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Epilepsy duration and seizure outcome in epilepsy surgery

A systematic review and meta-analysis

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Abstract

Objective

To conduct a systematic review and meta-analysis on the effect of earlier or later resective epilepsy surgery on seizure outcome.

Methods

We searched the electronic databases PubMed, EMBASE, and Cochrane Library for studies investigating the association of epilepsy duration and seizure freedom after resective surgery. Two reviewers independently screened citations for eligibility and assessed relevant studies for risk of bias. We combined data in meta-analyses using a random effects model. We assessed the certainty of evidence according to Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Results

Twenty-five studies were included, 12 of which had data suitable for meta-analyses. Comparing seizure outcome if epilepsy surgery was performed before vs after 2, 5, 10, and 20 years of epilepsy duration, and comparing epilepsy duration <5 years to >10 years, we found significant effects favoring shorter duration with risk differences ranging from 0.15 to 0.21 and risk ratios ranging from 1.20 to 1.33 ($p < 0.01$ for all comparisons). According to GRADE, we found low certainty of evidence favoring shorter epilepsy duration before surgery.

Conclusion

People with shorter epilepsy duration are more likely to be seizure-free at follow-up. Furthermore, there is a positive association between shorter duration and seizure freedom also for very long epilepsy durations. Patients who might benefit from epilepsy surgery should therefore be referred for presurgical assessments without further delay, regardless of epilepsy duration. The low certainty of evidence acknowledges concerns regarding study heterogeneity and possible residual confounding.

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Glossary

GRADE = Grading of Recommendations Assessment, Development, and Evaluation; **ILAE** = International League Against Epilepsy; **RCT** = randomized controlled trial; **RD** = risk difference; **RR** = risk ratio; **SBU** = Swedish Agency for Health Technology Assessment and Assessment of Social Services.

Epilepsy surgery is an evidence-based treatment option for people with drug-resistant epilepsy.[1–3] Drug resistance is defined by the Task Force of the International League Against Epilepsy (ILAE) Commission on Therapeutic Strategies as failure of adequate trials of 2 tolerated, appropriately chosen and used antiepileptic drug schedules to achieve sustained seizure freedom.[4] This definition facilitates for nonspecialists to recognize patients with drug-resistant epilepsy and refer them promptly to specialist centers for evaluation of epilepsy surgery or other specialized treatments.

Despite this, referral patterns have not undergone any major changes over the last decades.[1,2,5,6] Although the importance of early referral has been emphasized repeatedly,[7] epilepsy surgery is still considered by many neurologists to be the last resort.[8] Many patients who are offered surgery have had drug-resistant epilepsy for half of their lives.[9] A number of observational studies have suggested that a short duration of epilepsy is associated with better seizure outcome after resective epilepsy surgery. If corroborated, this finding further underscores the importance of early referral. However, the study designs vary, the cohorts are often limited, and varying resection types have been studied.

The aim of this study was therefore to assess the evidence comparing the effect of earlier or later resective epilepsy surgery on seizure outcome after surgery in a systematic review and meta-analysis.

Methods

Inclusion criteria

The review was part of a larger project investigating the effect, safety, cost-effectiveness, and ethical aspects of several methods for treatment and diagnosis of epilepsy, conducted at the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU), and initiated in collaboration with the National Board of Health and Welfare. Main selection criteria and methods of analysis for the review were specified and documented in advance. The systematic review was conducted in accordance with the PRISMA statement,[10] following an a priori but unpublished protocol available on request.

The criteria for eligibility were the following:

- Population. Individuals with drug-resistant epilepsy at all ages, study population ≥30.
- Intervention and comparison. Resective epilepsy surgery performed at different time intervals after epilepsy onset.
- Outcomes and measures. (1) Postsurgical seizure outcome expressed as proportions of patients with seizure freedom grouped by various presurgical epilepsy durations or regression analysis or other measure of association between presurgical epilepsy duration and postsurgical seizure freedom (reported as odds ratio, risk ratio, hazard ratio); (2) surgery-related complications related to presurgical epilepsy duration. Furthermore, seizure freedom should be reported as ILAE Class I (seizure-free without aura), ILAE Class I + II (seizure-free with or without aura),[11] Engel Class Ia (seizure-free), or Engel Class I (no disabling seizures).[12] Seizure freedom should be assessed at the earliest 12 months after surgery (an exception was made if a small minority of the study population was assessed earlier). Studies that only reported mean or median duration of epilepsy for patients grouped by seizure outcome were not included.
- Study design. Randomized controlled trials (RCT) or observational studies with prospective or retrospective design.
- Language limitations. English, Swedish, Norwegian, or Danish language.
- Publication type. Publications in peer-reviewed journals published in 2000 or later.

Search strategy

We searched the literature in Cochrane Controlled Register of Trials (Central), PubMed (NLM), and EMBASE (Elsevier) on 2 occasions, covering literature published from 2000 to November 10, 2017. The search terms "epilepsy" and "surgery" and related terms were used. The detailed search strategy is available in appendix e-1 (doi.org/10.5061/dryad.g8c0vm8). We examined the reference lists of included studies for additional relevant studies.

Study screening and selection

Two reviewers screened the titles and abstracts independently. Full-text articles were retrieved if one or both reviewers considered a study potentially eligible. At least 2 reviewers read the full texts, and any disagreement regarding eligibility was resolved by discussion. Only unique nonoverlapping study populations were included.

Two reviewers independently assessed eligible studies for risk of bias using a standardized tool developed at SBU for observational studies (sbu.se/en/method/). We scored studies as having high, medium, or low risk of bias, based on the following domains: selection bias (including assessment of

confounders), performance bias, detection bias, attrition bias, reporting bias, and potential conflicts of interest. Only studies with low or medium risk of bias were included.

Standard protocol approvals, registrations, and patient consents

No additional ethical approval was required for this systematic review and meta-analysis.

Data extraction

For all included studies, we extracted country, patient characteristics such as age, sex, and type of epilepsy, type of surgery, method of data collection, definition of seizure freedom, length of follow-up after surgery, and outcome. Proportions of patients with seizure freedom at different epilepsy durations expressed as n/N were extracted or recalculated from percentages when possible. The full extracted study data are available in appendix e-2 (doi.org/10.5061/dryad.g8c0vm8).

Synthesis and statistical analysis

Meta-analyses were performed using Review Manager (RevMan) version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), employing the Mantel-Haenszel method for binary outcomes. We used a random effects model for all analyses, as clinical heterogeneity was present in the included studies. Outcomes were expressed as risk difference (RD) and risk ratio (RR) with 95% confidence intervals. We considered p values <0.05 as significant. The degree of statistical heterogeneity was assessed using the I^2 index.

Assessment of evidence

The certainty of evidence was assessed according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE), where evidence levels are expressed as strong, moderate, low, or insufficient.[13] Preliminary certainty of the evidence is classified as high if the results are based on data from RCT, otherwise as low. Each outcome is assessed separately and can be rated down from the preliminary level by the 5 risk domains in GRADE: overall risk of bias across studies, inconsistency, indirectness, imprecision, and publication bias. Observational studies can be upgraded from the initial level based on large magnitude of effect, presence of dose–response gradient, or presence of opposing confounding effects.

Data availability

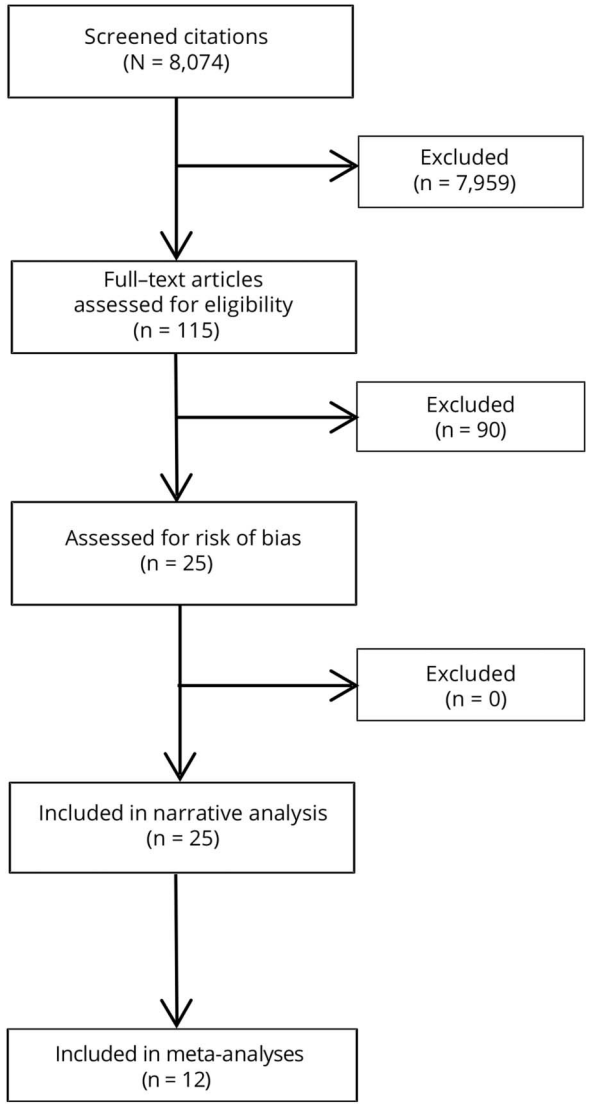
Data are available to qualified investigators on request to the corresponding author.

Results

Search results and study selection

The electronic database search strategy yielded 8,074 citations, from which 115 articles were obtained and examined in full text. Of these, 25 studies fulfilled the eligibility criteria (figure 1).[6,14–37] All the included studies were observational studies with varying study design. As expected, we found no RCT that investigated the targeted question. We found no study that reported on association between presurgical epilepsy duration and surgery-related complications.

Figure 1 PRISMA flow diagram for the literature search and study selection



Characteristics of included studies

In total, the studies included data from 3,746 patients with drug-resistant epilepsy who had undergone resective surgery. For details, we refer to the extracted study data (appendix e-2, doi.org/10.5061/dryad.g8c0vm8). Most studies were retrospective analyses of patient data from national or local databases or medical records. Some studies included only temporal lobe resections,[14,17,21–23,26,27,33] frontal lobe resections,[32] posterior resections,[16,24,31] or all extratemporal resections,[19] while other studies included resections regardless of the location. Several cohorts comprised only epileptogenic lesions.[6,17,21,25,29,30] Age range, sex ratio, study period, and follow-up time varied across the studies.

Most studies included both children and adults, while 4 cohorts comprised only children and adolescents up to the age of 18 years,[17,31,32,34] and 5 only adults.[14,19,22,23,36] Several studies included patients under 5 years of age.[17,18,20,21,24,30–32,34,35] All studies reported seizure freedom (including or excluding aura) in accordance with the eligibility criteria. Various measurements for associations of presurgical epilepsy duration and postsurgical seizure freedom were reported in the studies, such as proportions, odds ratio, and hazard ratio.

Risk of bias assessment

All eligible studies were classified as having an overall moderate risk of bias; hence, no study was excluded due to high risk of bias. This was partly a consequence of the criteria decided upon at the eligibility state as regards reporting of outcome and length of follow-up. Known predictors for seizure outcome, such as MRI findings, histopathology, and preoperative seizure frequencies, were not reported in relation to epilepsy duration. We recognized that confounding effects could be present and that the direction of these potential biases (favors short duration or favors long duration) was difficult to predict.

Synthesis of outcomes

We used 2 approaches to evaluate the assembled effect from the included studies. First, a narrative synthesis was undertaken, where we examined all the included studies for the reported effect on association between epilepsy duration and postsurgical seizure outcome. According to the narrative examination, most of the studies reported associations in favor of shorter duration[6,15–19,21–35]; in some cases, these results were statistically significant. A few studies reported results that suggested no association (e.g., odds ratio close to 1),[14,20,36] and one study reported on association in favor of longer duration.[37]

Second, we used a meta-analysis approach, where data from studies reporting proportions of seizure freedom before and after a certain time of presurgical epilepsy duration were assembled in meta-analyses. The breakpoints (before vs after 2, 5, 10, and 20 years of epilepsy duration, respectively) were chosen so that the most frequently reported data were used. Twelve studies (n = 1,545) reported data on this format.[6,15,22,24,27,28,30,31,33–35,37]

The results from the meta-analyses are summarized in figure 2. Three studies (n = 288) reported data on seizure freedom at epilepsy duration <2 years compared to >2 years,[6,31,34] 4 studies (n = 551) reported seizure freedom at epilepsy duration <5 years compared to >5 years,[6,24,30,34] 10 studies (n = 1,376) reported data on <10 years compared to >10 years.[6,15,22,24,27,30,33–35,37] Three studies (n = 346) reported data on <20 years compared to >20 years.[6,22,28] Finally, we compared epilepsy duration <5 years to >10 years, in order to investigate if a larger time gap in epilepsy duration resulted in a larger effect. Data for this comparison were found in 4 studies (n = 430).[6,24,30,34] All comparisons showed significant effects favoring shorter duration with RD ranging from 0.15 to 0.21 and RR ranging from 1.20 to 1.33 ($p < 0.01$ for all comparisons).

Strength of evidence

We assessed the strength of evidence for the general question of association between presurgical epilepsy duration and postsurgical seizure freedom. Thus, the specific comparisons targeted in the meta-analyses (before vs after 2, 5, 10, or 20 years of epilepsy duration) were not judged individually. The assessment was based both on the narrative analysis of all the included studies and on the meta-analyses.

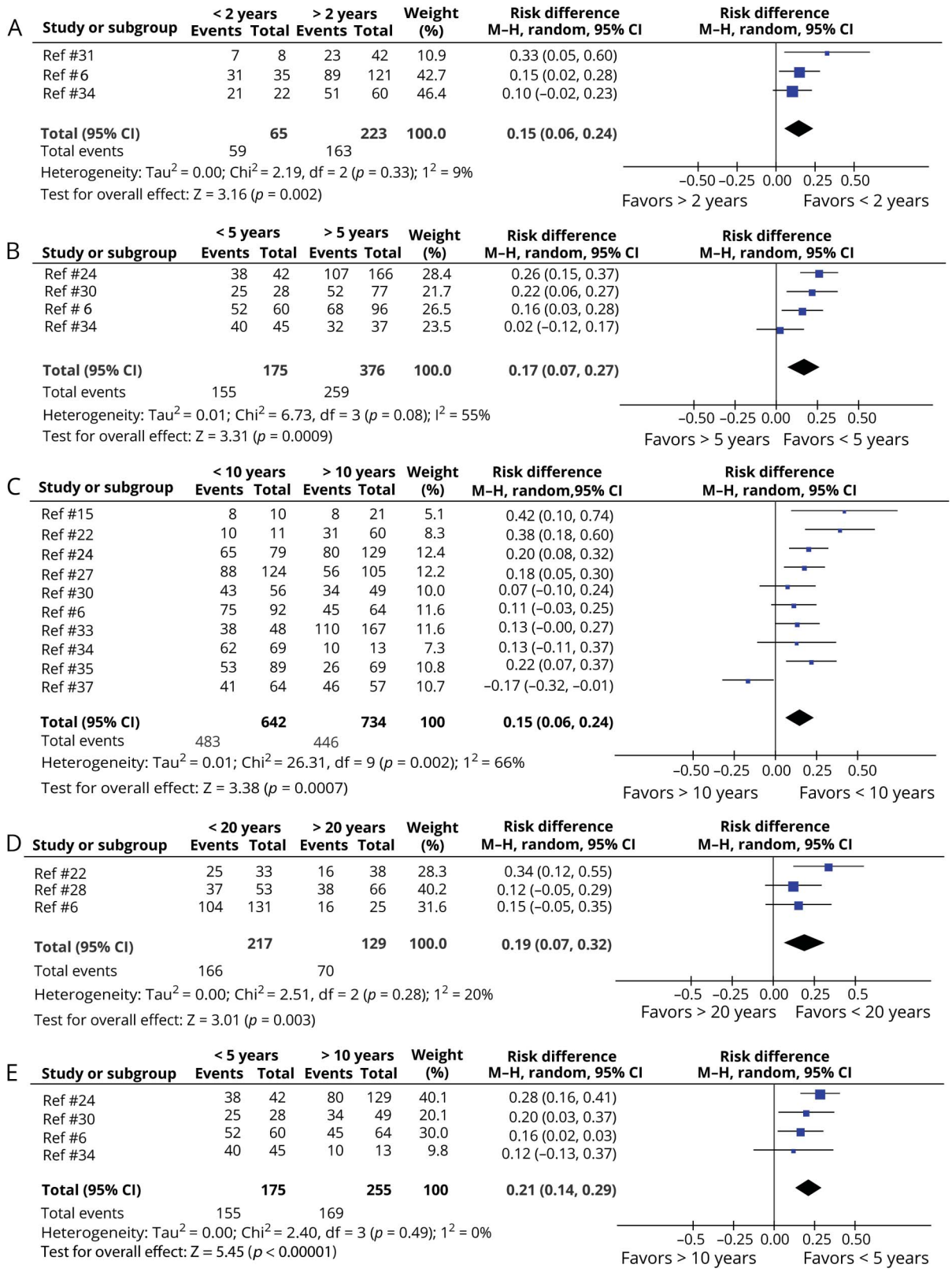
The grading of evidence started at "low," as the material in this review consisted of observational studies. The estimate of association varies among the studies, but most of them suggest an association favoring shorter epilepsy duration. The meta-analyses support this assumption by showing significant effects favoring shorter epilepsy duration for all comparisons. We recognized that the individual studies had some weaknesses regarding risks of bias and that there were some concerns regarding inconsistency and indirectness. However, these factors did not justify downgrading the evidence level from the already low starting point. Nor were there reasons strong enough to upgrade the evidence level. Hence, this review provides low certainty of evidence for an association between shorter presurgical epilepsy duration and a higher proportion of patients with postsurgical seizure freedom (for summary of findings, see the table).

Discussion

The present study shows an association between shorter duration of epilepsy and better seizure outcome after resective epilepsy surgery in a systematic review and meta-analysis. The discussion about the importance of earlier epilepsy surgery has been around for a long time and motivated US researchers to initiate an ambitious RCT, ERSET, to determine whether surgery in patients with drug-resistant temporal lobe epilepsy soon after failure of 2 antiepileptic drug trials is superior to continued medical management.[2] A sample size of 200 participants was originally planned, but the trial had to be terminated prematurely. Only 38 patients were recruited with a mean epilepsy duration of 10.9 years,[2] which though it may seem rather long is much shorter than the mean epilepsy duration of 19.7 years in the first randomized controlled trial.[1] Nevertheless, even in this limited cohort, resective surgery and antiepileptic drug treatment resulted in a lower probability of seizures during the second year of follow-up than continued drug treatment alone.

In the ERSET study, the authors comment that obtaining referrals from the community was difficult, although they do not discuss the reasons for this further.[2] Among the reasons most often cited for not referring patients are that health care providers are negative to the treatment option of epilepsy surgery,[38]

Figure 2 Meta-analysis of seizure freedom with respect to different epilepsy durations



CI = confidence interval; M-H = Mantel-Haenszel.

or that they are not aware of which patients to refer.[39] It is also understandable that patients may be hesitant early on to accept open brain surgery for their epilepsy, though several studies have illustrated that they tend to overestimate the risks.[38,40–42]

Table Findings for the association of epilepsy duration to surgery outcome

Outcome	Comparison/analysis	No. of participants (studies)	Absolute effect, RD (95% CI)	Relative effect, RR (95% CI)	Strength of evidence (GRADE)
Seizure freedom	Duration <2 years compared to >2 years	288 (3)	0.15 (0.06; 0.24)	1.20 (1.05; 1.39)	Low certainty of evidence
	Duration <5 years compared to >5 years	551 (4)	0.17 (0.07; 0.27)	1.24 (1.08; 1.42)	Favors shorter duration
	Duration <10 years compared to >10 years	1,376 (10)[a]	0.15 (0.05; 0.24)	1.25 (1.09; 1.43)	
	Duration <20 years compared to >20 years	346 (3)	0.19 (0.07; 0.32)	1.33 (1.08; 1.65)	
	Duration <5 years compared to >10 years	430 (4)	0.21 (0.14; 0.29)	1.32 (1.19; 1.46)	
	Narrative analysis including all studies	3,746 (25)	N/A	N/A	
Complications		0 (0)	N/A	N/A	Insufficient evidence
					No studies identified

Abbreviations: CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; RD = risk difference; RR = risk ratio.
[a]One study[15] with data for <12.2 compared to >12.2 years has been included.

The proportion of patients with seizure freedom was higher in the ERSET trial than the earlier study, where the mean epilepsy duration was longer. However, the patient selection differed between the 2 trials, as ERSET included only patients determined to have surgically remediable mesial temporal lobe epilepsy,[2] while in the earlier study patients were randomized before the presurgical investigation.[1]

The major strength of the present review is the rigorous protocol for selection and evaluation of the studies. Due to the relatively strict inclusion criteria, studies that might have added a high risk of bias were rejected at the eligibility stage.

We acknowledge that confounding factors might be present in studies favoring shorter epilepsy duration. Patients with epileptogenic lesions and highly congruent preoperative investigations, which are indicators of better seizure outcome, are likely to have surgery earlier than, for instance, patients with normal MRI or complex electroclinical patterns. On the other hand, it is conceivable that patients with higher seizure frequency are selected for presurgical evaluation earlier, which allows for a confounding effect in the opposite direction. The individual studies seldom report the results of preoperative investigations in relation to epilepsy duration. Therefore, we were not able to analyze possible confounding effects arising from different subgroups of patients being selected for surgery earlier. Unknown predictors of seizure outcome may also confound the effect.

The results of the individual meta-analyses are to be interpreted with caution, since populations and surgical procedures vary between studies. Some patients are included in more than one meta-analysis; hence, the meta-analyses should be interpreted as subgroup analyses of different breakpoints.

As shown in the narrative analysis, shorter epilepsy duration is favored in most individual studies, regardless of the population and specific intervention. Several studies include only cases with epileptogenic lesions, which makes early selection of cases with favorable prognosis less likely to explain the results in these studies. Furthermore, the different time intervals studied in the meta-analyses all favor shorter epilepsy duration. We therefore judge that although selection bias may be present in individual studies, the analyses support an association between shorter epilepsy duration and better seizure outcome. The low certainty of evidence acknowledges the inherent weaknesses in the observational study methodology and the risk for residual bias.

Some studies have reported an association between lower age at surgery and a higher proportion of patients with sustained seizure freedom.[43,44] As younger people obviously have had their epilepsy for a shorter time than older adults, the patient's age at surgery may confound the association between epilepsy duration and seizure outcome. However, a positive association was also found in studies considering both age and epilepsy duration at the time of surgery.[18,27–29]

This review was based on observational studies with moderate risk of bias, which explains the concluding evidence level "low certainty." Randomized studies are usually considered the best evidence base for demonstrating an effect, but for ethical and practical reasons, such studies are not feasible for the targeted question. However, forthcoming methodologically sound observational studies of large, prospectively followed cohorts that

include strategies to control for confounding factors may strengthen the evidence for this research question.[45]

Finally, we note that few studies report duration of epilepsy after 2 adequate drug trials. Some patients with epilepsy have a long course before drug resistance develops. Based on our study, it is not possible to tell if the duration of drug-resistant epilepsy is a more important predictor than the total epilepsy duration. It is desirable that future studies analyze both variables to clarify this matter.

Duration of epilepsy is the only known modifiable factor that is associated with favorable seizure outcome after epilepsy surgery. This underlines the importance of early referral of patients with drug-resistant epilepsy to improve outcomes. In the meta-analyses, people with shorter epilepsy duration were more likely to be seizure-free at follow-up regardless of the studied cutoff, indicating that earlier surgery is always to be preferred. On the other hand, we found a positive association between shorter duration and seizure freedom also for very long epilepsy durations. This indicates that for patients who are suitable epilepsy surgery candidates, presurgical investigations should be suggested and planned without further delay regardless of epilepsy duration.

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Disclosure

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Appendix Authors

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Kristina Malmgren, MD, PhD	University of Gothenburg and Sahlgrenska University Hospital	Author	Design and conceptualization of study, data acquisition, data analysis and interpretation, drafting and revising the manuscript
Karin Wilbe Ramsay, PhD	Swedish Agency for Health Technology Assessment and Assessment of Social Services, Stockholm	Author	Design and conceptualization of study, data acquisition, data analysis and interpretation, drafting and revising the manuscript

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