Overrepresentation of epilepsy in children with type 1 diabetes is declining in a longitudinal population study in Finland

Matti Sillanpää[1,2], Maiju M. Saarinen[1,2,3], Tapani Rönnemaa[4], Mika Gissler[5,6,7], Dieter Schmidt[8]

[1] Department of Child Neurology, University of Turku and Turku University Hospital, Turku, Finland
[2] Department of General Practice, University of Turku and Turku University Hospital, Turku, Finland
[3] Doctoral Programme of Clinical Research, University of Turku, Turku, Finland
[4] Department of Medicine, University of Turku and Turku University Hospital, Turku, Finland
[5] National Institute for Health and Welfare (THL), Helsinki, Finland
[6] Research Centre for Child Psychiatry, University of Turku, Turku, Finland
[7] Karolinska Institute, Department of Neurobiology, Care Sciences and Society, Division of Family Medicine, Stockholm, Sweden
[8] Epilepsy Research Group, Berlin, Germany

Short title: Incidence of epilepsy in type 1 diabetes

All correspondence to:
Prof. Matti Sillanpää, MD PhD
Department of General Practice, 20014 University of Turku, Turku, Finland
Tel. +358 029 4504465
Fax. +358 029 4505040
matti.sillanpaa@utu.fi

Number of words: 3097

Number of figures: 1

Number of tables: 2

Summary: 200 words

ABSTRACT

Aim

The aim was to determine temporal changes in increased risk of epilepsy among children with type 1 diabetes.

Methods

The incidence of epilepsy up to age 15 in children with prior type 1 diabetes was analysed regarding the general Finnish child population using data from the Finnish nationwide hospital register. Type 1 diabetes and epilepsy were identified by the International Classification of Diseases 9th and 10th revision codes. Epilepsy was defined according to ILAE guidelines. The analyses were done using negative binomial regression models.

Results

Preceding type 1 diabetes was diagnosed in 6162 (0.91%) of the 679,375 general population children. Incidence rate of new-onset epilepsy among children with type 1 diabetes was higher than in controls (140 versus 82 per 100,000 person-years at risk, respectively). The excess incidence diminished with time (p=0.033 for diabetes to birth cohort interaction), from over two-fold in birth cohort 1990–1993 [incidence rate ratio 2.2 (95% CI 1.7–2.9)] to 40% in birth cohort 1998–2000 [1.4 (95% CI 1.001–1.9)].

Conclusions

In a population study setting, children with type 1 diabetes had an increased, but slowly declining risk of developing epilepsy. Future research may elucidate the underlying mechanisms.

KEY NOTES

- The risk of epilepsy was analysed in Finnish children with and without prior type 1 diabetes mellitus at the age of 0–14 years in the years 1990–2014
- Children with type 1 diabetes had an increased, but slowly declining risk of developing epilepsy compared to the general child population
- Epilepsy should be added to the list of treatable neurological comorbidities of diabetes mellitus

Key words: Childhood seizures; Comorbidity; Incidence of epilepsy; Register study; Type 1 diabetes

INTRODUCTION

While the coincidence of type 1 diabetes mellitus and epilepsy is being increasingly reported (1,2), so far, only two reports provide population-based estimates of the coincidence of the two diseases (3,4). In a Taiwanese population study of patients ≤18 years of age followed for 10 years by Chou *et al.* (3), the cohort with type 1 diabetes was almost three times as likely to develop epilepsy as the control cohort. However, the study had certain methodological problems.(5) In particular, the patients with diabetes and epilepsy included incident and prevalent cases of epilepsy, and therefore the data were not applicable for the evaluation of epilepsy incidence.(5) The only other population-based study, reported from the UK by Dafoulas *et al.* (4), also gave an over three-fold excess risk of epilepsy among patients ≤18 years of age. However, the study gave no data on the diagnostic process for epilepsy. The data originated from the The Health Improvement Network database which, while broadly representative of the UK population, was based on assessment by family doctors. In epilepsy studies, the family doctor based methodology is not without certain validity problems (6) and misdiagnoses (7). Studies on children with epilepsy in the UK are subject to similar problems (8).

While the mechanisms between type 1 diabetes and epilepsy remain unclear (1), the two studies of epilepsy in children with type 1 diabetes (3,4) suggested a remarkable excess incidence. In the general child populations of industrialised countries, the incidence of epilepsy has been declining during the past few decades (9-11). No data are available on changes in the incidence of epilepsy in patients with type 1 diabetes, neither of the previous studies (3,4) having compared the long-term trajectories of a large number of patients with type 1 diabetes in epilepsy.

Our purpose was to examine the incidence and long-term trends in the incidence of epilepsy in Finnish children with type 1 diabetes in a large population-based study

using national register data. Our hypothesis was that the incidence of epilepsy is higher in children with type 1 diabetes than in the general child population, and that it is slowly decreasing along with its incidence in the general population.

PATIENTS AND METHODS

The target population consisted of 11 consecutive Finnish birth cohorts. The participants were followed up from birth to 15 years of age. The 25-year study period covered the years 1990 to 2014.

The study data were collected from the Hospital Discharge Register, established in 1967, currently called the Care Register for Health Care and maintained by THL, the National Institute for Health and Welfare. In addition to inpatient hospital data, outpatient specialist unit data were included in the Care Register from 1998 to 2014. The diagnoses in the Care Register were coded using the International Classification of Diseases (ICD): revision 9 up to and including 1995 and revision 10 in 1996–2014. The treating physician recorded the ICD codes into the local patient data system. Thereafter, the diagnoses were reviewed for consistency at the local and national levels by hospitals and the National Institute for Health and Welfare, the data keeper. Finally, the Care Register ran an internal quality control before the data were documented in the register database. For the diagnosis of type 1 diabetes, the ICD-9 codes 2500B, 2501B, 2504B, 2505B and 2508B were used for the years 1990 to 1995 and the ICD-10 code E10 for the years 1996 to 2014. For the types of seizures and epilepsies, the contemporary guidelines of the International League Against Epilepsy were followed (12,13). Accordingly, two unprovoked seizures or one unprovoked seizure with a high risk of recurrence were considered as epilepsy. To identify the patients with epilepsy in the register, the ICD-9 code 345 was used for the years 1990 to 1995 and the ICD-10 code G40 for the years 1996 to 2014.

In Finland, starting the treatment of type 1 diabetes is centralised to tertiary and secondary care hospitals, and in all patients below 16 years of age the treatment is started as inpatients by trained paediatric specialists. It is also the national medical

practice to routinely refer children with any type of suspected epileptic seizure disorder to a specialist unit with paediatric neurological expertise (14,15). The diagnosis of epilepsy is ascertained by board-certified child neurologist, or, in few cases, by a paediatrician or adult neurologist. In all children diagnosed with epilepsy, the seizures are verified to be unprovoked. In addition to clinical examination, the diagnosis is based in all cases on EEG and in most cases on additional appropriate laboratory investigations, when necessary. At the onset of epileptic seizures, 97% of the children are hospitalised (14,16). All Finnish hospitals are obliged by law to report all diagnoses of all inpatients and, since 1998, of all inpatients and outpatients to the administrative Care Register using the current ICD codes selected and documented by the treating physician. Accordingly, the Care Register covers virtually all the children with type 1 diabetes or epilepsy or both, diagnosed during the observation period.

The person-years at risk (PYR) of the total child population born in 1990–2000 and permanently residing in Finland, at age 0–14 years during the years 1990–2014 were derived from the population statistics of Statistics Finland. The register data were summarised by birth cohort into annual blocks of the number of children with first-ever diagnosis of epilepsy separately for children with and without prior type 1 diabetes. The year of the first diagnosis of epilepsy was used as the proxy for the time of onset of epilepsy. Follow-up was ended by the year of the first diagnosis of epilepsy, the 15th birthday, or 31 December 2014, whichever occurred first.

Statistical analyses

Incidence rates (IRs) of epilepsy are given as the number of newly diagnosed cases per 100,000 PYR, separately for the cohorts of children with and without type 1 diabetes. Children born in 1990–2000 who had a complete follow-up of 15 years by

2014 were included in the analyses. As the data on controls originated from census data unmatched to the participants with type 1 diabetes, no surrogate criteria for the time of diagnosis of diabetes were available for them. Thus, to obtain comparable estimates of PYR for the incidence rate ratio (IRR) calculations, the follow-up of all participants began from birth. The data were analysed using generalised linear models. Poisson distribution was rejected due to overdispersion (deviance 2.67, chi-squared goodness of fit test $p<0.001$) and replaced with negative binomial distribution (deviance 1.00, chi-squared goodness of fit test $p=0.47$). Presence of type 1 diabetes, one-year birth cohort, and the interaction between them, were the predictors in the models. Modelling the birth cohort effect as quadratic rather than linear did not improve the model fit; thus, the simpler model of linear shape was used in the final analyses. The models included no covariates. To control for annual random variation, temporal estimates of IRs with 95% confidence intervals (CIs) were calculated from a model with birth cohorts categorised according to three periods, 1990–1993, 1994–1997, and 1998–2000. All the analyses were made using a 95% confidence level. Statistical analyses were carried out using SAS version 9.4 software (SAS Institute, Cary, North Carolina, USA).

Ethical Approval

According to the Medical Research Act, issued by the Ministry of Social Affairs and Health of Finland, no institutional review board approval is required for register-based research in Finland. No approval of this study needed to be acquired as only anonymised and aggregated data were used. Patient consent was not required because the data were taken from the Care Register, which can be collected and used for statistical and research purposes without informed consent.

RESULTS

Among the total population of 679,375 children, type 1 diabetes was ascertained in 6162 children (0.9%) and epilepsy in 8512 children (1.3%). Both type 1 diabetes and epilepsy occurred in 128 (0.02%) of the 679,375 children. Epilepsy was nearly twice as common among children with type 1 diabetes as among controls (2.1% versus 1.2%). (Table 1)

Please insert Table 1 here

The overall estimate of incidence rates (IRs) of epilepsy at age 0–14 years within the cohort of all children born in 1990–2000 was 140 per 100,000 PYR for children with type 1 diabetes and 82 per 100,000 PYR for controls, with the IRR 1.7 (95% CI 1.4–2.0) representing a 70% excess incidence of epilepsy among children with preceding type 1 diabetes. The ratio did not, however, remain constant during the study period (p=0.037 for diabetes to birth cohort interaction). Towards the later birth cohorts, there was a non-significant decrease in the incidence of epilepsy among children with type 1 diabetes [IRR for linear one-year birth cohort 0.95 (95% CI 0.90–1.01)] and a slight increase among the controls [1.02 (95% CI 1.00–1.03)]. The levels of the temporal estimates of IR in combined birth cohorts 1990–1993, 1994–1997, and 1998–2000 are given in Table 2. Epilepsy incidence remained higher in children with type 1 diabetes than in the controls during all three periods (Fig.1), while the ratio diminished with time from 2.2-fold to 1.4-fold (Table 2). As shown by the slopes in the trend model, the temporal change within the two groups was non-significant between the earliest and latest combined birth cohorts 1990–1993 versus 1998–2000 [IR 0.89 (95% CI 0.79–1.01) for children with type 1 diabetes, and 1.44 (95% CI 0.96–2.16) for controls].

Please insert Fig.1 and Table 2 here

DISCUSSION

Our study presents the incidence of epilepsy in children with type 1 diabetes mellitus in a large, nationwide population, with long-term follow-up. We found that, among children with type 1 diabetes, the incidence rate of new-onset epilepsy was higher than in the general child population, and it remained elevated in the birth cohorts from 1990 to 2000. The increased morbidity was in line with our hypothesis. In contrast to our expectations, no significant temporal decrease in the incidence of epilepsy was found in either children with or without type 1 diabetes. However, as the slight temporal changes occurred in opposite directions, the relative effect lowered the incidence rate ratios between the groups from 2.2 in the earliest to 1.4 in the latest birth cohorts. Yet, despite the fall in excess incidence, the risk of epilepsy prior to age 15 remained 40% higher for a child with versus without type 1 diabetes.

According to the two previous population studies on epilepsy in children with type 1 diabetes (3,4), the risk of epilepsy was three times as high as in the controls (in Taiwan 234 versus 68 per 100,000 and in the UK 132 versus 44 per 100,000, for children with and without type 1 diabetes, respectively). The incidence ratio estimates from the cohorts with matched controls are expectedly higher than in the present study, because the matching reduces the incidence among the controls by excluding most of the infants and toddlers with the highest risk of epilepsy. In addition, the estimates in the type 1 diabetes group with follow-up from birth rather than onset of type 1 diabetes are reduced, due to the increased number of follow-up years. While these estimates have no direct interpretation at the level of the individual patient, they reflect the cumulative situation within and, more important, between birth cohorts up to age 15. Even at the population level, epilepsy is more common in children with prior type 1 diabetes than among children who have no preceding type 1 diabetes.

Our results were based on national register data. National administrative registers are well accepted by the Finnish population and considered valid (17). There are few, if any, doubts about missing cases in the hospital admissions. It is warranted to assume that there is very good, if not perfect, coverage of all children with type 1 diabetes, and those with diabetes and epilepsy in particular, as the treatment of these children always needs long-term and active follow-up and frequent hospital visits for both epilepsy and diabetes.

The reliability of the administrative register information in childhood onset epilepsy has been validated in a study comparing the hospital record data of a regional birth cohort 1987 (n=8708) with the register data of the same area in children aged up to seven years. The cumulative incidence of epilepsy in the hospital record data was well comparable to the register data (7.1 versus 6.8 per 1000, respectively) (18). Our total estimate of epilepsy incidence for general population controls aged 0–14 years is in line with recent estimates for the total population at the same age, calculated from the register data of another national authority, the Finnish Social Insurance Institution. The reference data were based on the Special Reimbursement Register, which lists all the persons who have been granted a 100% refund for drug expenses by the Social Insurance Institution expert board for certain specialist-verified chronic diseases including diabetes mellitus and epilepsy (11).

The present epilepsy incidence rates of 77 to 87 per 100,000 among controls remain well within the range of 70 to 87 per 100,000 calculated from the Special Reimbursement Register records during the years 1988–2002 (11).

Contrary to the estimates based on the Special Reimbursement Register data, in the present study the incidence of epilepsy among controls increased slightly

towards the later cohorts. This is probably an artefact due to the change that took place in the recording practice in 1998, when the Care Register hospital discharge data base was first complemented with the outpatient data. The increase suggests that, throughout the follow-up, a small percentage of the children were diagnosed with epilepsy without hospitalisation. This is, however, unlikely in the case of children with preceding type 1 diabetes, as epileptiform seizures require careful monitoring of glycaemic control in patients with diabetes. The proportion of combined inpatient and outpatient data increases gradually within the studied birth cohorts covering 47% of the follow-up time for the eldest children born in 1990, and 100% for those born in the latest period 1998–2000. However, even in the latest cohorts with full data from both inpatient and outpatient wards, a 40% excess incidence of epilepsy in children with T1DM was still found.

Compared with the incidence in the general population, the higher incidence of new-onset epilepsy in type 1 diabetes patients cannot be readily explained. Despite massive efforts and investments, our current insight into the mechanisms of epilepsy alone is still limited (19), and the underlying mechanisms of type 1 diabetes are still elusive in many aspects (20). The association between diabetes and epilepsy is most likely based on several different mechanisms (2). One potential route is through the autoimmune system, as epilepsy is a common comorbid disease in several autoimmune disorders (21). Specific autoimmune antibodies associated with idiopathic epilepsy are increasingly identified (22), including glutamic acid decarboxylase (GAD) antibodies characteristically present at the onset of type 1 diabetes (23). While GAD catalyses the conversion of glutamic acid, the main excitatory amino acid in the brain, to the main inhibitory neurotransmitter gamma-aminobutyric acid, the antibody-induced inhibition of GAD may lead to neuronal discharges and seizures through imbalance in gamma-aminobutyric acid synthesis and release (1,24). Another potential hypothesis includes metabolic

disturbances associated with hypoglycaemia or hyperglycaemia. Seizures induced by altered metabolic conditions during hypoglycaemia or hyperglycaemia might lower the seizure threshold and lead to overt epilepsy in some patients (1,24). In addition to direct brain injury, another underlying mechanism might be harmful cerebral adaptation in the uptake and utilisation of non-glucose energy substrates, such as lactate, during recurrent hypoglycaemic episodes (25).

In the present study, we found a tendency towards a decrease in the incidence of epilepsy among children with type 1 diabetes during the follow-up. The decline in the incidence might support the hypothesis suggesting the role of dysglycaemia in epileptogenesis. Improved glycaemic control has been reported by several paediatric cohorts from the same time period. In a community-based Finnish study of children with type 1 diabetes at age 0–15, the proportion of patients with very poor glycaemic control (glycated haemoglobin (HbA1c) level ≥10 % [≥86 mmol/mol]) was reduced from over 30% to less than 10% during the years 2000 to 2008 (26). A similar decrease was found in children and adolescents in Denmark during 1996–2005 (27), as well as in Germany and Austria, where the proportion of paediatric patients with poor glycaemic control decreased from 40% to 16% between 1995 and 2005 (28). Simultaneously, decreasing trends in the incidence rates of severe hypoglycaemia and hypoglycaemic coma have been reported, especially among patients with good glycaemic control (HbA1c level 6–8% [42–64 mmol/mol]) (29,30). If metabolic predisposition is a key issue in the comorbid occurrence of epilepsy and type 1 diabetes, these results might suggest a decline in the future incidence of epilepsy in type 1 diabetes throughout the Western countries with modern treatment practices including ample use of continuous glucose monitoring and insulin pump therapy in paediatric diabetes clinics.

While our study was population-based with extended follow-up of children with type 1 diabetes, it has limitations. Typical of register-based studies, we lacked medical details of the study participants, which might have been confounding factors. We also lacked access to individual patient data to verify the correctness of the recorded diagnoses. However, the risk of misdiagnoses is likely to be very low, considering that the diagnoses were made by certified treating specialists. The lack of pairwise matched controls prevented us from conducting more specific analyses regarding the time elapsed after the diagnosis of diabetes. The population-level approach also affects the acquired estimates, with the result that they are not directly comparable to those from matched-control studies. While the incidence of type 1 diabetes may possibly be higher in Finland than in other European countries, there is no evidence in the literature that type 1 diabetes in Finland might differ in terms of pathogenesis or clinical features from that found in other countries. The strengths of our study include the large study cohort, the nationwide study population, the long observation period, and the complete 15-year follow-up of all birth cohorts.

CONCLUSIONS

Our study indicated a strong association between epilepsy and type 1 diabetes. Children with type 1 diabetes have an increased risk of contracting epilepsy adding it to the list of treatable neurological comorbidities of diabetes mellitus. While the excess risk of epilepsy has declined during the last few decades, the higher incidence in children with type 1 diabetes is still a public health issue. Further research is needed in order to explore both the underlying mechanisms of the increased risk and the factors behind the decline in the excess risk of epilepsy in children with type 1 diabetes.

ACKNOWLEDGEMENTS

We thank Rosemary Mackenzie, M.A. for expert language revision.

FINANCE

This work was supported by grants from the University of Turku Graduate School UTUGS, the Finnish Epilepsy Research Foundation, and the Turku University Foundation.

ABBREVIATIONS

CI, confidence interval; GAD, glutamic acid decarboxylase; ICD, International Classification of Diseases; IR, incidence rate; IRR, incidence rate ratio; PYR, person-years at risk.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

REFERENCES

(1) Verrotti A, Scaparrotta A, Olivieri C, Chiarelli F. Seizures and type 1 diabetes mellitus: current state of knowledge. *Eur J Endocrinol* 2012;167(6):749-758.

(2) Mastrangelo M, Tromba V, Silvestri F, Costantino F. Epilepsy in children with type 1 diabetes mellitus: Pathophysiological basis and clinical hallmarks. *Eur J Paediatr Neurol* 2019;23(2):240-247.

(3) Chou IC, Wang CH, Lin WD, Tsai FJ, Lin CC, Kao CH. Risk of epilepsy in type 1 diabetes mellitus: a population-based cohort study. *Diabetologia* 2016;59(6):1196-1203.

(4) Dafoulas GE, Toulis KA, Mccorry D, Kumarendran B, Thomas GN, Willis BH, et al. Type 1 diabetes mellitus and risk of incident epilepsy: a population-based, open-cohort study. *Diabetologia* 2017;60(2):258-261.

(5) Sander JW, Novy J, Keezer MR. The intriguing relationship between epilepsy and type 1 diabetes mellitus. *Diabetologia* 2016;59(7):1569-1570.

(6) Leach JP, Lauder R, Nicolson A, Smith DF. Epilepsy in the UK: Misdiagnosis, mistreatment, and undertreatment? The Wrexham area epilepsy project. *Seizure* 2005;14(7):514-520.

(7) Scheepers B, Clough P, Pickles C. The misdiagnosis of epilepsy: findings of a population study. *Seizure* 1998;7(5):403-406.

(8) Cross JH. Pitfalls in the diagnosis and differential diagnosis of epilepsy. *Paediatrics Child Health* 2009;19(5):199-202.

(9) Christensen J, Vestergaard M, Pedersen MG, Pedersen CG, Olsen J, Sidenius P. Incidence and prevalence of epilepsy in Denmark. *Epilepsy Res* 2007;76:60-65.

(10) Sillanpää M, Kälviäinen R, Klaukka T, Helenius H, Shinnar S. Temporal changes in the incidence of epilepsy in Finland: Nationwide study. *Epil Res* 2006;71(2-3):206-215.

(11) Saarinen MM, Sillanpää M, Schmidt D, Virta LJ. Long-term changes in the incidence of childhood epilepsy. A population study from Finland. *Epilepsy Behav* 2016;58:81-85.

(12) Commission on revised classification of epilepsy 1989. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 1989;30(4):389-399.

(13) Commission. Commission on Epidemiology and Prognosis. Guidelines of epidemiologic studies on epilepsy. *Epilepsia* 1993;34:592-596.

(14) Rantala H, Ingalsuo H. Occurrence and outcome of epilepsy in children younger than 2 years. *J Pediatr* 1999;135(6):761-764.

(15) Hirvonen M, Ojala R, Korhonen P, Haataja P, Eriksson K, Gissler M, et al. The incidence and risk factors of epilepsy in children born preterm: A nationwide register study. *Epilepsy Res* 2017;138:32-38.

(16) Sillanpää M. Epidemiology and long-term Turku outcome of childhood-onset epilepsy and mortality. Personal experiences. Part I. *J Epileptol* 2015;23(2):136-144.

(17) Sund R. Quality of the Finnish Hospital Discharge Register: a systematic review. *Scand J Public Health* 2012;40(6):505-515.

(18) Gissler M, Järvelin MR, Hemminki E. Comparison between research data and routinely collected register data for studying childhood health. *Eur J Epidemiol* 2000;16(1):59-66.

(19) Liu F, Wang Y, Li M, Wang W, Li R, Zhang Z, et al. Dynamic functional network connectivity in idiopathic generalized epilepsy with generalized tonic-clonic seizure. *Hum Brain Mapp* 2017;38(2):957-973.

(20) Katsarou A, Gudbjörnsdottir S, Rawshani A, Dabelea D, Bonifacio E, Anderson BJ, et al. Type 1 diabetes mellitus. *Nat Rev Dis Primers* 2017;3:17016.

(21) Ong MS, Kohane IS, Cai T, Gorman MP, Mandl KD. Population-level evidence for an autoimmune etiology of epilepsy. *JAMA Neurol* 2014;71(5):569-574.

(22) Liimatainen S, Peltola M, Sabater L, Fallah M, Kharazmi E, Haapala AM, et al. Clinical significance of glutamic acid decarboxylase antibodies in patients with epilepsy. *Epilepsia* 2010;51(5):760-767.

(23) Parikka V, Näntö-Salonen K, Saarinen M, Simell T, Ilonen J, Hyöty H, et al. Early seroconversion and rapidly increasing autoantibody concentrations predict prepubertal manifestation of type 1 diabetes in children at genetic risk. *Diabetologia* 2012;55(7):1926-1936.

(24) Marcovecchio ML, Petrosino MI, Chiarelli F. Diabetes and epilepsy in children and adolescents. *Curr Diab Rep* 2015 Apr;15(4):21.

(25) Trico D, Herzog RI. Metabolic brain adaptations to recurrent hypoglycaemia may explain the link between type 1 diabetes mellitus and epilepsy and point towards future study and treatment options. *Diabetologia* 2017;60(5):938-939.

(26) Saha M, Keskinen P. Lasten ja nuorten diabeteksen hoitotulokset paranevat. *Suomen Lääkärilehti* 2009;64:27-32.

(27) Hojberg AS, Hansen D, Svensson J, Johannesen J, Eising S, Birkebaek NH, et al. First 10 years with the Danish Registry of Childhood Diabetes. *Ugeskr Laeger* 2007;169(22):2106-2108.

(28) Gerstl EM, Rabl W, Rosenbauer J, Grobe H, Hofer SE, Krause U, et al. Metabolic control as reflected by HbA1c in children, adolescents and young adults with type-1 diabetes mellitus: combined longitudinal analysis including 27,035 patients from 207 centers in Germany and Austria during the last decade. *Eur J Pediatr* 2008 Apr;167(4):447-453.

(29) O'Connell SM, Cooper MN, Bulsara MK, Davis EA, Jones TW. Reducing rates of severe hypoglycemia in a population-based cohort of children and adolescents with type 1 diabetes over the decade 2000-2009. *Diabetes Care* 2011;34(11):2379-2380.

(30) Karges B, Rosenbauer J, Kapellen T, Wagner VM, Schober E, Karges W, et al. Hemoglobin A1c levels and risk of severe hypoglycemia in children and young adults with type 1 diabetes from Germany and Austria: a trend analysis in a cohort of 37,539 patients between 1995 and 2012. *PLoS Med* 2014;11(10):e1001742.

Table 1. Number of children born in 1990–2000, and person-years at risk (PYR) during the follow-up from 0 to 14 years of age until 31 December 2014 for children with type 1 diabetes and controls without type 1 diabetes in a Finnish population cohort.

	Number of children	PYR
Total	679,375	10,302,425
Type 1 diabetes		
Total	6,162	91,410
With epilepsy	128	
Controls		
Total	673,213	10,211,015
With epilepsy	8,384	

Table 2. Incidence rates (IRs) per 100,000 person-years at risk and incidence rate ratios for epilepsy among Finnish children with type 1 diabetes mellitus (T1DM) and controls without T1DM. Confidence intervals (95% CI) according to negative binomial regression models with T1DM and birth cohort as predictors.

Birth cohorts		Estimate	95% CI
1990–1993			
	IR of children with T1DM	173	(132–229)
	IR of children without T1DM	78	(72–84)
	IR ratio: T1DM/No-T1DM	2.23	(1.68–2.97)
1994–1997			
	IR of children with T1DM	125	(92–170)
	IR of children without T1DM	84	(78–90)
	IR ratio: T1DM/No-T1DM	1.50	(1.09–2.00)
1998–2000			
	IR of children with T1DM	121	(85–172)
	IR of children without T1DM	87	(80–95)
	IR ratio: T1DM/No-T1DM	1.39	(0.97–2.00)

FIGURE LEGENDS

Fig 1. Incidence rate with 95% confidence intervals of epilepsy per 100,000 person-years of children with prior diagnosis of type 1 diabetes (filled diamonds) and controls (hollow diamonds) in subsequent birth cohorts from 1990 to 2000.

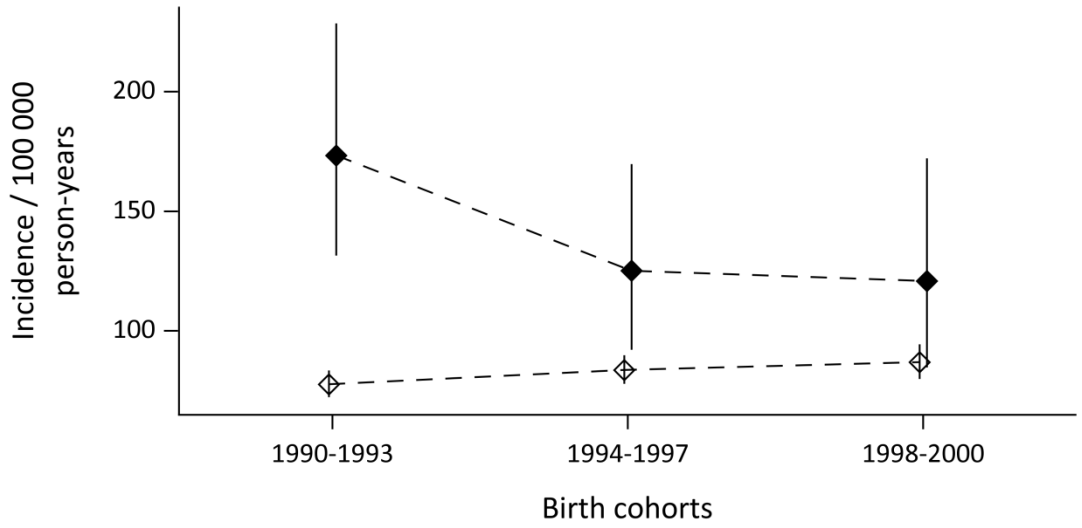

Fig 1. Incidence rate with 95% confidence intervals of epilepsy per 100,000 person-years of children with prior diagnosis of type 1 diabetes (filled diamonds) and controls (hollow diamonds) in subsequent birth cohorts from 1990 to 2000.