worse social outcomes.
Patients without disabilities had only slightly lowered fertility and marriage rates.

1. Introduction

Childhood-onset epilepsy (COE) has been repeatedly associated with lower than expected marriage rates.[1,2,3] Still, it is unclear which patients are most affected. Patients with symptomatic etiology of epilepsy seem to have fewer marriages, whereas idiopathic etiology has been related to outcome rates comparable to those in general population[4]. Disabilities seem to be the largest contributor to lower marriage rates in adults with COE[3,5], though institutional care or social components such as stigma may also be involved. Marriage can provide social and financial support and seems to facilitate patients' coping with epilepsy[6].

Patients with COE have lower fertility when compared to unaffected controls. [1,2,7] and adult-onset and active epilepsy have also been associated with lowered fertility in large population-based studies.[8,9] Both physical and social factors likely contribute to lowered fertility. Epileptic seizures and treatment of epilepsy alter hormonal function and may affect reproductivity[10]. Lower pregnancy rates are probably not entirely due to infertility, as epilepsy itself and potentially teratogenic antiepileptic medication[11] with other social considerations[12] can influence the decision of having children.

Research of fertility in patients with epilepsy has its intricacies, since COE has been associated with increased pregnancy rates outside of stable relationship[13,14]. For this reason, assessing both fertility and marriage can provide a wider perspective on the effect of COE on patients' ability to start a family later in life.

We assumed that fertility and marriage rates would be lower among adults among COE patients at their adulthood, especially among those with severe epilepsy in terms of symptomatic etiology and worse seizure control.

2. Methods

Setting and study population

The study cohort is based on a population-based prevalence sample of 329 patients with COE.[15] The cohort inception date was 31th December 1992, and comprised of all patients with COE treated for epilepsy in Tampere University Hospital (TAUH) department of pediatric neurology, pediatric department or the outpatient clinic between years 1980 – 1992. Additionally, patients were identified from Pirkanmaa Social Services Association of Communes medical records, the only organization providing services for mentally retarded children in the catchment area. The catchment area included the city of Tampere and 34 mainly rural municipalities around Tampere. The catchment population at the time of the cohort inception was 431,963 with 83,464 children aged 0 – 15 years. TAUH is the only hospital in this district with pediatric departments and responsible for providing all pediatric neurology services for this population.

During a retrospective review of patient charts for the purposes of this publication (by author C.S. in year 2017), one eligible patient was identified and included to the study cohort, while this patient was not included in the original cohort. Three patients in the original cohort had to be excluded due to incomplete identification data. Ten patients had deceased during the data collection period and before the actual inception date and were therefore excluded from this analysis. Five patients had sent a privacy request to the Population Registry Center (PRC) prohibiting the use of their data for research purposes, and therefore these patients were removed. Hence, a total of 312 patients were eligible for linkage to the PRC database. For these patients, a reference population of 1,248 persons (matching ratio of four referents per patient) was randomly selected by the PRC with matching on year of birth, gender and municipality based on characteristics on the inception date. Nine subjects had deceased or moved abroad before age 16, thereby 307 patients and 1,244 referents were finally included in the analysis. Development of the study population is described in figure 1.

Data sources

We used the unique personal identification numbers assigned to all Finnish residents as the key in deterministic record linkages to obtain register data on the outcomes (marriages, separation and children) from the Population Register Center (PRC) up to January 2018. In Finland, citizens, permanent residents and public officers are legally obligated to provide information to the PRC, ensuring completeness of the database. In our cohort, none of the individuals had missing data from PRC.

Study was originally initiated for the estimation of population prevalence of COE and it comprised of all subjects fulfilling the inclusion criteria i.e. involved a census rather than a sample of the target population and the sample size could not be expanded. Therefore, no power calculations were available for the current analysis. Our patient identification and diagnosis was done according to ILAE guidelines by two experienced pediatric neurology specialists. Data on epilepsy etiology, age of onset, initial seizure frequency before and after initiation of treatment, antiepileptic drug treatment, disabilities, dominant seizure type, epilepsy syndrome, and EEG recordings were abstracted from medical records on data collection forms. Seizure semiology and epileptic syndromes were identified and classified in accordance with the International League Against Epilepsy (ILAE) definitions of 1981[16] and 1989[17] in use at the time, respectively.

Analysis

Evaluation of fertility was done by analyzing time till birth of the first child and chance of marriage was evaluated in time till first marriage, with follow-up starting on the 16th birthday. Follow-up ended at the outcome event, death, emigration or the common closing date (January 22th 2018) of the study. In the analysis of marital status, the main outcome was time to first marriage. A secondary analysis was performed evaluating the hazard of divorce (time to divorce from the start of marriage).

We used the semi-parametric Cox proportional hazards regression modelling to calculate hazard ratios (HR) with their 95% confidence intervals (95% CI) for outcomes among patients with COE relative to referents. The statistical package used was IBM SPSS version 14.

Age, as a continuous variable, and gender were adjusted as potential confounders. Adjustment was used since these confounders were used by the PRC when sampling the reference population. The potential effect modification by epilepsy-related covariates was evaluated in analyses that were stratified by epilepsy etiology, age of onset, mental or motor handicap, seizure frequency (before treatment and on treatment measured as mean number of seizures during 1991-1992 i.e. 2 years before the inception date) and the number of antiepileptic drugs used on the inception day. Other treatments (barbiturate anesthesia, ACTH, epilepsy surgery) during 1980-1992 were also included. Disabilities were categorized as either mental or motor disability. Motor disability included cerebral palsy, mono-, di-, hemi-, and tetraplegia and –paresis. Mental disabilities were defined as mild or severe based on IQ or evident developmental delay. These conditions could exist simultaneously.

Ethical issues

The study protocol was reviewed by the ethical review committee of the Pirkanmaa Hospital District (tracking No R17109). In accordance with the Finnish regulations, a consent was not required for an entirely register-based study, as the study subjects were not contacted. A permission for the use of the register data was required and issued by the PRC before data gathering on patients and referents.

3. Results

The COE cohort included 307 patients of whom 164 were male and 143 female (Table 1), whereas the 1,244 participants in the reference cohort comprised of 661 males and 583 females. Of our patient cohort, 99 had at least one child during their median follow-up time of 10.8 years (IQR 7.4-15.1), while 713 referents had their first child with a median follow-up of 11.3 years (IQR 7.8-14.8). Of the patients with COE, 87 were married at least once with a median follow-up of 11.8 years (IQR 9.2-15.0) from the start of follow-up, compared to 618 referents with a median of 11.7 years (IQR 8.5-14.6) of follow-up.

Overall, patients with COE were less likely to be married (HR 0.49 95% CI 0.39-0.61) or to have a child (HR 0.47 95% CI 0.38-0.58) than matched referents during the follow-up (Table 2). Patients with any disability had very low rates of marriage and fertility, while the rates among patients without disabilities were closer to those seen among referents. Male patients were less likely to get married (HR 0.47 95% CI 0.33-0.66) and had lowered fertility (HR 0.42 95% CI 0.30-0.57) when compared to male referents in an age-adjusted analysis. Female patients had similarly lower rates of marriage (HR 0.51 95% 0.38-0.68) and fertility (HR 0.52 95% CI 0.39-0.68), when compared with female referents in a similar model.

Patients with symptomatic etiology had lower rates of both marriage (HR 0.21, 95% CI 0.12 – 0.36) and fertility (HR 0.18, 95% CI 0.11 – 0.31) than other etiological groups. Patients with idiopathic etiology were more likely to get married and have a child than other patients (HR 0.73 CI 95% 0.53-1.01, HR= 0.72 CI 95% 0.53-0.98). Patients with age of onset of less than two years had lower rates of marriage (HR 0.29, 95% CI 0.18 - 0.46) and fertility (HR 0.20, 95% CI 0.12 - 0.31) than other age groups. Of the patients with age of onset less than 2 years, 80 patients of 116 (69%) had some disability.
Weekly seizures before treatment predicted lower marriage (HR 0.39, 95% CI 0.28 - 0.55) and fertility rates (HR 0.36, 95% CI 0.26 - 0.49). Seizure-free patients had higher fertility and marriage rates, while poor seizure control on treatment was associated with substantially lowered rates of marriage (HR 0.20, 95% CI 0.10-0.41) and fertility (HR 0.13, 95% CI 0.06-0.28).

There was no statistically significant difference in divorce rates from first marriage between COE (22/87, 25.3%) and referents (121/618, 19.6%), with a HR of 1.37 (95% CI 0.87 – 2.16).

A sub-group of patients without disabilities was separated for further analysis using the same models and clinical factors as the whole patient population. (Supporting information) Hazard ratios where still lower when compared with the reference population, but better when compared to the whole patient population.

4. Discussion

In this retrospective, population-based study with complete follow-up through comprehensive, nationwide registries, patients with COE had lowered fertility and marriage rates at young adulthood compared to referents without COE.

Patients without disabilities had only slightly lowered rate of fertility and a non-significant reduction in marriage rates relative to the reference population. Among patients, more favorable outcomes were also associated with idiopathic etiology, monotherapy, later age of onset and lower seizure rates. Some clinical factors such as symptomatic etiology, early age of onset, AED polytherapy and high seizure frequency were associated with significantly lower rates of fertility and of marriage.

Variables predicting less impairment in social outcomes, such as idiopathic etiology and lower seizure rates, have also been associated with better seizure outcomes[18], but superior seizure outcomes do not necessarily translate into favorable social outcomes[19]. Our results also corroborated this, as seizure-free patients did better than other patients, but still had lower rates than the referents in both main outcomes.

Male patients with COE had less children and marriages, but in an analysis comparing male and female patient groups, both were similarly affected in comparison to the sex-matched reference group. This suggests that the effect of COE on fertility and marriage rates is unaffected by sex despite lower rates in male patients.

Fertility and marriage rates showed similar patterns demonstrating that patients with COE are less likely to start a family. If marriage rates were considerably higher than the rates of first child, this would have suggested a lowered fertility resulting from troubles conceiving but similarly affected marriage and fertility rates do not support that hypothesis, but are more consistent with lower marriage rates leading to reduced birth rates.

We had detailed data on multiple epilepsy-related clinical variables predicting adult social outcomes. Our patient identification and diagnosis by two experienced pediatric neurologists followed ILAE guidelines in use at the time the cohort was established, assuring consistent diagnostic classification. Hospital-based cohorts are frequently affected by selection bias, since persons with epilepsy in a population can be treated in a variety of hospitals and health care organizations. Our cohort can be regarded as population-based and representative, as the treatment of COE in the study area is centralized to TAUH and medical records where reviewed also from Pirkanmaa Social Services Association of Communes to identify patients with mental retardation possibly treated outside TAUH at the time of the data collection, ensuring comprehensive coverage of patients COE in our study area. The reference cohort was randomly selected by the PRC from an exhaustive database including the entire of population in our study area, resulting in a population-based cohort. Owing to complete registry-based follow-up, no individuals were lost to follow-up, eliminating information and selection biases due to attrition.

Finland provides universal coverage of a publicly funded health insurance, granting Finnish patients with epilepsy access to treatment with fully reimbursed antiepileptic medication regardless of socioeconomic status and wealth. Such exhaustive coverage likely widens the patient selection compared with settings where health care access is more limited. The effect of health care on COE patient´s social outcomes has not been widely studied, but a study in Canada (with also extensive public health care) showed no influence of wealth on seizure outcome among COE patients, though income affected social outcomes. The Canadian study found that patients from poor families had more frequently adverse adult social outcomes than those from wealthy families, even though there were no clear differences in clinical outcomes .[20] This suggests that accessible healthcare improved equity in outcomes of epilepsy treatment, but adequate seizure treatment is not enough to avert other social problems particularly in patients with COE from a poor background. Additionally, COE is more common in families with low social status[21], which might result in patients on average coming from a lower socioeconomic background than our referents. In such situation, the patient population might face more adverse social factors unrelated to epilepsy, leading to worse outcomes in our study, since we were unable to directly control for socioeconomic status, although we matched referents by municipality.

Our patient cohort was established 25 years ago, which limits the accuracy of time-dependent factors, e.g. treatment and seizure frequency on treatment. These baseline variables describe the clinical status of patients in 1992 and should not be considered as indicators of subsequent treatment and seizure control. The patient sample is a prevalence cohort of COE, with a different case-mix than an incidence cohort comprising entirely of newly diagnosed cases. Inclusion of all patients seen at our institution at the inception date is likely to results in over-representation of patients with a long duration of the disease including treatment-resistant epilepsy, as those in remission no longer require follow-up at pediatric neurology.

Patients with COE in general and also in our study population have a high prevalence of disabilities (60% in our study). Although we did have information on patients´ disabilities, we were unable to completely distinguish the effect of disabilities from the effects of clinical factors in the analysis. This is due to the small group of patients without disabilities (N=169). Worse outcomes observed with some clinical factors in the main analysis may actually arise from these factors being common in patients with disabilities.

In conclusion, marriage rates and fertility in patients with COE are affected by their disease in adulthood and some clinical factors increase the adverse social outcomes. Even patients who achieve remission, have low seizure rates or are without disabilities have worse social outcomes compared to the general population.

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Disclosure of Conflicts of interests

None of the authors has any conflict of interest to disclose.

Ethical Publication Statement

We confirm that we have read the Journals position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

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Table 1. Baseline characteristics and outcomes among patients with COE and the reference population				
	Adults with COE, n = 307		Reference population, n = 1,244	
	Male (%)	Female (%)	Male (%)	Female (%)
N	164 (53)	143 (47)	661 (53)	583 (47)
Age at inception date (years)				
0-4	29 (18)	22 (15)	118 (18)	93 (16)
5-9	44 (27)	48 (34)	176 (27)	199 (34)
10-15	91 (56)	73 (51)	367 (55)	291 (50)
At least one marriage	37 (23)	50 (35)	283 (43)	335 (57)
At least one offspring	40 (24)	59 (41)	330 (50)	383 (66)
Number of offspring				
0	124 (76)	83 (58)	329 (50)	193 (33)
1	14 (9)	18 (13)	109 (16)	116 (20)
2	16 (10)	33 (23)	155 (23)	175 (30)
3	8 (5)	5 (3)	46 (7)	70 (12)
4+	2 (1)	4 (3)	22 (3)	29 (5)
Any Disability	84 (51)	54 (38)		
Motor Disability	31 (19)	35 (24)		
Mental Disability	67 (41)	47 (33)		
Mild or moderate (50≤IQ<70)	40 (24)	24 (17)		
Severe (50>IQ)	27 (17)	23 (16)		
Other Neurological diagnosis (e.g. ADHD)	25 (15)	12 (8)		
COE = Childhood-onset epilepsy, Motor = Cerebral palsy, mono-, di-, hemi-, or tetraplegia or -paresis				

Table 2. Frequencies of outcomes by clinical characteristics on incidence date of 31.12.1992 in adult COE with hazard ratios relative to the reference population

			First Child			First Marriage		
Patient characteristic	Subgroup	Patients N	N	HR[1]	CI[2]	N	HR[1]	CI[2]
Epilepsy	All	307	99	0.47	0.38-0.58	87	0.49	0.39-0.61
Disability	No	169	85	0.76	0.61-0.95	78	0.80	0.64-1.02
	Any[3]	138	14	0.14	0.08-0.24	9	0.11	0.06-0.21
Etiology	Idiopathic	87	42	0.72	0.53-0.98	39	0.73	0.53-1.01
	Symptomatic	107	14	0.18	0.11-0.31	13	0.21	0.12-0.36
	Unknown	113	43	0.58	0.42-0.78	35	0.55	0.39-0.77
Age of onset (years)	0-1	116	15	0.20	0.12-0.31	17	0.29	0.18-0.46
	2-5	104	42	0.67	0.49-0.91	36	0.66	0.47-0.92
	6-15	87	42	0.60	0.43-0.81	34	0.52	0.37-0.74
Dominant seizure type	Focal	138	53	0.51	0.39-0.68	50	0.57	0.42-0.76
	Generalized	147	45	0.47	0.35-0.64	35	0.42	0.30-0.59
	Infantile Spasms	22	1	0.09	0.01-0.63	2	0.25	0.06-1.00
Treatment of epilepsy (AEDs[4] on 31.12.1992)	No treatment	22	9	0.75	0.39-1.45	9	0.56	0.29-1.08
	Monotherapy	133	58	0.64	0.48-0.84	53	0.63	0.48-0.82
	Polytherapy	120	29	0.31	0.20-0.47	21	0.35	0.25-0.51
	Surgery [5]	2	1			1		
	BA, ACTH[5]	30	2	0.22	0.07-0.68	3	0.11	0.03-0.45
Seizure frequency before treatment	yearly	81	31	0.53	0.39-0.80	27	0.56	0.38-0.83
	monthly	61	30	0.63	0.44-0.92	25	0.59	0.40-0.89
	weekly	165	38	0.36	0.26-0.49	35	0.39	0.28-0.55
Seizure frequency on treatment	>1year seizure free	170	76	0.65	0.51-0.82	68	0.64	0.50-0.83
	yearly	55	16	0.40	0.24-0.66	11	0.32	0.18-0.59
	monthly	82	7	0.13	0.06-0.28	8	0.20	0.10-0.41

[1.] Hazard ratio, adjusted for gender and age [2.] Confidence interval in adjusted model

[3.] Mental and/or motor disability

[4.] Antiepileptic drugs

[5.] Additional treatment given between years 1980-1992 such as barbiturates or adrenocorticotropic hormone

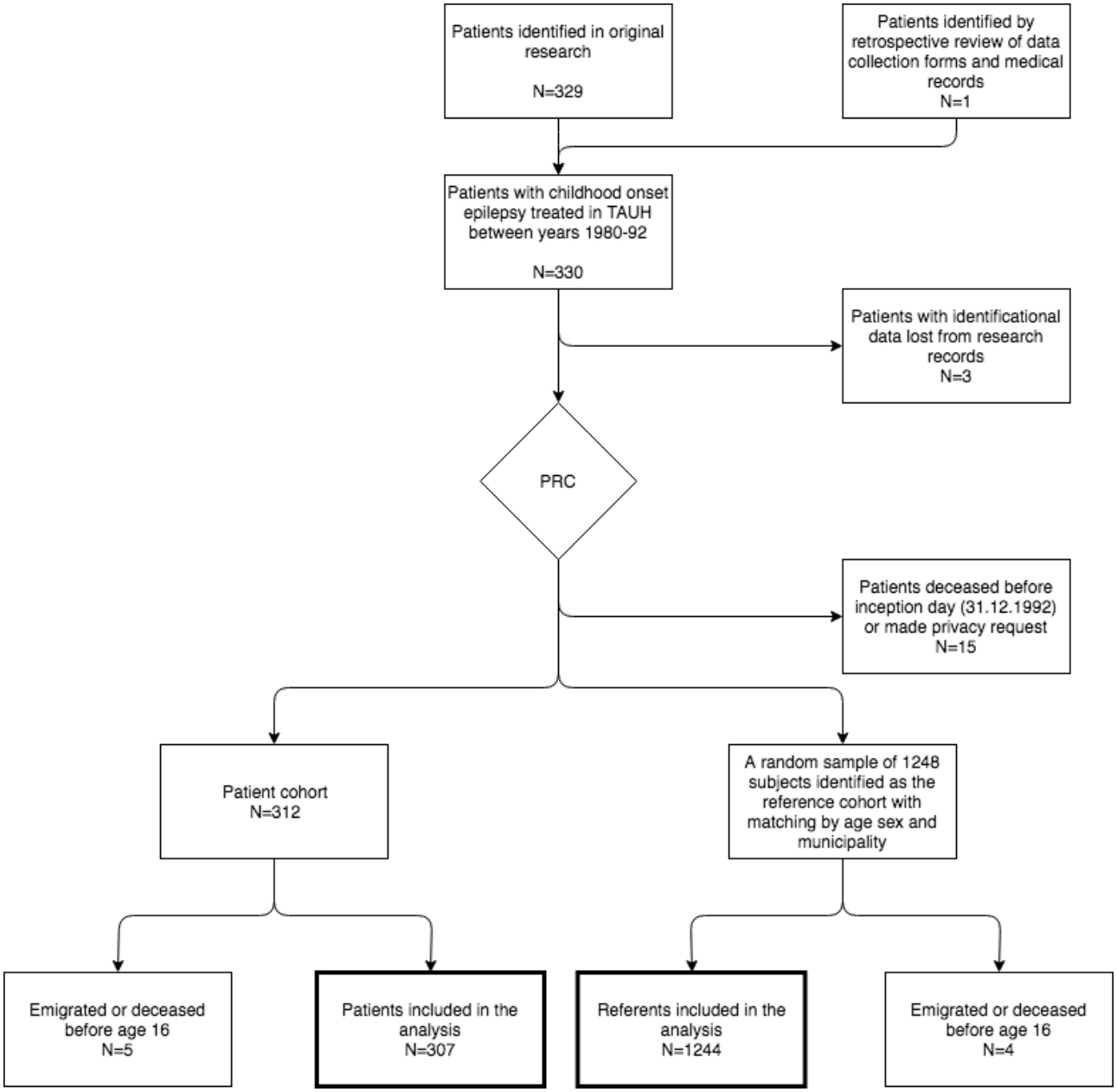

Figure 1. Formation of study population