Long-term changes in the incidence of childhood epilepsy. A population study from Finland.

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ABSTRACT

Background. The incidence of childhood epilepsy has changed during the past decades, but it is unclear whether it increased or decreased.

Methods. Changes in drug-treated childhood epilepsy between 1968 and 2012 were evaluated using the Finnish nationwide register of all children, aged ≤15 years, on antiepileptic drugs (AEDs) prescribed for the treatment of epilepsy. The first registered entitlement to full-refundable AEDs was used as proxy for newly diagnosed epilepsy. Incidence densities were calculated as ratios of annual new cases per 100,000 person-years in each calendar year during 1968 to 2012.

Results. The annual incidence density of newly treated childhood epilepsy increased from 35 in the 1960s to 87 per 100,000 person-years in the 1990s, and decreased thereafter to 61 per 100,000 person-years. Since 1996, the incidence density decreased 1–2% per year in children aged <1, 1–5 or 6–10 years (all 95% confidence intervals within 0.3%–3%), while no substantial change was seen in older children.

Conclusion. The incidence of drug-treated childhood epilepsy from the late 1960s to the early 1990s distinctly increased. The reasons for increase are not fully understood but, may include increasing ascertainment through improved diagnosis and a wider acceptance of AED treatment. Since the 1990s, a slight decline can be seen, probably reflecting the recent improvement in child health and safety.

Keywords. annual incidence density; childhood epilepsy; nationwide registers; population epidemiology; secular trends

Abbreviations.

AEDs: Antiepileptic Drugs

CI: Confidence Interval

ICDs: International Classifications of Diseases

IDR: Incidence Density Ratio

SII: The Finnish Social Insurance Institution

1. Introduction

In the literature, the reported incidences and secular changes of the incidences in childhood epilepsy are influenced by various study designs, and the results controversially suggest a range from declining to increasing incidence. Even the few long-term studies show various methodological limitations and different definitions of epilepsy, study populations of small size and different age ranges, inconsistent enrolment criteria, or short observation periods.[1-4] Longitudinal population studies from western countries reported decreasing annual incidences ranging between 0.5–6%.[4-6] Conflicting with those data, the Minnesota study from the same decades showed an increase in the mean annual incidence, from 39 to 54 per 100 000 between the periods 1965–1974 and 1975–1984, respectively.[5] A Danish register study showed a plateau or a slight decline in 1977–1990 followed by a steep increase from 1990 to 1995 and then again a decrease from 1995 to 2002.[2]

The incidence rates reported in the few previous population-based incidence studies of childhood epilepsy in the 1960s are low, ranging from 35 to 41 per 100,000 person-years.[5,7,8] Recent cross-sectional studies from the 2000s show considerably higher incidences, ranging from 50 to 86 per 100,000 within the same age cohort.[9-11]

Controversies in the literature between decreasing incidences in longitudinal studies and increasing incidences in cross-sectional studies prompted us to perform a nationwide long-term study on secular changes and their linearity in the incidence of childhood epilepsy. Based on cross-sectional studies showing a rising incidence from the 1960s to the 2000s and other studies suggesting a switch from an increase to a decrease of the incidence, we hypothesized that the incidence had risen from the 1960s, but that the extent of the change varied considerably during the last decades.

2. Study cohort and methods

2.1. Data source

The target population consisted of Finnish children aged <16 years during 1968–2012 (N=952,010 in 2012). For data collection, three national registers were used including the Population Register, the Special Reimbursement Register, and the Drug Purchase Register.

The nationwide Population Register, maintained by Population Register Centre, covers the permanently resident population and includes data on sex, live births, deaths, immigration, and emigration. The Finnish population is very stable, with less than 6% of children born abroad in 2012.

The Special Reimbursement Register, effective since 1964 and maintained by the Social Insurance Institution (SII), lists subjects who have been granted 100% refund for drug expenses by SII. Statement of a clinical diagnosis of epilepsy given by neurologist, child neurologist or paediatrician on contemporary International Classifications of Diseases (ICDs) is required in an application for the 100% reimbursement of AEDs. The procedure is similar for all non-institutionalized patients (no more than 0.01% of 0–17-year-olds are institutionalized[12]) who purchase their prescribed medication from the pharmacist's, regardless of place of treatment. The SII refunds begin at first documentation of the diagnosis of epilepsy. Thus, the date of first entitled AED reimbursement can be used as the date of the diagnosis of new-onset epilepsy. The Special Reimbursement Register, its structure, data collection principles, and the coverage of all Finnish citizens remained unchanged throughout the study period. The method of data collection is previously described in detail.[6] For the

present study, the four first years were omitted and the data collection was started from 1968 to minimize various enrolment biases.

The Drug Purchase Register, maintained by SII since 1994, includes all purchases of prescribed drugs refunded by SII. SII routinely refunds 40%–50% of prescribed drugs for all Finnish residents.[13] Thus, the register includes AED purchases by all Finnish residents, with or without entitled 100% special reimbursement. The drug reimbursement regulations restrict the refunded drug supply period to a maximum of three-months per purchase. Four or more consecutive AED purchases were considered to represent continuous AED use and a subsequent diagnosis of epilepsy.

The national administrative registers are well accepted by the Finnish population[14] and considered valid in Finland and other Scandinavian countries.[14-17]

The study cohort consisted of all 29,567 children (15,526 [53%] of them boys) who fulfilled the inclusion criteria of being Finnish resident; aged less than 16 years; with specialist-made diagnosis of epilepsy requiring drug treatment; and entitled for the first time to a 100% refund of AEDs for epilepsy during 1968 to 2012. The exclusion criteria included age of 16 years or more at onset of epilepsy; neonatal seizures only; temporary residence in Finland; institutionalization; or AEDs prescribed solely for indications other than epilepsy. The inclusion and exclusion criteria remained consistent throughout the study period.

The validity of the diagnosis of epilepsy, based on Special Reimbursement Register data, was ascertained using the Drug Purchase Register information of actual AED purchases (ATC code N03) during 1996–2012. First, all 11,142 study children who had 0–3 AED purchases

were classified as cases of potential misdiagnosis and removed from sensitivity analyses. Second, a control group of 22,172 children with no 100% reimbursement to epilepsy were selected by the Population Register Centre (2:1 matching with the 11,142 study subjects by age, sex and place of residence). Control children with ≥4 consecutive AED purchases were considered as potential undetected cases with childhood-onset epilepsy, unless they were granted reimbursement of AEDs to other indication.

2.2. Statistical analysis

Annual incidence densities for childhood epilepsy were calculated by dividing the number of newly diagnosed cases by the number of person years at risk.[18] The annual person-years within each dynamic risk cohort were calculated separately for boys and girls by averaging the number of children within each one-year age level December 31st of the target year and the preceding year. Neonatal deaths were excluded from the risk population, as well as children with epilepsy after the diagnosis.

Mean annual incidence densities of childhood-onset epilepsy per 100,000 person-years in 5-year calendar time intervals are given for all children and separately within four age groups (<1 year, 1–5 years, 6–10 years, and 11–15 years). Poisson regression models were used to calculate the estimates with 95% confidence intervals (95% CI) for the incidence densities and incidence density ratios (IDRs). The deviance and residual plots were used for model diagnostics. Due to nonlinearity of the annual incidence densities, the five-year intervals of the total 45-year observation period were used as a categorical predictor. Remaining overdispersion was controlled for by using Generalized Estimating Equations estimation, clustering the data by sex, one-year age group and one-year calendar time. In the analyses of the latest 17-year period 1996–2012 with all diagnoses based on ICD-10, the slopes of

temporal changes in the incidence densities were estimated from a Poisson regression model with year at diagnosis as a continuous predictor. The slopes were further evaluated with a sensitivity analysis, where only children with at least four AED purchases after the entitled reimbursement were accepted as newly diagnosed cases. As predictors, all models included age group at onset of epilepsy, sex, year at diagnosis, and their significant pairwise interactions. Confidence intervals in multiple comparisons were Bonferroni corrected. The quality of the reimbursement data during 1996–2012, as a source of epilepsy diagnosis, was assessed by calculating the sensitivity, specificity, and positive and negative predictive values among the patients and controls with or without ≥4 AED purchases. Statistical analyses were done using SAS V9.4 software (SAS Institute, Cary, NC, USA).

2.3. Ethics

In accordance with Finnish legislation (Personal Data Act 523/1999), no approval by an ethical committee or informed consent by study individuals are required for studies based on encrypted register data. The data permissions were admitted by SII (Diary no. 26/522/2013).

3. RESULTS

The nationwide incidence densities of childhood epilepsy on AED treatment from 1968 to 2012 in Finland increased during the first half, and decreased during the second half of the observation period in all age groups (Fig 1, Table 1). Adjusted for age and sex, the incidence was almost three-fold in the last vs. the first five-year period (Supplementary Table 1).

Please insert Fig. 1 here

Please insert Table 1 here

During the 45-year observation period from 1968 to 2012, the overall mean incidence density of epilepsy was 7% higher among boys than girls (IDR 1.07 [95% CI 1.03–1.10]) (Supplementary Table 1). IDRs between the sexes remained similar through the follow-up ($p=0.64$ for sex×time interaction, excluded from the model), but their direction and magnitude varied within the age groups ($p<0.001$ for sex×age group) (Fig. 2; Supplementary Table 1).

Please insert Fig. 2 here

Incidence densities of drug-treated epilepsy in infants were lowest of all age groups in the 1960s to the 1970s comprising 1–3% of all childhood epilepsies. During the 1980s, the incidence densities of the infants equalled and exceeded those of the older children. The increase continued up to the mid-1990s, and turned thereafter to a slow decrease, yet remaining substantially above the incidences of the older children. During the 1990s to the 2010s, over 10% of all children with childhood epilepsy were diagnosed in infancy. In 2008–2012, the incidence density in infants was nearly twice as high as in any of the older age groups (Supplementary Table 1). In early 1990s, a few years before the cusp in the infant incidence, less prominent top incidences appeared among older children, followed by relatively steep decrease during the next 5-year period. (Table 1; Fig. 2).

From 1996 to 2012, the annual incidence density decreased 1–2 % in children aged <1, 1–5 or 6–10 years (all 95% confidence intervals within 0.3%–3%). However, it remained stable in the age group of 11–15 years. (Supplementary Table 2).

The validation for the years 1996–2012 showed that 10,743 (96.4%) of the 11,142 children who were granted 100% refundable AEDs, had at least four consecutive drug purchases. When only those 10,743 children were included in the validation analysis, the results for temporal changes in the incidence densities remained virtually similar compared to those of all 11,142 children with special reimbursement for AEDs, apart from the non-significance in the decreasing trend among infants (Supplementary Table 2). Of the 22,172 controls, 36 (0.16%) had at least four AED purchases without entitled 100% reimbursement during 0–15 years of age, and were considered as potential non-detected cases. The reimbursement data detected continuous AED use with 99.7% sensitivity, 98.2% specificity, 96.4% positive predictive value, and 99.8% negative predictive value.

4. Discussion

Our data show that, during the years 1968–2012, the incidence densities of drug-treated childhood epilepsy first increased and then declined toward the end of follow-up with a peak density during 1988 to 1992. The increase was most prominent and continued to occur longer in infants than in older children.

A key issue is this: is our method valid? Did it reach all the relevant patients? Was the incidence in reality lower in the 1960s than four decades later? In the period of 1968–1972, the mean incidence was 35/100,000 in the present study. The same incidence of 35/100,000 was obtained in the Finnish clinical epidemiological study from 1964 [19], and very comparable 39/100,000 in the US study from 1964–1972.[5] There remain no true doubts about the incidence having been 35–40/100,000 in the 1960s.

The question then arises about an increasing trend in the incidence of drug-treated epilepsy during the first decades of follow-up. A change in the treatment pattern is the most obvious explanation, induced by increased knowledge among professionals, improved awareness of people with epilepsy and their relatives, and a more positive public attitude toward epilepsy. Altogether, these factors may have improved case finding and ascertainment and induced better motivation to start AED treatment, leading to higher rates of entitled reimbursements.

Professional knowledge on child neurology has markedly risen in the industrialized countries. In Finland, the number of public child neurologist positions rose from 15 to 48 between the years 1980 and 2000, with reasonably even distribution all over the country.[20] The number of board-certified child neurologists was doubled between 1986 and 1992, from 26 to 53.[20] In 1992, the mean specialist density in Finland was 1 to 18 000 children well equal to the international standards.[20] Continued education of professionals was substantially intensified in several ways: establishing the specialist association in 1978, the epilepsy research foundation in 1985, and the epilepsy research society in 1992; by getting access to advanced diagnostic tools; reporting encouraging research results;[21] and new-generation AEDs[22] for therapy. Knowledge increased among laymen by establishing national laymen's epilepsy organization in 1969 with regional associations over the country. According to a nationwide survey, the awareness of epilepsy among the Finnish population improved during the period of increasing incidence.[23,24] Still more importantly, a more positive atmosphere toward epilepsy followed more liberal Finnish legislation in 1969 by withdrawing the previous prohibition of marriages of people who had non-traumatic epilepsy and, on European level, the launching the European Parliament of the European White Paper on Epilepsy in 2001 to make people with epilepsy come from the shadows. The combined effect of all those factors undoubtedly made it easier for the families to seek medical aid for

seizures to be ascertained as epilepsy. As a sum effect of the above mentioned factors, the incidence curve gradually reached the real incidence around 1990. Thereafter, a slight – and probably real – decrease in the incidence became apparent, as shown in previous studies.[2,4,25]

Interestingly, an incidence profile similar to ours was reported by Christensen et al[2] based on the Danish hospital discharge register from 1977 to 2002. In line with our results, they reported a higher and later peak of childhood-onset epilepsy among infants than among older children. As an explanation, Christensen et al[2] stated that the period of 1990–1995 with a steep rise of the incidence covered, in addition to inpatients, also retrospectively registered outpatients whose systematic registration started from 1995. However, the proportion of outpatients covered less than a half of the increase observed during that period in the total population. Another explanation offered was the effect of the replacement of the ICD-8 with the ICD-10. According to Christensen (personal communication), changing classification per se will cause increase in the incidence. In the present study, peak incidence densities were seen only in infants around 1996, when ICD-9 was replaced with ICD-10 in Finland.

Increasing incidence of epilepsy among the infants conflicts with improved perinatal care and lowered risk for acquired brain injuries during the 1990s. According to the nationwide study on the secular trends in infant epilepsy in Finland, there is a peak in the incidence density of focal epilepsy (but not generalized epilepsy) around the year 1993.[26] So far, however, there are no good explanations for the increasingly high and relatively steady incidence density in infants.

A decreasing trend in the incidence of epilepsy reported recently[2,4,6] was confirmed by our study. Some reasons may be suggested for the decline in the last two decades including more effective vaccination programs,[27,28] substantially lower risk of post-traumatic epilepsy due to significant decline in the documented postnatal traumatic brain injuries,[29,30] constantly low rates of deliveries of very-low-birthweight children (0.8–1.0%) since 1987,[12] and a greater awareness of benign epileptic syndromes in infancy and childhood not necessitating drug treatment.[4,25]

Although our study design was similar to several Finnish studies[6,25,31,32] and comparable to other population studies,[2,5] with proper case finding and valid ascertainment, limitations exist. While the SII data are widely used in scientific research in Finland due to their validated quality and easy accessibility, some concerns still remain, especially when the data are exploited through several decades. The SII reimbursement is voluntary, and some patients may have rejected it due to reluctance to be nationally registered as having epilepsy. In addition to fear of the stigmatization, one obvious reason for the reluctance was the low prices of the AEDs used up to the 1980s when the expense for the required neurologist statement clearly exceeded the costs for the medication itself. The substantially more expensive new-generation AEDs,[22] launched in Finland since the late 1980s, in all probability, increased the pressure for first ever reimbursement applications even for some prevalent patients and may in part explain the observed peak in the incidence. As is inevitable in register studies, our data may have not revealed all the subjects who in reality had epilepsy and should, according to the contemporary practice parameters, have needed drug therapy. In a Finnish clinical study, however, virtually all eligible children who had epilepsy were documented.[33] Similarly, in a Finnish birth cohort follow-up study, the incidence rate of childhood epilepsy was in consonance with the register-based incidence in the same geographic area.[34] The registers used by us are estimated to cover 97% of all newly

diagnosed cases of epilepsy of all ages and even a higher percentage of children during the latest decades of the follow-up.[6]

Despite the limitations, the strengths of our study include nationwide and stable study population; very long-term follow-up, consistent inclusion criteria throughout the whole period; excellent coverage of patients regardless of place of treatment; specialist-ascertained diagnosis of epilepsy; and proven compatibility between the register data and the clinical records data. Furthermore, on sensitivity analysis of the quality of the reimbursement data, the agreement proved excellent.

In conclusion, the incidence of drug-treated childhood epilepsy based on the documented use of antiepileptic drugs for epilepsy steeply increased up to the 1990s probably due to the improved case ascertainment. Reasons for the two-fold increase in the incidence may reflect improved diagnosis and a wider acceptance of AEDs. The slight decrease since the 1990s is thought to reflect the recent improvement in child health and safety. Finally, the antiepileptic drug reimbursement register seems to be a valid and reliable method for assessing the incidence of childhood epilepsy.

Contributors All authors conceived the study design. MMS analysed the data and drafted the first version of the manuscript. MS, DS and LJV critically revised the manuscript for important intellectual content. All authors approved the final version for publication.

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Figure legends

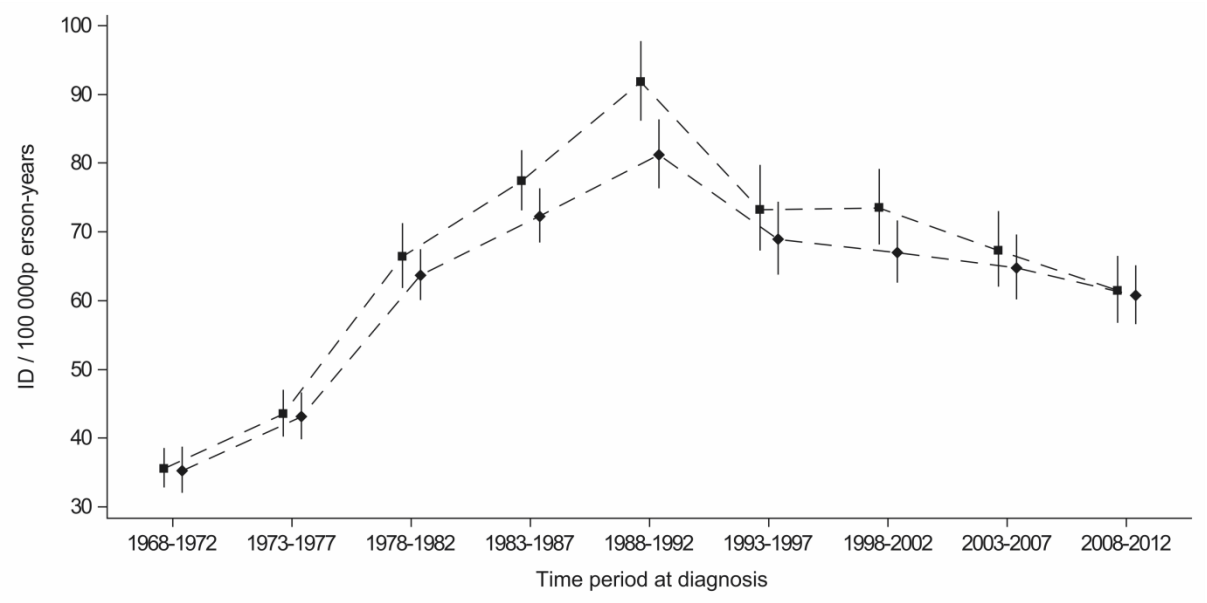
Figure 1. Mean annual incidence densities (ID) with 95% confidence intervals per 100,000 person-years of epilepsy in children aged 0–15 over years 1968–2012 by 5-year periods. ♦=girls; ■=boys.

Figure 2. Mean annual incidence densities (ID) with 95% confidence intervals of childhood epilepsy per 100,000 person-years in Finnish children by 5-year time periods within age groups. ♦=age <1 year; ●=1–5 years; ■=6–10 years; ▲=11–15 years.

Table 1. Number of new cases and incidence densities of childhood epilepsy during 1968–2012 in Finnish children aged 0–15 years.

Time period	No. of events		No. of person-years at risk[a]	Incidence density per 100 000 person-years		
	All	% Boys		All	Boys	Girls
Total	29,567	53 %	46,942,878	63.0	64.8	61.1
Age <1 year						
1968–1972	23	67 %	325,965	7.1	9.6	4.4
1973–1977	53	47 %	311,193	17.0	15.7	18.5
1978–1982	120	49 %	317,495	37.8	36.3	39.3
1983–1987	233	51 %	317,023	73.5	72.8	74.2
1988–1992	374	54 %	319,042	117.2	123.4	110.8
1993–1997	460	55 %	315,340	145.9	157.3	134.0
1998–2002	377	55 %	283,597	132.9	142.0	123.4
2003–2007	380	55 %	286,755	132.5	142.6	122.0
2008–2012	349	54 %	299,112	116.7	122.4	110.7
Age 1–5 years						
1968–1972	516	53 %	1,791,385	28.8	30.2	27.4
1973–1977	550	54 %	1,537,060	35.8	37.6	33.8
1978–1982	1,045	52 %	1,583,722	66.0	67.3	64.7
1983–1987	1,261	54 %	1,614,908	78.1	83.1	72.9
1988–1992	1,325	56 %	1,569,008	84.5	92.6	76.0
1993–1997	1,181	56 %	1,624,592	72.7	79.9	65.2
1998–2002	1,129	54 %	1,511,235	74.7	78.8	70.5
2003–2007	973	53 %	1,424,561	68.3	70.1	66.4
2008–2012	934	52 %	1,485,188	62.9	63.4	62.4
Age 6–10 years						
1968–1972	806	53 %	1,929,422	41.8	43.3	40.2
1973–1977	902	51 %	1,796,088	50.2	50.7	49.8
1978–1982	1,190	54 %	1,538,094	77.4	82.1	72.4
1983–1987	1,298	55 %	1,600,176	81.1	87.1	74.8
1988–1992	1,518	56 %	1,625,738	93.4	101.4	85.0
1993–1997	1,181	52 %	1,589,146	74.3	75.8	72.7
1998–2002	1,195	55 %	1,633,745	73.1	79.5	66.6
2003–2007	1,005	52 %	1,520,524	66.1	67.3	64.8
2008–2012	853	53 %	1,443,468	59.1	60.8	57.3
Age 11–15 years						
1968–1972	812	48 %	2,044,394	39.7	37.1	42.4
1973–1977	909	50 %	1,928,545	47.1	46.1	48.2
1978–1982	1,055	50 %	1,800,449	58.6	57.5	59.7
1983–1987	1,014	59 %	1,548,654	65.5	62.4	68.7
1988–1992	1,219	51 %	1,606,712	75.9	75.1	76.7
1993–1997	855	47 %	1,641,281	52.1	48.0	56.4
1998–2002	834	49 %	1,600,093	52.1	50.3	54.1
2003–2007	863	50 %	1,644,018	52.5	51.7	53.4
2008–2012	775	49 %	1,535,156	50.5	48.4	52.7

[a]51% boys in total population and in all subgroups.



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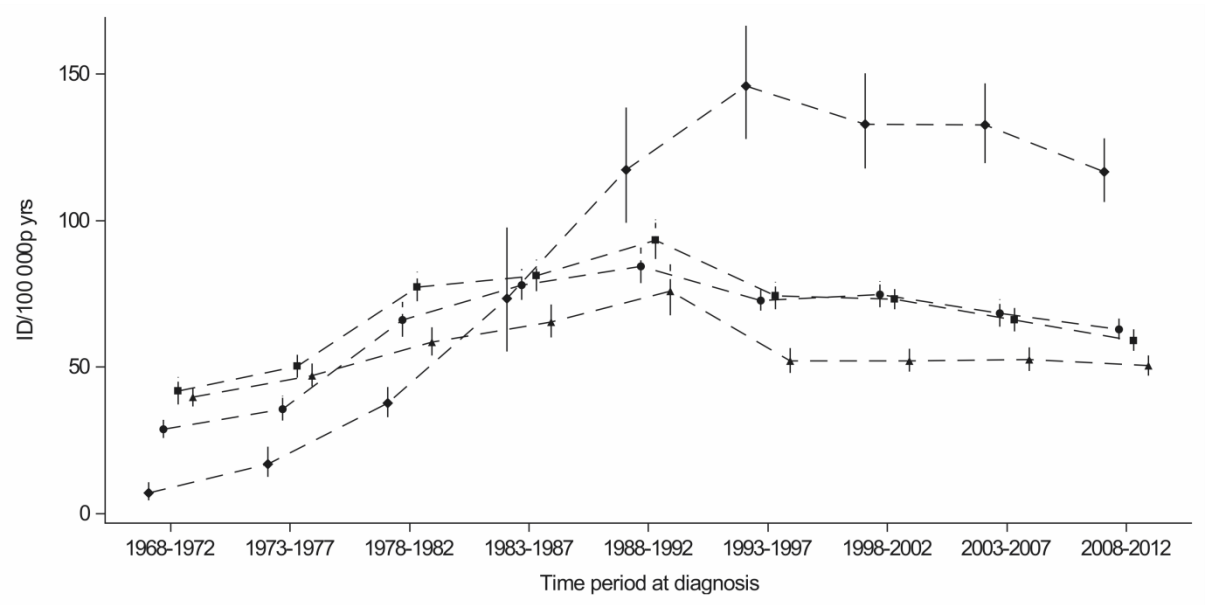

Figure 2. Mean annual incidence densities (ID) with 95% confidence intervals of childhood epilepsy per 100,000 person-years in Finnish children by 5-year time periods within age groups. ♦=age <1 year; ●=1–5 years; ■=6–10 years; ▲=11–15 years.

Supplementary Table 1. Incidence density ratios (IDRs) with 95% confidence intervals (95% CI) for children with epilepsy during 1968–2012. IDRs from Poisson regression, calculated for boys vs. girls, younger vs. older children and 2008–2012 vs. earlier time periods. Confidence intervals were Bonferroni-corrected in multiple comparisons within same predictor or interaction term.

	IDR	**95% CI**
Boys vs. girls	1.07	1.03–1.10
Age		
0 vs. 1–5 years	1.01	0.92–1.12
0 vs. 6–10 years	0.91	0.82–1.01
0 vs. 11–15 years	1.13	1.02–1.25
1–5 vs. 6–10 years	0.90	0.86–0.94
1–5 vs. 11–15 years	1.11	1.06–1.17
6–10 vs. 11–15 years	1.23	1.18–1.29
Time period 2008–2012 vs.		
1968–1972	2.83	2.39–3.37
1973–1977	1.97	1.75–2.22
1978–1982	1.18	1.09–1.28
1983–1987	0.92	0.83–1.02
1988–1992	0.75	0.69–0.81
1993–1997	0.85	0.79–0.92
1998–2002	0.87	0.81–0.94
2003–2007	0.91	0.84–0.99
Boys vs. girls at age[a]		
0 years	1.11	0.98–1.26
1–5 years	1.12	1.06–1.19
6–10 years	1.11	1.05–1.17
11–15 years	0.93	0.87–0.99
During 2008–2012[a]		
0 vs. 1–5 years	1.86	1.59–2.16
0 vs. 6–10 years	1.97	1.68–2.32
0 vs. 11–15 years	2.31	1.95–2.72
1–5 vs. 6–10 years	1.06	0.94–1.20
1–5 vs. 11–15 years	1.24	1.09–1.41
6–10 vs. 11–15 years	1.17	1.02–1.34

[a]P-values <0.001 for interactions of age group×sex and age group×time period.

Supplementary Table 2. Incidence density ratios (IDR) with 95% confidence intervals (95%CI) for children with epilepsy during 1996–2012. A=Entitled antiepileptic drug reimbursement data (total no. of cases 11 142). B=Combined reimbursement and drug purchases data (total no. of cases 10 743). IDRs from Poisson regression, calculated for boys vs. girls, younger vs. older children and change per annum. Confidence intervals were Bonferroni corrected for multiple comparisons within same predictor or interaction term.

	A: Reimbursement data		**B: Reimbursement and AED purchases data**	
	IDR	**95% CI**	**IDR**	**95% CI**
Boys vs. girls	1.07	1.02–1.11	1.07	1.03–1.12
Age				
0 vs. 1–5 years	1.87	1.72–2.04	1.67	1.52–1.83
0 vs. 6–10 years	1.93	1.77–2.10	1.71	1.56–1.88
0 vs. 11–15 years	2.48	2.27–2.72	2.21	2.01–2.43
1–5 vs. 6–10 years	1.03	0.97–1.10	1.03	0.96–1.10
1–5 vs. 11–15 years	1.33	1.24–1.42	1.32	1.24–1.42
6–10 vs. 11–15 years	1.29	1.21–1.38	1.29	1.20–1.38
Boys vs. girls within age group[a]				
0 years	1.16	1.01–1.34	1.17	1.01–1.37
1–5 years	1.08	0.99–1.17	1.08	0.99–1.18
6–10 years	1.11	1.02–1.21	1.12	1.02–1.21
11–15 years	0.93	0.85–1.02	0.94	0.85–1.03
Slope for annual change	0.988	0.984–0.992	0.989	0.985–0.993
Slopes for annual change within age group[b]				
0 years	0.983	0.970–0.997	0.987	0.972–1.002
1–5 years	0.988	0.980–0.997	0.987	0.979–0.996
6–10 years	0.982	0.974–0.991	0.983	0.974–0.991
11–15 years	0.999	0.990–1.009	0.999	0.989–1.016

[a]P <0.001 for sex×age group interaction
[b]p=0.004 for time period×age group interaction