Drug and Alcohol Dependence 232 (2022) 109305

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Alcohol consumption on unprovoked seizure and epilepsy: An updated meta-analysis

Kyoung Nam Woo [a,1], Kihun Kim [b,1], Dai Sik Ko [c], Hyun-Woo Kim [a,*], Yun Hak Kim [d,e,**]

[a] Department of Neurology, Pusan National University, Republic of Korea
[b] Department of Occupational and Environmental Medicine, Kosin University Gospel Hospital, Republic of Korea
[c] Division of Vascular Surgery, Department of Surgery, Gachon University Gil Medical Center, Republic of Korea
[d] Department of Biomedical Informatics, School of Medicine, Pusan National University, Republic of Korea
[e] Department of Anatomy, School of Medicine, Pusan National University, Republic of Korea

ARTICLE INFO

Keywords:
Epilepsy
Alcohol consumption
Dose-response relationship
Cohort study
Case-control study

ABSTRACT

Background: Epilepsy is one of the most common neurological disorders, affecting approximately 50 million people worldwide. Although a positive association between alcohol consumption and epilepsy has been demonstrated in previous meta-analyses of case-control studies, the results of several recently published large cohort studies are contradictory. Therefore, we conducted an updated meta-analysis that included more recent data to clarify the association between alcohol consumption and epilepsy.

Methods: The search was performed on 25 January 2021 using the Embase and MEDLINE databases. Cohort or case-control studies were eligible for inclusion in this study. We used restricted cubic spline analysis to perform a dose-response meta-analysis.

Results: A total of eight studies, including three cohort and five case-control studies, were included in our meta-analysis. The pooled risk of epilepsy was 1.70 (1.16–2.49) in alcohol users compared to non-drinkers. Subgroup analysis of 50 g units showed that the epilepsy risk increased as alcohol intake increased. The pooled risk of cohort studies was 1.00 (0.65–1.54), and the pooled risk of case-control studies was 2.61 (1.29–5.29). According to the dose-response analysis, the regression coefficient was 1.009 (1.004–1.014), indicating a significant positive dose-response relationship.

Conclusion: Unlike the case-control studies, the cohort studies did not reveal a significant association between alcohol consumption and epilepsy. Further large cohort studies for the general population are required to assert a definite causal relationship between alcohol consumption and epilepsy and to identify a potential threshold.

1. Introduction

Epilepsy is one of the most common neurological diseases and is associated with social stigma, psychiatric comorbidity, and high economic costs (Allers et al., 2015). Globally, it is estimated that 50 million individuals are affected by epilepsy (Zack and Kobau, 2017). In the Global Burden of Disease Study 2015, epilepsy was responsible for more than 12 million disability-adjusted life-years (DALYs), contributing to 0.5% of the total DALYs from all causes and 5.0% of the DALYs attributable to neurological disorders (Feigin et al., 2017). Alcohol consumption is a relatively common and modifiable lifestyle risk factor that may increase the risk of seizures and epilepsy. Alcohol withdrawal seizure is known as a disease in which seizures are generated in relation to alcohol, but chronic alcohol consumption itself is known to lower the seizure threshold.

Previous studies on the relationship between alcohol consumption and seizures have mainly focused on provoked seizures, such as alcohol intoxication or withdrawal seizures (Freedland and McMicken, 1993; Hillbom et al., 2003). However, few studies have investigated the effect of alcohol on the occurrence of unprovoked seizures. In 2010, Samokhvalov et al. performed a meta-analysis to estimate the risk of alcohol consumption on the occurrence of unprovoked seizures or epilepsy. Six case-control studies were included and showed that alcohol users had an increased risk of unprovoked seizure or epilepsy with a

* Correspondence to: Department of Neurology, Pusan National University Yangsan Hospital, Yangsan 50612, Republic of Korea.
** Correspondence to: Department of Anatomy and Department of Biomedical Informatics, Pusan National University, Yangsan 50612, Republic of Korea.
E-mail addresses: hwkim24@pusan.ac.kr (H.-W. Kim), yunhak10510@pusan.ac.kr (Y.H. Kim).
[1] Kyoung Nam Woo and Kihun Kim contributed equally to this work as first authors.

https://doi.org/10.1016/j.drugalcdep.2022.109305
Received 14 November 2021; Received in revised form 13 December 2021; Accepted 14 December 2021
Available online 11 January 2022

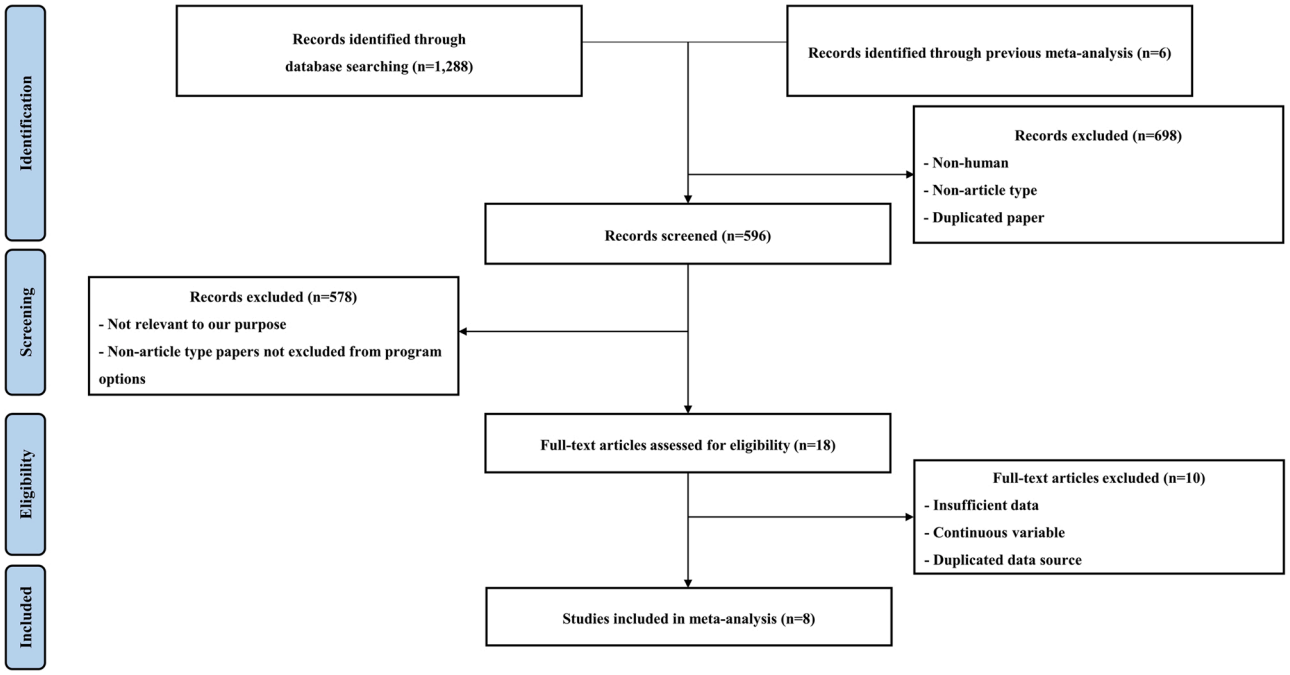

Fig. 1. PRISMA flow diagram.

Table 1
Characteristics of included studies.

Authors (s)	Place and time of study	Gender	Study designs	Number of samples	Exposure categories	Outcome
Brown et al. (2020)	U.S., 2005–2011	Both	Cohort	29,342	Alcohol intake not specified	Post-SDH epilepsy
Johnson et al. (2018)	U.S., 1987–2013	Both	Cohort	10,420 Case number 596	None; 1–7 alcoholic drinks per week; > 7 alcoholic drinks per week	Late-onset epilepsy
Dworetzky et al. (2010)	U.S., 1989–2005	Both	Cohort	104,934 Case number 119	None; 0.1–15.0 g/day; 15.1–30.0 g/day	Seizure and epilepsy
Zeng et al. (2003)	China, 2000	Both	Case-control	Cases 81 Controls 81	Alcohol intake not specified	Primary epilepsy
Leone et al. (2002b)	Italy, Jan 1995-Oct 1998	Both	Case-control	Cases 69 Controls 102	Non-drinkers and occasional drinkers; average daily intake of absolute alcohol (ADAA)≤ 50; 51–100; > 100 g/day	Remote symptomatic epileptic seizure
Leone et al. (1997)[a]	Italy, Feb 1992–Oct 1993	Both	Case-control	Cases 153 Controls not specified	Non-drinkers (drank no more than once a year) and occasional drinkers (drank at least once a year, but less than once a month); Current drinkers ranged by average daily alcohol intake (ADAA) 1–25; 26–50;51–100; 101–200 g/day	Idiopathic first generalized tonic-clonic seizure
Leone et al. (1997)[a]	Italy, Feb 1992–Oct 1993	Both	Case-control	Cases 41 Controls not specified	Non-drinkers (drank no more than once a year) and occasional drinkers (drank at least once a year, but less than once a month); average daily alcohol intake (ADAA) 1–25; 26–50;51–100; 101–200 g/day	Remote symptomatic first generalized tonic-clonic seizure
Stephen et al. (1988)[a]	U.S., Dec 1981–Feb 1984	Males	Case-control	Cases 145 Controls 128	Abstainers (both current and lifetime); drinkers ranged by average daily alcohol intake (ADAA) 1–50; 51–100; 101–200; 201–300; > 300 g/day	Unprovoked seizures
Stephen et al. (1988)[a]	U.S., Dec 1981–Feb 1984	Females	Case-control	Cases 71 Controls 139	Abstainers (both current and lifetime); drinkers ranged by average daily alcohol intake (ADAA) 1–50; 51–100; 101–200; 201–300; > 300 g/day	Unprovoked seizures
Ogunniyi et al. (1987)[a]	Nigeria, Sep 1983–Dec 1984	Both	Case-control	Cases 155 Controls 155	Alcohol intake not specified	Epilepsy

[a] Several studies had two sets of data, named correspondingly a and b. For statistical purposes, the datasets taken from the same study were used separately.

pooled relative risk (RR) of 2.19 (95% confidence interval [CI] 1.82–2.63). Furthermore, there was a dose-response relationship, with RRs of 1.17 (95% CI 1.13–1.21), 1.81 (95% CI 1.59–2.07), 2.44 (95% CI 2.00–2.97), and 3.27 (95% CI 2.52–4.26) for consuming 12, 48, 72, and 96 g of alcohol daily, respectively (Samokhvalov et al., 2010). However, this study was comprised of small case-control studies and may not represent the entire population. Therefore, it is necessary to analyse additional cohort research and large studies to explain the correlation between alcohol consumption and seizures.

The association between alcohol consumption and epilepsy was confirmed to be positive in the existing meta-analysis of case-control studies (Samokhvalov et al., 2010). In recent years, some large cohort studies on this topic have been published. In contrast with a previous meta-analysis, some of these cohort studies showed that moderate alcohol consumption was negatively associated with a risk of epilepsy (Dworetzky et al., 2010; Johnson et al., 2018). Additionally, it was

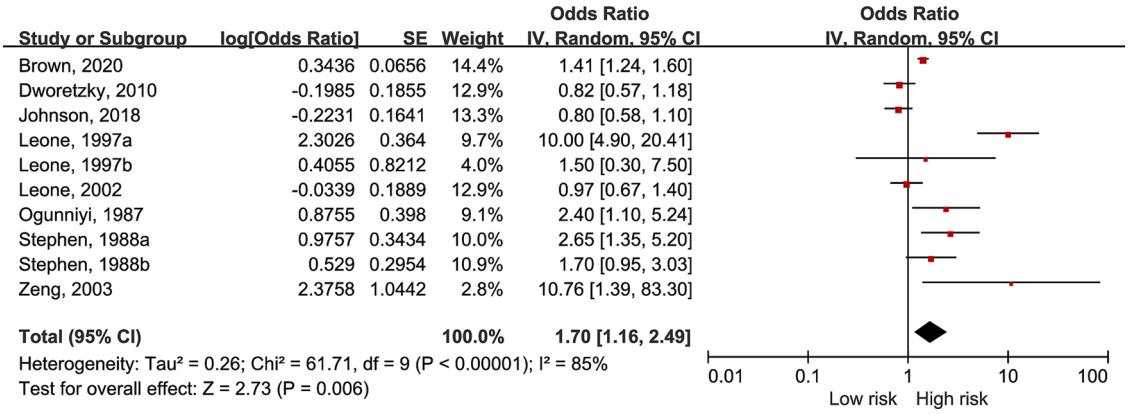

Fig. 2. Forest plot of the risk of epilepsy for alcohol-users compared to non-drinkers.

Table 2
Subgroup analysis according to alcohol consumption and study design.

Categories	Number of results	OR
Alcohol consumption		
≤ 50 g	5	1.26 (0.92–1.72)
> 50 g	5	3.47 (1.27–9.48)
51–100 g	5	1.94 (0.89–4.23)
> 100 g	4	9.48 (3.38–26.55)
101–200 g	2	10.38 (1.45–74.38)
> 200 g	2	14.92 (6.13–36.33)
Study design		
Cohort studies	3	1.00 (0.65–1.54)
Case-control studies	7	2.61 (1.29–5.29)

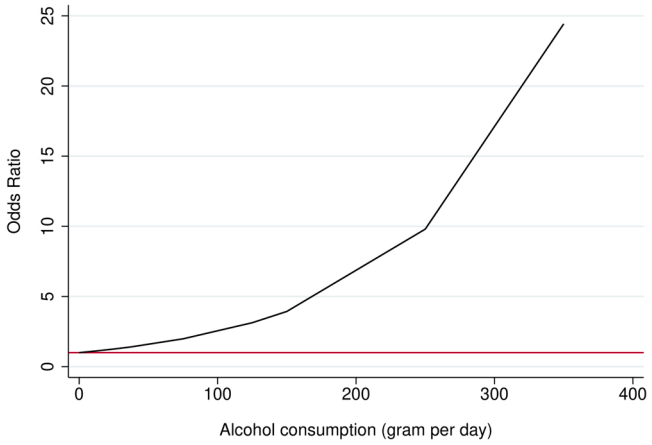

Fig. 3. Dose-response relationship between average consumption of daily alcohol and risk of epilepsy.

thought that the previous meta-analysis contained some issues such as database duplication and accuracy of diagnostic criteria.

Considering these discrepancies, It was considered necessary to conduct a new meta-analysis including the latest diagnostic criteria and cohort studies. Therefore, we conducted an updated meta-analysis that included more recent data to clarify the association between alcohol consumption and epilepsy.

2. Methods

2.1. Protocol and registration

This systematic review was conducted in accordance with the PRISMA guidelines (Page et al., 2021). The study protocol was registered at PROSPERO (Registration number: CRD42021241960).

2.2. Eligibility criteria

We included studies that reported the risk of epilepsy morbidity or unprovoked seizures associated with alcohol consumption. Cohort or case-control studies were eligible for inclusion in this study. Studies were excluded if the main outcome was a provoked seizure or if the study population included patients who had previously been diagnosed with epilepsy. Papers with duplicate databases or inclusion errors were excluded.

2.3. Search strategy

The search was performed on 25 January 2021 using the Embase and MEDLINE databases. The search terms were as follows: (alcohol OR ethanol OR booze OR liquor OR drinking) AND (seizure OR epilepsy OR brain disorder OR brain disease OR epilepsia OR grand mal) AND (risk OR ratio OR prevalence OR incidence OR mortality OR morbidity OR odds OR hazard). The search was limited to titles and abstracts, but was not restricted by language or publication year.

2.4. Selection criteria

Two authors (KNW and KK) independently conducted the literature search and checked the titles and abstracts for each study. The same authors reviewed full-text articles for inclusion. Disagreements were resolved through discussion.

2.5. Data extraction

We extracted the following data in the screening phase: title, abstract, journal, author name, publication year, and publication type. Through a full-text assessment, additional information was extracted on study design, number of samples, effect measures, study period, WHO region, exposure category, and type of disease.

2.6. Summary measures

Effect measures, such as relative risk, odds ratio, and hazard ratio, were integrated as odds ratios. Schmidt and Kohlmann (2008) stated that the odds ratio may provide an acceptable approximation of relative risk, and vice versa. It could be applied when the prevalence or incidence does not exceed 10% in the target group (Schmidt and Kohlmann, 2008). Hazard ratio was considered equal to RR since hazard ratio is a form of RR independent of study period (Stevens and Heneghan, 2012). Among the papers that used relative risk and hazard ratios, those that met the above criteria were converted to odds ratios for the

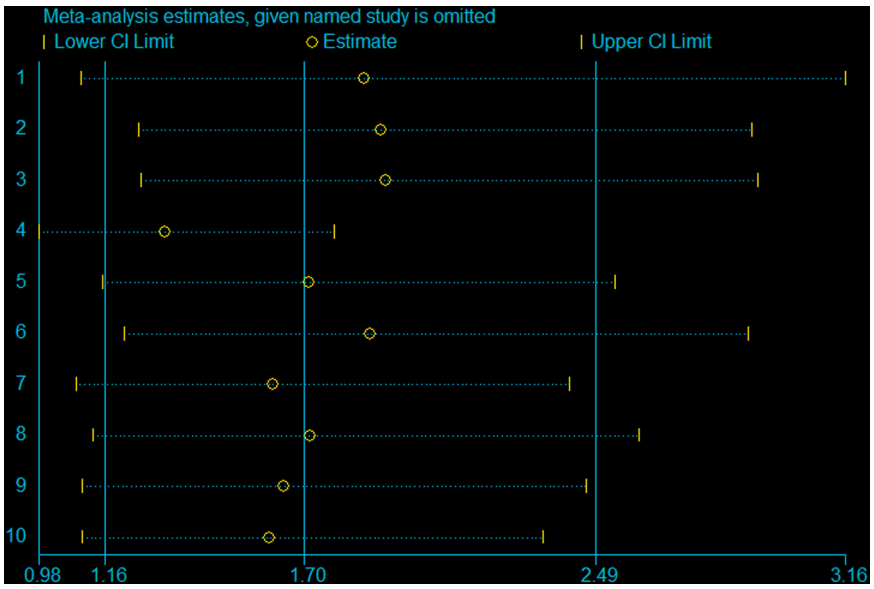

Fig. 4. Sensitivity analysis for overall epilepsy risk.

meta-analysis.

Effect measures were extracted preferentially from the number of samples over the adjusted values. We performed subgroup analyses according to alcohol consumption and study design. To verify a more quantitative dose-response relationship, the risk was analysed by separating alcohol intake into units of 50 g.

Moreover, we used the restricted cubic spline analysis proposed by Orsini et al. (2012) to perform a dose-response meta-analysis. The linearity of the dose-response relationship was confirmed through a linearity test of the regression coefficient for each dose category by segmenting the alcohol consumption. The regression coefficient was calculated using the two-stage dose-response model proposed by Berlin et al. (1993). Additionally, a dose-response graph was constructed. The dose-response analysis was performed using STATA 13 software.

2.7. Risk of bias in individual studies

The Newcastle–Ottawa scale was used to qualitatively assess the risk of bias in the included studies (Peterson et al., 2011). The authors (KNW, KK) independently assessed the risk of bias in the included studies and verified the quality of the evidence. If there was a discrepancy in the assessment, it was resolved through discussion. Study scores were converted into three categories of evidence: 'good', 'fair', and 'poor', according to the Agency for Healthcare Research and Quality standard.

2.8. Statistical analyses

The classification of I^2 statistics, as presented by Higgins et al., was used to evaluate the heterogeneity of the effect measures. (Higgins et al., 2003) The heterogeneity was considered low, moderate, and high for I^2 values of 25%, 50%, and 75%, respectively. If the heterogeneity exceeded 50%, the random effect method was used; otherwise, the fixed-effect method was used. If an integrated value was required within the study, the calculation was performed using the Higgins method (Higgins et al., 2003). Forest plot was drawn for visualize the pooled risk. In order to analyze the effect of a single study on the pooled effect measures, the study was omitted one by one through sensitivity analysis and the pooled effect was re-calculated.

2.9. Publication bias

The risk of publication bias was evaluated using funnel plots created using Review Manager 5 (RevMan 5). Egger's regression test was performed using Stata 13 software to statistically evaluate publication bias.

2.10. Certainty assessment

We used the GRADE approach, a structure that rates the confidence in risk estimates as high, moderate. Low, or insufficient, based on 8 considerations; study limitation, directness, consistency, precision, reporting bias, dose-response association, Plausible confounding that would decrease observed effect, and strength of association (magnitude of effect) (Berkman et al., 2014).

3. Results

3.1. Study selection and characteristics

A total of 1288 records were screened based on their titles and abstracts. A full-text review of 18 papers was conducted, and a total of eight studies, including three cohort and five case-control studies, were included in our meta-analysis (Fig. 1) (Brown et al., 2020; Dworetzky et al., 2010; Johnson et al., 2018; Leone et al., 1997, 2002b; Ogunniyi et al., 1987; Stephen et al., 1988; Zeng et al., 2003). Compared to the previous meta-analysis, three cohort and one case-control studies were newly added. Two case-control studies included in the previous meta-analysis were excluded because one used duplicated data and the other included epilepsy patients (described below). The studies by Leone et al. (1997, 2002) are comprised of the same data, except whether the datasets included first medically evaluated seizures or not (Leone et al., 1997, 2002a). Another study by Leone et al. (1994) included epilepsy patients and the results of subgroup analysis for the patients experiencing their first seizure were not presented (Leone et al., 1994). Therefore, we excluded two studies by Leone et al. (2002, 1994) in this meta-analysis. The characteristics of the included studies are presented in Table 1.

3.2. Synthesis of results

3.2.1. Overall effect of alcohol consumption

The pooled risk of epilepsy was 1.70 (1.16–2.49) in alcohol-users compared to non-drinkers (Fig. 2).

Table 3
Quality assessment of included studies.

Study (cohort)	Selection Representativeness of the sample	Selection of the non-intervention cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability based on design and analysis	Outcome Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts	Assessment
Brown et al. (2020)	1	1	1		2	1	1	1	Good
Johnson et al. (2018)	1	1	1	1	2	1	1	1	Good
Dworetzky et al. (2010)	1	1	1	1	2	1	1	1	Good
Study (case-control)	**Selection Is the case definition adequate?**	**Representativeness of cases**	**Selection of Controls**	**Definition of Controls**	**Comparability based on design and analysis**	**Outcome Assessment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**	**Assessment**
Zeng et al. (2003)	1		1	1	2		1	1	Good
Leone et al. (2002b)	1	1		1	2		1		Poor
Leone et al. (1997)	1	1		1	2		1		Poor
Stephen et al. (1988)		1		1	1		1	1	Fair
Ogunniyi et al. (1987)	1	1		1	2	1	1	1	Good

3.2.2. Subgroup analysis according to alcohol consumption

The results of the subgroup analysis according to alcohol intake are summarized in Table 2. The subgroup analysis of 50-g units revealed a dose-response relationship in which the risk increases as alcohol intake increases.

3.2.3. Subgroup analysis according to study design

Individual risks were calculated by separating the cohort and case-control studies. The risk of synthesizing cohort studies was 1.00 (0.65–1.54), and that for case-control studies was 2.61 (1.29–5.29) (Table 2).

3.2.4. Dose-response analysis

Only case-control studies were included in the dose-response analysis. According to the cubic spline analysis, the linearity was analysed, and the linearity assumption was not rejected with a p-value of 0.075. Accordingly, the regression coefficient was 1.009 (1.004–1.014), showing a significant positive dose-response relationship. A dose-response graph is shown in Fig. 3. Particularly, risk showed a steep increase above approximately 150 g/day and 250 g/day of alcohol consumption.

3.3. Sensitivity analysis

According to sensitivity analysis, no single result with a significant effect on the overall effect was observed (Fig. 4).

3.4. Risk of bias within studies

Three cohort studies were evaluated as ‘good’ quality. Of the five case-control studies, two were rated as ‘good’, one as ‘fair’, and two as ‘poor’. Detailed assessments of the risk of bias are presented in Table 3.

3.5. Publication bias

Funnel plot was drawn for result for overall epilepsy risk (Fig. 5). No significant publication bias was observed in the funnel plot for overall epilepsy risk according to Egger’s regression test ($p = 0.352$) (Data are not shown).

3.6. Certainty assessment

The strength of evidence was evaluated through eight domains for the primary outcome. According to the GRADE approach, the quality of evidence was low (Table 4).

4. Discussion

Our meta-analysis revealed a pooled OR of 1.70 (1.16–2.49), suggesting that alcohol consumption is associated with a significantly increased risk of epilepsy. The subgroup analysis of 50-g units revealed a dose-response relationship in which the risk increased as alcohol intake increased. These results are consistent with those of a previous meta-analysis.

An interesting finding was that cohort studies did not show a significant association between alcohol consumption and epilepsy in the subgroup analysis. Rather, two out of three cohort studies showed that alcohol consumption was associated with a lower risk of epilepsy, although this was not significant. Cohort studies often include a larger number of control subjects, longer follow-up periods, and are less prone to bias, such as selection and recall biases. Therefore, cohort studies usually provide a stronger association between exposure and disease than case-control studies, despite having limitations for diseases with low incidence levels. Most case-control studies included in our meta-analysis only assessed alcohol consumption in the six months prior to the onset of seizures. According to Devetag et al., it usually takes heavy

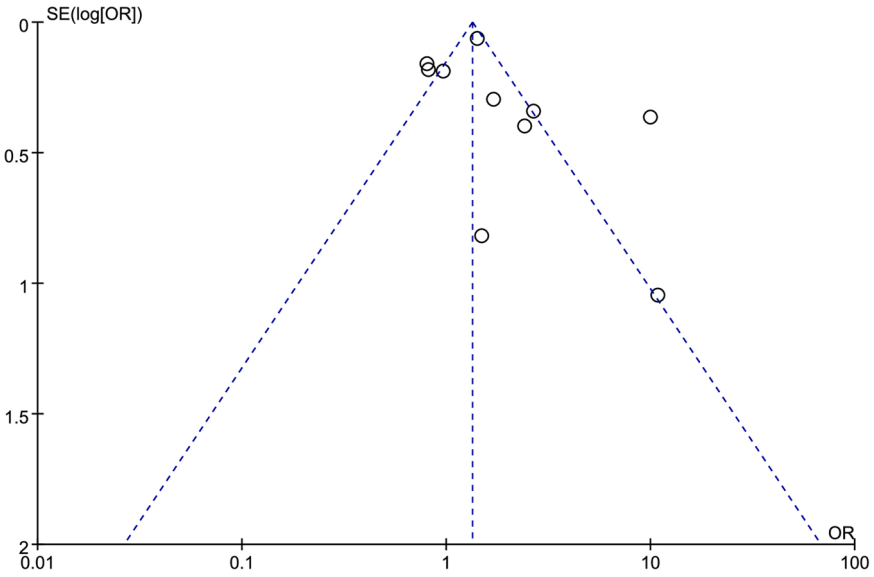

Fig. 5. Funnel plot for overall epilepsy risk.

Table 4
GRADE approach for the primary outcome.

Outcome	Quality assessment								Grade
	Required domains					Additional domains			
	Study limitations	Consistency	Directness of evidence	Precision	Reporting bias	Dose-response association	Plausible confounding that would decrease observed effect	Strength of association (magnitude of effect)	
Epilepsy	**Low**[a]	**Inconsistent**[b]	**Direct**	**Precise**	**Undetected**[c]	**Present**	**Present**[d]	**Weak**[e]	⨁⨁ **Low**

[a] All included studies are observational, and the risk of bias in two included studies was evaluated as 'poor'.
[b] Considerable heterogeneity ($I^2 = 85\%$).
[c] According to Egger's regression test ($p = 0.352$).
[d] Age, sex, and smoking.
[e] OR = 1.70.

drinkers five or more years to develop repetitive unprovoked seizures (Devetag et al., 1983). Considering these temporal relationships and differences in study design, alcohol may not actually increase the risk of epilepsy, as seen in our subgroup analysis for cohort studies. Furthermore, the study population of cohort studies in our meta-analysis was limited to young women (Dworetzky et al., 2010), elderly (Johnson et al., 2018), and post-SDH patients (Brown et al., 2020). This limitation makes it difficult to confirm or generalize the results of the subgroup analysis. In order to resolve the discrepancy observed in our study, further large cohort studies of the general population over a longer period of time are needed.

4.1. Limitations

The data is separately presented by the different types of seizures, we only included the datasets on unprovoked seizures, which included idiopathic and remote symptomatic seizures, in order to exclude withdrawal seizures. Despite our attempts, alcohol withdrawal seizures may still have been included in our meta-analysis. In the studies by Leone et al. (1997, 2002) and Stephen et al. (1988), for example, no assumptions were made regarding the effects of alcohol withdrawal. Seizures occurring during alcohol withdrawal were therefore divided into idiopathic, acute, or remote symptomatic solely based on the absence or presence of an insult to the central nervous system (CNS), and its time relation with seizures. To provide a meta-analysis with greater definitional clarity, it is important to disassociate withdrawal seizures from seizures unrelated to withdrawal. The majority of alcohol withdrawal seizures occur 6–48 h after cessation of alcohol intake (Newman et al., 2021). To differentiate the withdrawal effect of alcohol, drinking patterns and the time relation to the previous drink are considered more important than average daily alcohol consumption. In the absence of this information, it is difficult to distinguish clearly between withdrawal seizures and unprovoked seizures in chronic alcohol users.

As in the previous meta-analysis, we combined different outcomes of unprovoked first-time seizures and epilepsy. Epilepsy was defined as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizure (Fisher et al., 2005). In 2014, the Task Force of the ILAE proposed a practical clinical definition of epilepsy by any of the following conditions: (1) at least two unprovoked (or reflex) seizures occurring > 24 h apart; (2) one unprovoked (reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome (RS et al., 2014). In the absence of clear information about the risk of recurrence in various clinical situations, it is still difficult to use in clinical practice. Therefore, we also included data on unprovoked first-time seizures under the assumption that patients who have experienced at least one unprovoked seizure have an enduring predisposition to recurrent seizures.

4.2. Future directions

The major strength of our study is that we included a number of long-

term cohort studies that had large study populations. Considering the limitations mentioned above, however, further clinical studies are required to establish a definite causal relationship between alcohol consumption and epilepsy and to identify a potential threshold. Additionally, assessment of the risk of alcohol consumption in various clinical situations, such as types of CNS insult and the time relation of alcohol consumption with seizures, will be important for primary prevention. In order to increase the applicability to the general population, future studies should be conducted in which age, sex, and smoking, which are potential confounders have been adjusted.

5. Conclusion

We conducted an updated meta-analysis that included more recent data to clarify the association between alcohol consumption and epilepsy. The results showed that alcohol users had an increased risk of unprovoked seizure or epilepsy, exhibiting a dose-response relationship based on case-control studies, which is consistent with the previous meta-analysis (Samokhvalov et al., 2010). However, no such trend was found in cohort studies, and the risk did not increase. Further large cohort studies of the general population are required to assert a definite causal relationship between alcohol consumption and epilepsy and to identify a potential threshold. Additionally, assessment of the risk of alcohol consumption in various clinical situations is recommended.

Ethics approval and consent to participate

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

Funding

This work was supported by the Medical Research Center (MRC) Program (Grant number NRF-2018R1A5A2023879), the Basic Science Research Program (Grant number NRF-2020R1C1C1003741), and the Collaborative Genome Program for Fostering New Post-Genome Industry (Grant number NRF-2017M3C9A6047610) through a National Research Foundation of Korea grant funded by the Korean government.

Role of funding source

Nothing declared.

CRediT authorship contribution statement

HYK and YHK conceptualized and designed the study. KNW and KK collected, selected, and analyzed the data. KNW and KK wrote the manuscript. HYK and YHK revised the manuscript.

Data Availability

The data covered in this meta-analysis are available from the corresponding author upon reasonable request.

Acknowledgments

Not applicable.

Role of funder

The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests

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

References

Allers, K., Essue, B.M., Hackett, M.L., Muhunthan, J., Anderson, C.S., Pickles, K., Scheibe, F., Jan, S., 2015. The economic impact of epilepsy: a systematic review. BMC Neurol. 15 (1), 1–16.

Berkman, N.D., Lohr, K.N., Ansari, M., McDonagh, M., Balk, E., Whitlock, E., Reston, J., Bass, E., Butler, M., Gartlehner, G., 2014. Grading the Strength of A Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update.

Berlin, J.A., Longnecker, M.P., Greenland, S., 1993. Meta-analysis of epidemiologic dose-response data. Epidemiology 4, 218–228.

Brown, S.C., King, Z.A., Kuohn, L., Kamel, H., Gilmore, E.J., Frontera, J.A., Murthy, S., Kim, J.A., Omay, S.B., Falcone, G.J., 2020. Association of race and ethnicity to incident epilepsy, or epileptogenesis, after subdural hematoma. Neurology 95 (21), e2890–e2899.

Devetag, F., Mandich, G., Zaiotti, G., Toffolo, G., 1983. Alcoholic epilepsy: review of a series and proposed classification and etiopathogenesis. Ital. J. Neurol. Sci. 4 (3), 275–284.

Dworetzky, B.A., Bromfield, E.B., Townsend, M.K., Kang, J.H., 2010. A prospective study of smoking, caffeine, and alcohol as risk factors for seizures or epilepsy in young adult women: data from the Nurses' Health Study II. Epilepsia 51 (2), 198–205.

Feigin, V.L., Abajobir, A.A., Abate, K.H., Abd-Allah, F., Abdulle, A.M., Abera, S.F., Abyu, G.Y., Ahmed, M.B., Aichour, A.N., Aichour, I., 2017. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Neurol. 16 (11), 877–897.

Fisher, R.S., Boas, W.V.E., Blume, W., Elger, C., Genton, P., Lee, P., Engel Jr, J., 2005. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 46 (4), 470–472.

Freedland, E.S., McMicken, D.B., 1993. Alcohol-related seizures, part I: pathophysiology, differential diagnosis, and evaluation. J. Emerg. Med. 11 (4), 463–473.

Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ 327 (7414), 557–560.

Hillbom, M., Pieninkeroinen, I., Leone, M., 2003. Seizures in alcohol-dependent patients. CNS Drugs 17 (14), 1013–1030.

Johnson, E.L., Krauss, G.L., Lee, A.K., Schneider, A.L., Dearborn, J.L., Kucharska-Newton, A.M., Huang, J., Alonso, A., Gottesman, R.F., 2018. Association between midlife risk factors and late-onset epilepsy: results from the atherosclerosis risk in communities study. JAMA Neurol. 75 (11), 1375–1382.

Leone, M., Bottacchi, E., Gionco, M., Nardozza, V., Sironi, L., 1994. Alcohol and epileptic seizures: a case control study. Alcologia 6, 215–219.

Leone, M., Bottacchi, E., Beghi, E., Morgando, E., Mutani, R., Amedeo, G., Cremo, R., Gianelli, M., Ceroni, L.R., 1997. Alcohol use is a risk factor for a first generalized tonic-clonic seizure. Neurology 48 (3), 614–620.

Leone, M., Bottacchi, E., Beghi, E., Morgando, E., Mutani, R., Cremo, R., Ceroni, L.R., Floriani, I., 2002a. Risk factors for a first generalized tonic-clonic seizure in adult life. Neurol. Sci. 23 (3), 99–106.

Leone, M., Tonini, C., Bogliun, G., Monaco, F., Mutani, R., Bottacchi, E., Gambaro, P., Rocci, E., Tassinari, T., Cavestro, C., 2002b. Chronic alcohol use and first symptomatic epileptic seizures. J. Neurol. Neurosurg. Psychiatry 73 (5), 495–499.

Newman, R.K., Gallagher, M.A.S., Gomez, A.E., 2021. Alcohol Withdrawal. StatPearls [Internet].

Ogunniyi, A., Osuntokun, B., Bademosi, O., Adeuja, A., Schoenberg, B.S., 1987. Risk factors for epilepsy: case-control study in Nigerians. Epilepsia 28 (3), 280–285.

Orsini, N., Li, R., Wolk, A., Khudyakov, P., Spiegelman, D., 2012. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am. J. Epidemiol. 175 (1), 66–73.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372.

Peterson, J., Welch, V., Losos, M., Tugwell, P., 2011. The Newcastle-Ottawa scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analyses. Ottawa Hospital Research Institute, Ottawa.

RS, R.S.F., Acevedo, C., Arzimanoglou, A., et al., 2014. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 55 (4), 475–482.

Samokhvalov, A.V., Irving, H., Mohapatra, S., Rehm, J., 2010. Alcohol consumption, unprovoked seizures, and epilepsy: a systematic review and meta-analysis. Epilepsia 51 (7), 1177–1184.

Schmidt, C.O., Kohlmann, T., 2008. When to use the odds ratio or the relative risk? Int. J. Public Health 53 (3), 165–167.

Stephen, K.N., Hauser, W.A., Brust, J.C., Susser, M., 1988. Alcohol consumption and withdrawal in new-onset seizures. N. Engl. J. Med. 319 (11), 666–673.

Stevens, R., Heneghan, C., 2012. Against all odds? Improving the understanding of risk reporting. Br. J. Gen. Pract. 62 (596), e220–e223.

Zack, M., Kobau, R., 2017. Letter re: Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. Neurology 89 (6), 641-641.

Zeng, J., Hong, Z., Huang, M., Jin, M., 2003. A case-control study on the risk factors and other socio-psychological factors of epilepsy. Zhonghua liu xing Bing. xue za zhi Zhonghua liuxingbingxue zazhi 24 (2), 116–118.