JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Type 1 diabetes and the risk of epilepsy: A meta-analysis

Shuhui Wu, Yanan Ding*

Department of Neurology, Liaocheng People's Hospital, Liaocheng, Shandong Province, China

Keywords
Epilepsy, Meta-analysis, Observational studies

***Correspondence**
Yanan Ding
Tel.: 86-13310621106
E-mail address:
dingyanan218@hotmail.com

J Diabetes Investig 2024; 15: 364–373

doi: 10.1111/jdi.14126

ABSTRACT

Aims/Introduction: An overrepresentation of epilepsy has been suggested in patients with type 1 diabetes (T1D). This meta-analysis was conducted to evaluate if type 1 diabetes is associated with a higher incidence of epilepsy.

Materials and Methods: Longitudinal observational studies which are relevant to the purpose of the meta-analysis were screened and obtained by searching PubMed, Embase, and Web of Science databases. Random-effects models were used when significant heterogeneity was observed; otherwise, fixed-effects models were used.

Results: Six observational studies involving 10 datasets of 8,001,899 participants were included, with six datasets including children and only one dataset including older people. Among them, 100,414 (1.25%) had type 1 diabetes. During the follow-up duration of 5.4–15.2 years (mean: 9.5 years), 98,644 cases (1.23%) of epilepsy were observed. Compared with participants with normoglycemia, those with type 1 diabetes were shown to have a higher incidence of epilepsy (risk ratio [RR]: 2.41, 95% confidence interval 1.69–3.44, $P < 0.001$; $I^2 = 95\%$) after adjustment of potential confounding variables including age and sex. Subgroup analysis showed consistent results in nested case–control and retrospective cohort studies, and in studies of children, non-elderly adult, and older participants (P for subgroup difference = 0.42 and 0.07). In addition, a stronger association of type 1 diabetes and epilepsy was suggested in studies with follow-up duration <10 years compared with those ≥10 years (RR: 3.34 vs 1.61, P for subgroup difference < 0.001).

Conclusion: Patients with type 1 diabetes may have a higher risk of epilepsy, which was mainly driven by datasets including children.

INTRODUCTION

Type 1 diabetes (T1D) is a prevalent metabolic disorder with autoimmune causes, particularly among children[1,2]. The pathophysiology of type 1 diabetes stems from the immune system-mediated destruction of pancreatic β-cells, influenced by various genetic and environmental factors[3,4]. A growing body of evidence indicates a 3–4% rise in the occurrence of type 1 diabetes over the past three decades[5]. Patients with type 1 diabetes exhibit a range of clinically established complications that can be attributed to impaired glucose metabolism, namely retinopathy, nephropathy, peripheral neuropathy, and cardiovascular disease[6,7]. Furthermore, type 1 diabetes has been associated with various immune disorders, including coeliac disease, hypothyroidism, hyperthyroidism, and Addison disease[8]. Notably, recent research indicates a potential heightened susceptibility among patients with type 1 diabetes to several neurocognitive disorders[9,10], including epilepsy[11]. Several observational studies have indicated a potential overrepresentation of epilepsy in individuals with type 1 diabetes[12–15], although the findings have not always been consistent[16]. Moreover, the potential elevated risk of the development of epilepsy among individuals with type 1 diabetes in comparison with those with normoglycemia remains uncertain. Due to this knowledge gap, the current study aimed to conduct a comprehensive review and meta-analysis to evaluate the correlation between type 1 diabetes and the occurrence of epilepsy.

MATERIALS AND METHODS

The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[17,18], as well as

Received 11 October 2023; revised 8 November 2023; accepted 23 November 2023

the Cochrane Handbook[19], during the entirety of the planning, conducting, and reporting phases.

Inclusion and exclusion criteria of studies

The development of inclusion criteria adhered to the PICOS recommendations and aligned with the objective of the meta-analysis.

P (patients): General population without epilepsy at baseline.

I (exposure): Participants with type 1 diabetes. Methods and criteria used for the diagnosis of type 1 diabetes were consistent with those used in the original study.

C (control): Participants without type 1 diabetes.

O (outcomes): Incidence of epilepsy between participants with and without type 1 diabetes at baseline. The diagnosis and confirmation of epilepsy were also consistent with the criteria used in the original study.

S (study design): Observational studies with longitudinal follow-up, which included nested case–control studies and cohort studies.

Reviews, editorials, previous meta-analyses, cross-sectional studies, studies including participants with type 2 diabetes rather than type 1 diabetes, studies that did not include controls with normoglycemia, or did not report the incidence of epilepsy were excluded. In cases where there was overlap in patient populations, the study with the largest sample size was included in the meta-analysis.

Search of databases

We conducted a comprehensive search of electronic databases, namely PubMed, Embase, and Web of Science, from their inception until August 15, 2023, in order to identify studies published up to that date. The search was carried out with the terms including (1) "type 1 diabetes" OR "T1D" OR "T1DM" OR "brittle diabetes mellitus" OR "juvenile onset diabetes" OR "insulin dependent diabetes" OR "autoimmune diabetes"; (2) "epilepsy" OR "epileptic" OR "epilepsia" OR "seizure" OR "seizures" OR "convulsion"; and (3) "cohort" OR "cohorts" OR "followed" OR "follow-up" OR "incidence" OR "occurrence" OR "longitudinal" OR "prospective" OR "retrospective" OR "prospectively" OR "retrospectively". Only studies of human participants that were published in English language were included. During our manual screening process, we thoroughly examined references from pertinent original and review articles to identify potentially relevant studies.

Data extraction and quality evaluation

Literature searches, data collection, and study quality assessments were carried out independently by the two authors. In case of discrepancies, discussion between the two authors was indicated to reach a consensus. Among the studies included in the analysis, we collected information regarding study information, demographic factors, and participant characteristics, methods for diagnosing type 1 diabetes and epilepsy, follow-up durations, as well as confounding factors that were adjusted when the association between type 1 diabetes and the incidence of epilepsy was reported. The study's quality was assessed using the Newcastle-Ottawa Scale (NOS)[20], which evaluates participant selection, group comparability, and outcome validity. The scale consisted of nine stars, with a higher number indicating a superior study.

Statistics

Risk ratios (RR) and their corresponding 95% confidence intervals (CI) were used to present the association between type 1 diabetes and the incidence of epilepsy during follow-up. RR data and the corresponding standard error (SE) were computed using either 95% CI or P values, and then subjected to logarithmic transformation to stabilize variance and to normalize distribution[19]. To assess the level of heterogeneity among studies, the Cochrane Q test and the I^2 statistic were employed[21]. An I^2 value exceeding 50% signifies substantial heterogeneity across the studies. In cases where significant heterogeneity was observed, a random-effects model was utilized; otherwise, a fixed-effects model was employed[19]. In order to assess the impact of individual studies on the results of the meta-analysis, a sensitivity analysis was conducted by systematically excluding one dataset at a time[22]. Additionally, subgroup analyses were performed to investigate the influence of various study characteristics on the outcome. These characteristics included study design, age of the participants, mean follow-up durations, and the adjustment of potential confounding factors. The selection of medians as cutoff values for defining subgroups was employed for continuous variables. The estimation of publication bias is conducted using a funnel plot, which relies on visual assessments of symmetry, in conjunction with Egger's regression asymmetry test[23]. The statistical analyses were performed using RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) and Stata software (version 12.0; Stata Corporation).

RESULTS

Database search and study identification

Figure 1 depicts the procedure of conducting a literature search and retrieving relevant studies. Initially, a total of 877 records were acquired from the database, out of which 238 duplicate entries were eliminated. Subsequently, 617 studies were excluded based on the screening of their titles and abstracts, as they did not align with the objectives of the meta-analysis. After conducting full-text reviews of 22 studies, 16 were excluded due to the reasons specified in Figure 1. Consequently, six studies were deemed suitable for the subsequent meta-analysis[24–29].

Study characteristics

The overview of the included studies is displayed in Table 1. Overall, three retrospective cohort studies[24,28,29] and the other three nested case–control studies[25–27] were included in the meta-analysis, which were published from 2014 to 2020 and

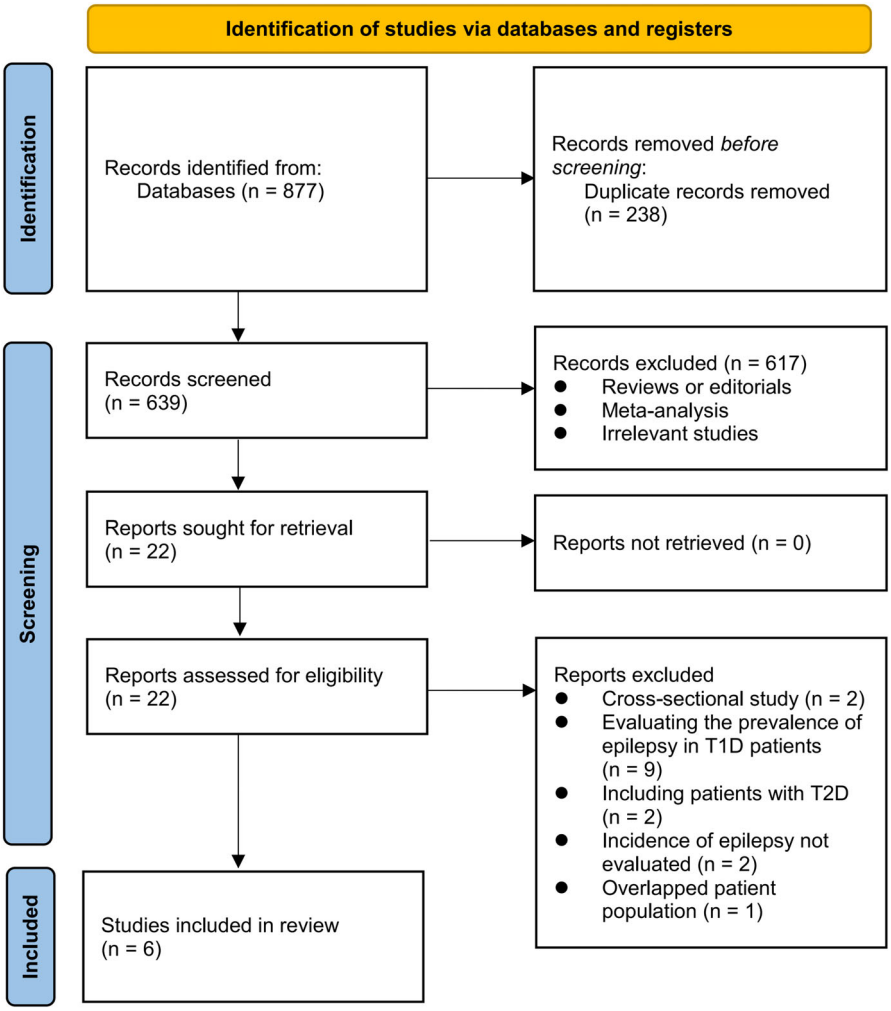

Figure 1 | Flowchart of database search and study inclusion.

performed in the United States, the Netherlands, China, the United Kingdom, Finland, and Norway. All of the studies included general populations. A total of 8,001,899 participants were included. Three studies included children only[25,26,28], while the other three studies include both children and adults[24,27,29], and reported the outcome according to the age group of the participants. Patients with type 1 diabetes were identified with database codes in all of the included studies except for one study[29], in which patients with type 1 diabetes were solely classified based on their utilization of insulin or its analogs. In this study, the authors mentioned that 'the Norwegian Directorate of Health did not recommend treating type 2 diabetes mellitus with insulin/insulin analogs in monotherapy during the entire study period. Thus, by excluding all patients who received oral antidiabetics and only including patients who received insulin or insulin analogs in monotherapy the dominating part of our study group should have type 1 diabetes mellitus'[29]. Accordingly, a total of 100,414 (1.25%) participants had type 1 diabetes at baseline. The mean follow-up durations of the studies were 5.4–15.2 years (mean: 9.5 years), and 98,644 cases (1.23%) of epilepsy were observed during follow-up. Potential confounding factors such as age and sex were controlled in all of the included studies, while for two of the included studies[26,27], other variables such as a history of head injury was also adjusted. Among the included studies, all had scores between six and seven stars, indicating that they were of moderate to good quality (Table 2).

Meta-analysis results

Overall, ten datasets from six observational studies were included in the meta-analysis[24–29]. A significant heterogeneity was observed among the included studies (P for Cochrane Q test <0.001, I^2 = 95%). Therefore, a random-effects model was used for the meta-analysis. Pooled results showed that compared with controls with normoglycemia, those with type 1 diabetes was associated with a higher incidence of epilepsy (RR:

Table 1 | Characteristics of the included studies

Study	Country	Design	Participants	Sample size	Age (years)	Male (%)	Diagnosis of T1D	No. of patients with T1D	Follow-up duration (years)	Validation of patients with epilepsy	No. of patients with epilepsy	Variables adjusted
Ong[24]	USA	RC	Nation-wide population	2,518,034	Children (<18) and non-elderly adults (18–65)	48.3	ICD codes	43,704	7	ICD codes	10,041	Age and sex
Fazeli Farsani[25]	The Netherlands	NCC	General population	4,505	Children (<19), mean: 10.1	50.8	ICD codes	915	5.4	Hospital records	19	Age and sex
Chou[26]	China	NCC	Nation-wide population	28,248	Children (<18), mean: 10.4	53.5	ICD codes	2,568	6.8	ICD codes	240	Age, sex, urbanization, intellectual disability, low birth weight and head injury
Dafoulas[27]	UK	NCC	Nation-wide population	24,610	Children (<18) and young adults (18–40), mean: 17.9	59	Database codes	4,922	5.4	Database codes	81	Age, sex, social deprivation, cerebral palsy, head injury and learning disability
Sillanpaa[28]	Finland	RC	Nation-wide population	679,375	Children (<15)	NR	ICD codes	6,162	15.2	ICD codes	8,512	Age and sex
Borsheim[29]	Norway	RC	Nation-wide population	4,747,127	Children (<20), non-elderly adults (20–60), and older people (60+)	45.4	Prescription records	42,143	10	Prescription records	79,751	Age and sex

ICD, International Classification of Disease; NCC, nested case–control; RC, retrospective cohort; T1D, type 1 diabetes.

Table 2 | Study quality evaluation *via* the Newcastle-Ottawa scale

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Control for age and sex	Control for other confounding factors	Assessment of outcome	Enough long follow-up duration	Adequacy of follow-up of cohorts	Total
Ong[24]	1	1	0	1	1	0	0	1	1	6
Fazeli Farsani[25]	1	1	0	1	1	0	1	1	1	7
Chou[26]	1	1	0	1	1	1	0	1	1	7
Dafoulas[27]	1	1	0	1	1	1	0	1	1	7
Sillanpaa[28]	1	1	0	1	1	0	0	1	1	6
Borsheim[29]	1	1	0	1	1	0	0	1	1	6

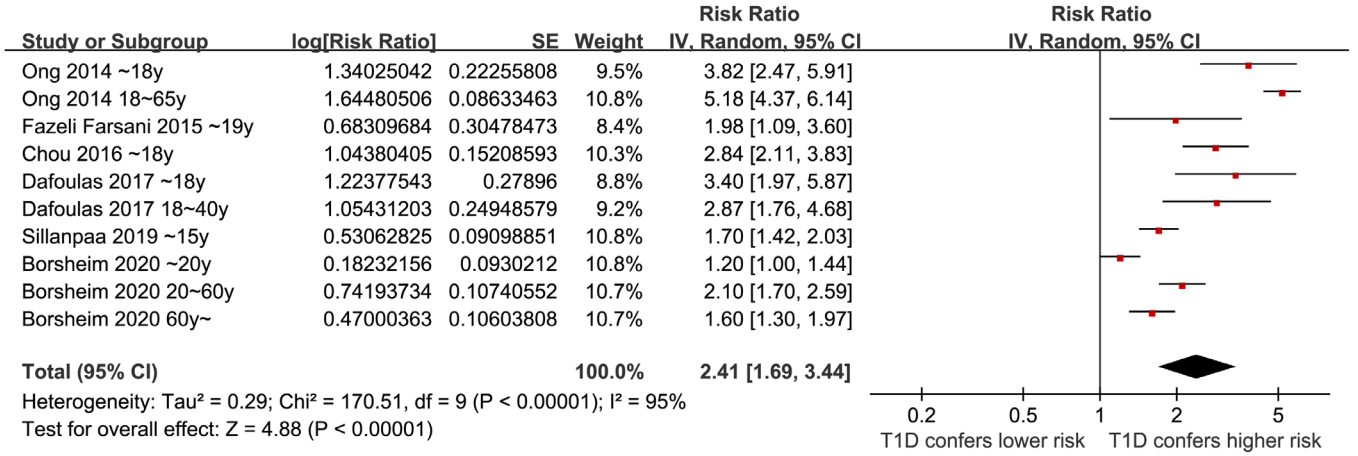

Figure 2 | Forest plots for the meta-analyses regarding the association between type 1 diabetes and the risk of epilepsy.

2.41, 95% CI: 1.69–3.44, $P < 0.001$; Figure 2). Sensitivity analysis was done by excluding one dataset at a time (RR: 2.14–2.63, P all <0.05). Specifically, excluding the three datasets from the study of Borcheim *et al.*[29] also retrieved similar results (RR: 2.94, 95% CI: 1.91–4.53, $P < 0.001$; $I^2 = 93\%$). Subgroup analysis showed consistent results in nested case–control and retrospective cohort studies (RR: 2.79 vs 2.25, P for subgroup difference = 0.42; Figure 3a), and in studies of children, non-elderly adult, and older participants (RR: 2.23, 3.17. and 1.60, P for subgroup difference = 0.07; Figure 3b). In addition, a stronger association between type 1 diabetes and epilepsy was observed in studies with a follow-up duration ≥10 years compared with those <10 years (RR: 3.34 vs 1.61, P for subgroup difference < 0.001; Figure 4a). Finally, a consistent association was observed in studies only adjusting age and sex, and in studies with adjustment for other factors besides age and sex (RR: 2.21 vs 2.94, P for subgroup difference = 0.27; Figure 4b).

Publication bias

The funnel plots illustrating the meta-analysis of type 1 diabetes and the incidence of epilepsy are depicted in Figure 5. Upon visual inspection, the plots exhibit symmetry, implying a minimal presence of publication bias. Furthermore, the application of Egger's regression tests yielded a P-value of 0.72, indicating a low probability of publication bias.

DISCUSSION

This meta-analysis involved the aggregation of data from ten datasets obtained from six observational studies. The findings indicated that individuals with type 1 diabetes exhibited a significantly heightened susceptibility to epilepsy when compared with those with normoglycemia. Additionally, consistent outcomes were obtained through sensitivity analysis, which involved the exclusion of one dataset at a time. Furthermore, subgroup analysis revealed that the relationship between type 1 diabetes and epilepsy risk remained unaffected by variables such as study design, patient age groups, and adjusted potential confounding factors. Interestingly, we found that the association between type 1 diabetes and the increased risk of epilepsy was stronger in studies with a follow-up duration of <10 years compared with those with a follow-up duration ≥10 years. Taken together, these finding suggest that type 1 diabetes may be a risk factor of epilepsy in children and adult populations.

To the best of our knowledge, only one meta-analysis published in 2017 evaluated the association between type 1 diabetes and epilepsy. This meta-analysis included three observational

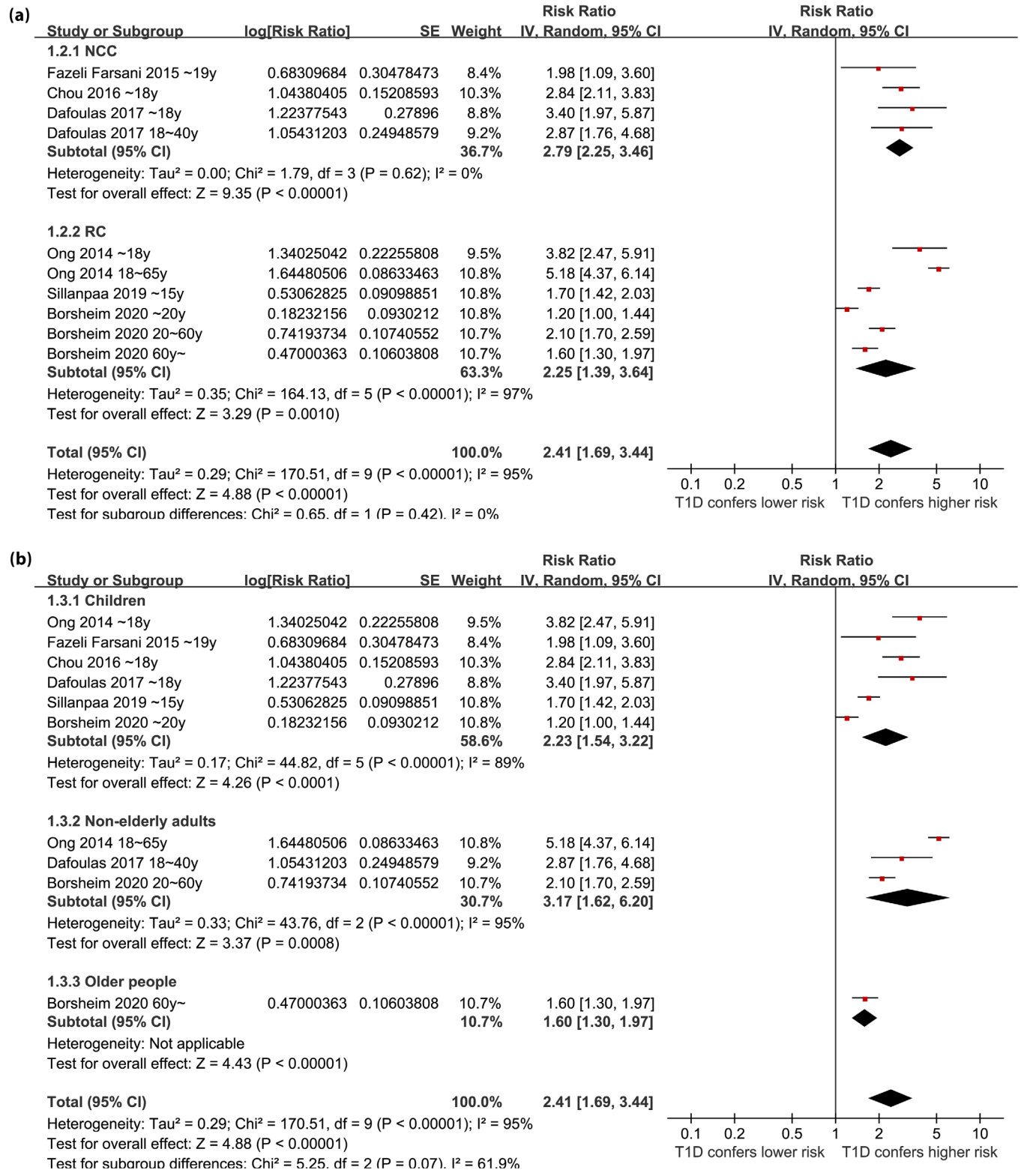

Figure 3 | Forest plots for the subgroup analyses regarding the association between type 1 diabetes and the risk of epilepsy; (a) subgroup analysis according to study design; and (b) subgroup analysis according to the age groups.

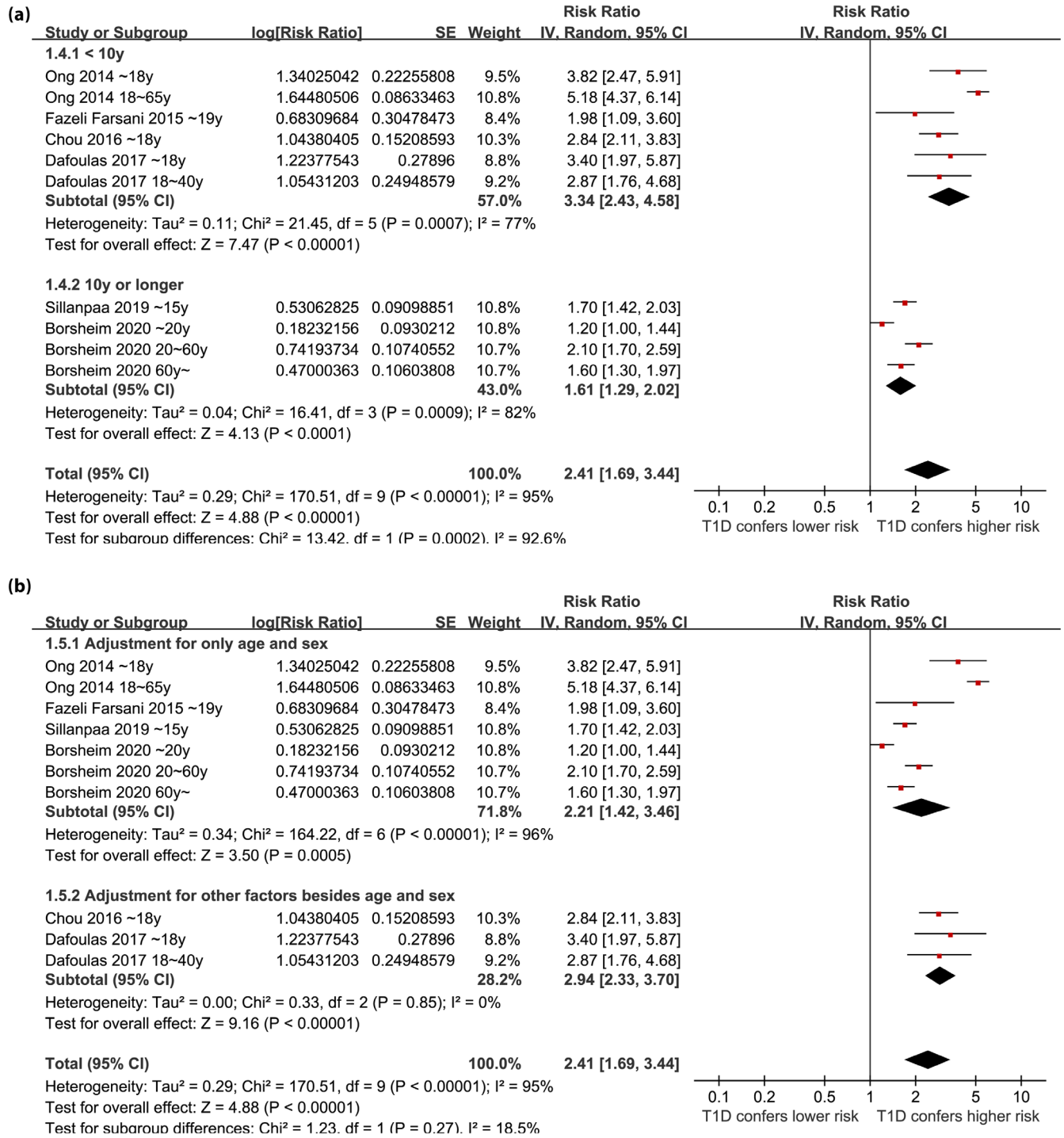

Figure 4 | Forest plots for the subgroup analyses regarding the association between type 1 diabetes and the risk of epilepsy; (a) subgroup analysis according to follow-up durations; and (b) subgroup analysis according to the variables adjusted.

studies, including one cross-sectional study and two cohort studies, and showed that type 1 diabetes may be related with epilepsy. Due to the limited study available, sensitivity and subgroup analysis was not able to be performed in the previous meta-analysis, and the potential influences of study characteristics on the association between type 1 diabetes and epilepsy remain unknown. Compared with the previous meta-analysis, our meta-analysis has several advantages. First, an extensive

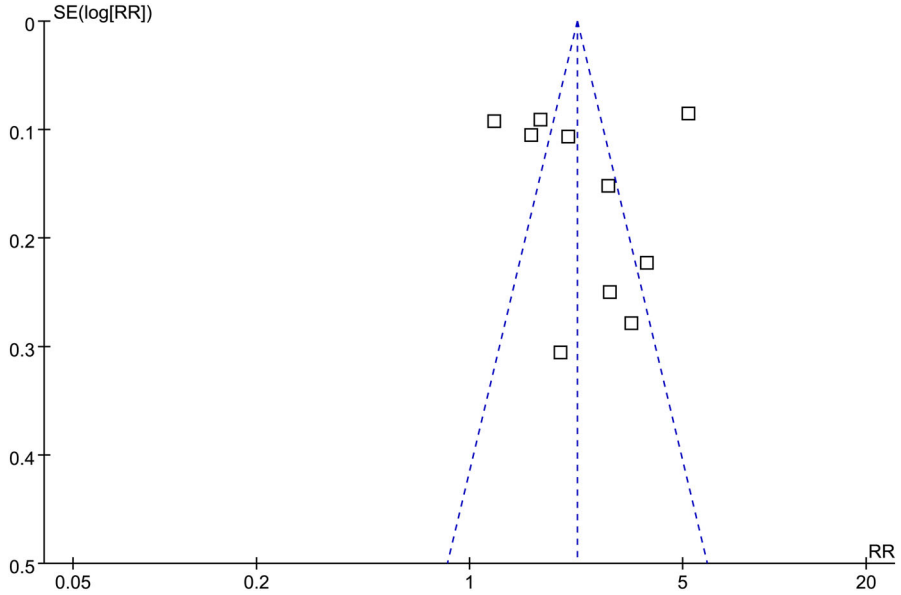

Figure 5 | Funnel plots for the publication bias underlying the meta-analysis regarding the association between type 1 diabetes and the risk of epilepsy.

literature search was carried out in three most commonly used electronic databases, which retrieved six up-to-date observational studies according to the aim of the meta-analysis. The sample size of the current meta-analysis was much larger than the previous one. Second, all of the included studies were with longitudinal follow-ups, which therefore could establish a potential relationship between type 1 diabetes and the incidence of epilepsy. Moreover, multivariate analyses were performed in all of the included studies when the association between type 1 diabetes and the incidence of epilepsy was evaluated, which suggested that the association was not likely to be confounded by factors such as age, sex, or history of brain injury. Finally, a series of sensitivity and subgroup analyses were performed, which showed that the results were not primarily driven by either of the included dataset or not significantly affected by study characteristics such as study design, age group, and adjustment of potential confounding factors. These findings highlight the stability and robustness of the finding. Taken together, these results suggest that type 1 diabetes may be a risk factor for epilepsy.

Our subgroup analysis suggested that the relationship between type 1 diabetes and an increased risk of epilepsy may be stronger in short-term studies (<10 years) compared with long-term studies (≥10 years). This is consistent with the findings of a previous large study in Finland which showed that children with type 1 diabetes had an increased, but slowly declining, risk of developing epilepsy[28]. The potential mechanisms underlying the association between type 1 diabetes and epilepsy remain unknown. Clinical studies have demonstrated the presence of electroencephalogram (EEG) irregularities in individuals diagnosed with type 1 diabetes, particularly among those with inadequate glycemic control[30]. These abnormalities include focal epileptiform abnormalities, reduced relative power of alpha, beta, and gamma frequencies in the temporal regions, as well as diminished EEG coherence[31–34]. Furthermore, there is a proposition suggesting that the presence of anti-glutamic acid decarboxylase antibodies (GAD-Abs) may serve as a significant connection between type 1 diabetes and epilepsy[35]. A significant number of patients with type 1 diabetes exhibited positive results for GAD-Abs, which may contribute to the development of epilepsy through various mechanisms[36]. These mechanisms include interference with the catalytic site of GAD on neurons through the neutralizing efficacy of GAD-Abs, activation of a cellular-mediated response against synaptic vesicles of GABAergic neurons following the formation of a membrane complex, and mimicry of GABA function through a direct interaction between GAD-Abs and GABA receptors[37–40]. Additionally, cerebral injury resulting from long-term persistent hyperglycemia and abrupt hypoglycemia has also been proposed as potential mechanisms for the pathogenesis of epilepsy in patients with type 1 diabetes[11]. However, the predominant molecular signaling pathways remain to be determined in future studies.

This study has limitations. First, only nested case–control and retrospective cohort studies were included, and these studies may be associated with recall and selection biases. The results of the meta-analysis should be validated in prospective studies. Second, although a subgroup analysis according to the age group failed to show a significant modification of age on the increased risk of epilepsy in patients with type 1 diabetes, the majority (6 out of 10) of datasets used in the meta-analysis included children with type 1 diabetes rather than

adults with type 1 diabetes, and only one dataset included older people with type 1 diabetes. Accordingly, the association between type 1 diabetes and an increased risk of epilepsy in this meta-analysis was mainly driven by datasets including children, and the association between type 1 diabetes and epilepsy in older people should be further validated in future studies. Furthermore, validation of the diagnosis of type 1 diabetes and epilepsy was mostly achieved by database codes rather than by clinical diagnosis among the included studies, which may be associated with the risk of misclassification. However, due to the low prevalence of type 1 diabetes and the low incidence of epilepsy, a large-scale prospective cohort study to indicate their relationship based on clinical evaluation was difficult to perform. In addition, in one of the included studies,[29] the classification of patients with type 1 diabetes was based solely on their utilization of insulin or its analogs, which may confound the results of the meta-analysis. However, sensitivity analyses by excluding the three datasets derived from this study showed consistent results. Moreover, a causative relationship between type 1 diabetes and epilepsy could not be determined based on the current meta-analysis because all of the included studies were observational. Finally, we could not exclude that there were unadjusted residual factors confounding the association between type 1 diabetes and epilepsy, such as antidiabetic treatments, dietary factors, and the incidence of severe hypoglycemia.

CONCLUSIONS

In conclusion, the results of the meta-analysis suggest that compared with participants with normoglycemia, patients with type 1 diabetes may be related to a higher risk of epilepsy. The results of the meta-analysis were primarily driven by studies including children with type 1 diabetes, while only one dataset including older people with type 1 diabetes. Although these results should be validated in prospective cohort studies, the current evidence supports that type 1 diabetes may be a risk factor for epilepsy in children and the adult population. Further studies are warranted to determine the underlying mechanisms and to explore whether optimizing glycemic control could reduce the risk of epilepsy in patients with type 1 diabetes.

DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: N/A.
Informed consent: N/A.
Approval date of Registry and the Registration No. of the study/trial: N/A.
Animal studies: N/A.

FUNDING STATEMENT

No funding was received for this study.

ACKNOWLEDGMENTS

None.

REFERENCES

1. Vanderniet JA, Jenkins AJ, Donaghue KC. Epidemiology of type 1 diabetes. *Curr Cardiol Rep* 2022; 24: 1455–1465.
2. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: A systematic analysis for the global burden of disease study 2021. *Lancet* 2023; 402: 203–234.
3. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. *Lancet* 2018; 391: 2449–2462.
4. Syed FZ. Type 1 diabetes mellitus. *Ann Intern Med* 2022; 175: ITC33–ITC48.
5. Norris JM, Johnson RK, Stene LC. Type 1 diabetes-early life origins and changing epidemiology. *Lancet Diabetes Endocrinol* 2020; 8: 226–238.
6. Piona C, Ventrici C, Marcovecchio L, *et al*. Long-term complications of type 1 diabetes: What do we know and what do we need to understand? *Minerva Pediatr (Torino)* 2021; 73: 504–522.
7. Tommerdahl KL, Shapiro ALB, Nehus EJ, *et al*. Early microvascular complications in type 1 and type 2 diabetes: Recent developments and updates. *Pediatr Nephrol* 2022; 37: 79–93.
8. Popoviciu MS, Kaka N, Sethi Y, *et al*. Type 1 diabetes mellitus and autoimmune diseases: A critical review of the association and the application of personalized medicine. *J Pers Med* 2023; 13: 422.
9. Shalimova A, Graff B, Gasecki D, *et al*. Cognitive dysfunction in type 1 diabetes mellitus. *J Clin Endocrinol Metab* 2019; 104: 2239–2249.
10. Cameron FJ, Northam EA, Ryan CM. The effect of type 1 diabetes on the developing brain. *Lancet Child Adolesc Health* 2019; 3: 427–436.
11. Mastrangelo M, Tromba V, Silvestri F, *et al*. Epilepsy in children with type 1 diabetes mellitus: Pathophysiological basis and clinical hallmarks. *Eur J Paediatr Neurol* 2019; 23: 240–247.
12. McCorry D, Nicolson A, Smith D, *et al*. An association between type 1 diabetes and idiopathic generalized epilepsy. *Ann Neurol* 2006; 59: 204–206.
13. Mancardi MM, Striano P, Giannattasio A, *et al*. Type 1 diabetes and epilepsy: More than a casual association? *Epilepsia* 2010; 51: 320–321.
14. Ramakrishnan R, Appleton R. Study of prevalence of epilepsy in children with type 1 diabetes mellitus. *Seizure* 2012; 21: 292–294.
15. Aguiar TS, Dantas JR, Cabral DB, *et al*. Association between high titers of glutamic acid decarboxylase antibody and epilepsy in patients with type 1 diabetes mellitus: A cross-sectional study. *Seizure* 2019; 71: 318–321.
16. O'Connell MA, Harvey AS, Mackay MT, *et al*. Does epilepsy occur more frequently in children with type 1 diabetes? *J Paediatr Child Health* 2008; 44: 586–589.
17. Page MJ, Moher D, Bossuyt PM, *et al*. PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews. *BMJ* 2021; 372: n160.

18. Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71.
19. Higgins J, Thomas J, Chandler J, *et al*. Cochrane handbook for systematic reviews of interventions version 6.2. *The Cochrane Collaboration*. 2021 www.training.cochrane.org/handbook.
20. Wells GA, Shea B, O'Connell D, *et al*. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses*. 2010 http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
21. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539–1558.
22. Patsopoulos NA, Evangelou E, Ioannidis JP. Sensitivity of between-study heterogeneity in meta-analysis: Proposed metrics and empirical evaluation. *Int J Epidemiol* 2008; 37: 1148–1157.
23. Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629–634.
24. Ong MS, Kohane IS, Cai T, *et al*. Population-level evidence for an autoimmune etiology of epilepsy. *JAMA Neurol* 2014; 71: 569–574.
25. Fazeli Farsani S, Souverein PC, van der Vorst MM, *et al*. Chronic comorbidities in children with type 1 diabetes: A population-based cohort study. *Arch Dis Child* 2015; 100: 763–768.
26. Chou IC, Wang CH, Lin WD, *et al*. Risk of epilepsy in type 1 diabetes mellitus: A population-based cohort study. *Diabetologia* 2016; 59: 1196–1203.
27. Dafoulas GE, Toulis KA, McCorry D, *et al*. Type 1 diabetes mellitus and risk of incident epilepsy: A population-based, open-cohort study. *Diabetologia* 2017; 60: 258–261.
28. Sillanpaa M, Saarinen MM, Ronnemaa T, *et al*. Overrepresentation of epilepsy in children with type 1 diabetes is declining in a longitudinal population study in Finland. *Acta Paediatr* 2019; 108: 2235–2240.
29. Wie Borsheim A, Engeland A, Gilhus NE. Epilepsy and autoimmune diseases: Comorbidity in a national patient cohort. *Seizure* 2020; 75: 89–95.
30. Verrotti A, Scaparrotta A, Olivieri C, *et al*. Seizures and type 1 diabetes mellitus: Current state of knowledge. *Eur J Endocrinol* 2012; 167: 749–758.
31. Hyllienmark L, Maltez J, Dandenell A, *et al*. EEG abnormalities with and without relation to severe hypoglycaemia in adolescents with type 1 diabetes. *Diabetologia* 2005; 48: 412–419.
32. Asvold BO, Sand T, Hestad KA, *et al*. Quantitative EEG in type 1 diabetic adults with childhood exposure to severe hypoglycaemia: A 16 year follow-up study. *Diabetologia* 2011; 54: 2404–2408.
33. Sejling AS, Kjaer TW, Pedersen-Bjergaard U, *et al*. Hypoglycemia-associated EEG changes following antecedent hypoglycemia in type 1 diabetes mellitus. *Diabetes Technol Ther* 2017; 19: 85–90.
34. Gallardo-Moreno GB, Gonzalez-Garrido AA, Villasenor-Cabrera T, *et al*. Sustained attention in schoolchildren with type-1 diabetes. A quantitative EEG study. *Clin Neurophysiol* 2020; 131: 2469–2478.
35. Vidmar KK, Pollock AJ. Intractable seizures in children with type 1 diabetes: Implications of the ketogenic diet. *WMJ* 2022; 121: 292–296.
36. Nakajima H, Nakamura Y, Inaba Y, *et al*. Neurologic disorders associated with anti-glutamic acid decarboxylase antibodies: A comparison of anti-GAD antibody titers and time-dependent changes between neurologic disease and type I diabetes mellitus. *J Neuroimmunol* 2018; 317: 84–89.
37. Marcovecchio ML, Petrosino MI, Chiarelli F. Diabetes and epilepsy in children and adolescents. *Curr Diab Rep* 2015; 15: 21.
38. Baizabal-Carvallo JF, Alonso-Juarez M. Cerebellar disease associated with anti-glutamic acid decarboxylase antibodies: Review. *J Neural Transm (Vienna)* 2017; 124: 1171–1182.
39. Valinciute J, Juceviciute N, Balnyte R, *et al*. GAD65 antibody-associated epilepsy. *Medicina (Kaunas)* 2023; 59: 1135.
40. Daif A, Lukas RV, Issa NP, *et al*. Antiglutamic acid decarboxylase 65 (GAD65) antibody-associated epilepsy. *Epilepsy Behav* 2018; 80: 331–336.