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**ADMINISTRATIVE INFORMATION****Support** - None.**Review Stage at time of this submission** - Data analysis.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2023110049**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 November 2023 and was last updated on 11 November 2023.**INTRODUCTION**

**Review question / Objective** The frequency of subclinical epileptiform discharges (SED) in patients with Alzheimer's disease (AD).

**Condition being studied** Subclinical epileptiform discharge (SED), defined as seizure patterns on electroencephalography (EEG) unaccompanied by clinical epileptic manifestations, is a biomarker of cortical hyperexcitability. Studies have found a higher prevalence of SED in patients with AD than in healthy controls. Nevertheless, the variability in data on the prevalence of SED, ranging from 3% to 52%, may be attributed to methodological differences and cohort heterogeneity.

**METHODS**

**Search strategy** PubMed, Cochrane Library, ClinicalKey, Embase, ScienceDirect, and ProQuest.

**Participant or population** Patients with Alzheimer's dementia.

**Intervention** No intervention.

**Comparator** Not applicable.

**Study designs to be included** Observational study, using electroencephalogram to exam the occurrence of subclinical epileptiform discharges in patients with AD.

**Eligibility criteria** Inclusion criteria; (1) clinical studies that involve adult human subjects; (2) subjects diagnosed with AD; (3) studies that examine epileptiform discharge via scalp EEG; and (4) formally published articles. Studies that did not meet these criteria were excluded, such as (1) case reports, case series, or review articles; (2) nonclinical studies; (3) studies that did not involve patients diagnosed with AD; and (4) studies that included solely AD patients with seizures or epilepsy diagnosis.

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**Information sources** Information sources included electronic databases, and we will contact the authors for missing data.

**Main outcome(s)** Two authors, WC Yeh, and YS Li, performed separate systematic literature searches using the following keywords: “epileptiform,” or “epileptic,” or “epileptogenic” and “electroencephalogram” or “EEG” and “Alzheimer’s dementia” on various databases, including PubMed, Cochrane Library, ClinicalKey, Embase, ScienceDirect, and ProQuest, up to October 30, 2023. After removing duplicate studies, two authors separately screened the title and abstract and evaluated the eligibility of the papers (Fig. 1). A list of potentially relevant studies was selected for full-text review. Any inconsistencies were addressed by a third author, CY Hsu, to reach a final consensus. After the selection process, only 13 articles were included in this study, whereas 56 were excluded.

**Data management** Two authors (WC Yeh, and YS Li) collected data from eligible studies separately. They extracted patient information, such as age, gender, severity of disease, and the rate of epileptiform discharge recorded on EEG. If the study included a healthy control group, data were also collected for them.

**Quality assessment / Risk of bias analysis** Heterogeneity was examined using Q-statistics and their corresponding p-values. The I square statistic was used to evaluate the proportion of variation. A value of I square > 50% indicates high heterogeneity. Potential publication bias was detected using funnel plots when datasets were  $\geq 10$ . In cases where potential publication bias was suspected, Duval and Tweedie’s trim-and-fill tests were performed to adjust effect sizes.

**Strategy of data synthesis** Because of the anticipated heterogeneity, we selected a random-effects meta-analysis.<sup>18</sup> The meta-analysis procedure was performed using Comprehensive Meta-Analysis software, version 3 (Biostat Inc., Englewood, NJ, USA). For each analysis, a two-tailed p-value of <0.05 was considered statistically significant.

**Subgroup analysis** We performed subgroup analyses to compare SED occurrence rates between routine and extended EEG protocols and between patients with EOAD and late-onset AD. The relative risk of SED was analyzed between AD patients and healthy controls.

**Sensitivity analysis** A sensitivity analysis using the one-study-removal method to examine the possible influence of outliers on the results.

**Language restriction** No.

**Country(ies) involved** Taiwan.

**Keywords** Alzheimer’s dementia, cortical hyperexcitability, electroencephalogram, subclinical epileptiform discharge.

**Contributions of each author**

Author 1 - Wei-Chih Yeh - Wei-Chih Yeh, the first author, was responsible for the literature search, statistical procedure, and manuscript drafting.

Author 2 - Ying-Sheng Li - Ying-Sheng Li contributed to the manuscript revision and data interpretation.

Author 3 - Chung-Yao Hsu - Chung-Yao Hsu contributed as the corresponding author and was responsible for concept formation, manuscript revision, and manuscript submission.