



FACULDADE DE MEDICINA
UNIVERSIDADE D
COIMBRA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

ALEXANDRE MAIA ROLDÃO ALFERES

***QUOCIENTE DE INTELIGÊNCIA APÓS CIRURGIA DA EPILEPSIA EM
IDADE PEDIÁTRICA – UMA REVISÃO SISTEMÁTICA E META-ANÁLISE***

REVISÃO SISTEMÁTICA

ÁREA CIENTÍFICA DE NEUROPEDIATRIA

Trabalho realizado sob a orientação de:

DOUTORA CRISTINA DUARTE PEREIRA

PROFESSORA DOUTORA BÁRBARA CECÍLIA BESSA DOS SANTOS OLIVEIROS PAIVA

MARÇO/2021

Intelligence quotient outcome following epilepsy surgery in pediatric age – a Systematic Review and Meta-Analysis

Short running title: IQ after pediatric epilepsy surgery

Alexandre Roldão Alferes^{1,*}, Bárbara Oliveiros^{2,3,**} PhD, Cristina Pereira^{1,4,***} MD

¹ Faculty of Medicine, University of Coimbra, Portugal

² Laboratory of Biostatistics and Medical Informatics, Faculty of Medicine, University of Coimbra, FMUC, Portugal

³ Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, FMUC, Portugal

⁴ Department of Neuropediatrics, Hospital Pediátrico - Centro Hospitalar e Universitário de Coimbra (CHUC), Centro de Referência de Epilepsia Refratária do CHUC, Member of the ERN EpiCARE, Coimbra, Portugal

*Address: Faculdade de Medicina, Universidade de Coimbra (FMUC) – Polo das Ciências da Saúde, Azinhaga de Santa Comba, Celas, 3000-548 Coimbra

E-mail: am_rolld@hotmail.com

**Address: Faculdade de Medicina, Universidade de Coimbra (FMUC) – Polo das Ciências da Saúde, Azinhaga de Santa Comba, Celas, 3000-548 Coimbra

E-mail: boliveiros@fmed.uc.pt

***Address: Centro de Desenvolvimento da Criança do Hospital Pediátrico – Centro Hospitalar e Universitário de Coimbra. Avenida Afonso Romão. 3000-602 Coimbra

E-mail: cristina.pereira@chuc.min-saude.pt

The authors declare that there are no conflicts of interest with this work.

Table of Contents

Table of Contents	1
Scientific Divulgration	2
Abstract	3
Keywords	4
Resumo	5
Palavras-chave	6
Abbreviations	7
Introduction	8
Rationale	8
Objectives	9
Methods	9
Protocol and Registration	9
Eligibility Criteria	10
Information Sources and Search Strategy	10
Study Selection	11
Data Collection Process and Data Items	11
Risk of Bias Assessment	11
Summary Measures	12
Synthesis of Results	12
Additional Analysis	12
Results	13
Study Selection and Characteristics	13
Risk of Bias Assessment	19
Results of Individual Studies	20
Overall effect of epilepsy surgery on post-operative IQ values	20
Effect of curative vs palliative surgical procedures in post-operative IQ values ...	21
Factors with prognostic value for post-operative IQ	23
Synthesis of Results	24
Additional Analysis	25
Discussion	26
Summary of Evidence	26
Limitations	27
Conclusions	28
Funding	28
Acknowledgements	28
References	29
Appendices	34

Scientific Divulcation

A protocol for this Systematic Review and Meta-Analysis was registered in PROSPERO with the code number [CRD42020216548] (Appendix I).

A full-text Review Article manuscript was submitted to Epileptic Disorders with the code number “ED-2021-03-0083” (Appendix II) and is currently under review process. Author Guidelines 2021 for Epileptic Disorders were followed to write the manuscript.

Abstract

Rationale: There is a deep-rooted correlation between refractory epilepsy in pediatric age and intelligence development. However, little is known about whether surgical procedures used in pediatric epilepsy treatment can affect intelligence quotient or not. Several studies report significant intelligence quotient improvements while others report no statistically significant modifications. Factors that might influence post-operative intelligence quotient are also a matter of study in several articles.

Aims: To evaluate whether surgery for pediatric epilepsy treatment improves, worsens or has no impact on intelligence quotient scores, to ascertain whether these results differ between curative and palliative surgical procedures and to analyze which factors have prognostic value for post-operative intelligence quotient.

Methods: A systematic review with meta-analysis was conducted with the keywords "epilepsy", "epileptic", "surgery", "surgical", "Wechsler Scale" and "intelligence tests" in the databases PubMed, the Cochrane Library, EMBASE and ClinicalTrials.gov. Only studies in English, French, Spanish or Portuguese published since 2000 with more than 10 participants (children with epilepsy submitted to a surgical procedure for epilepsy treatment), a follow-up after surgery equal to or longer than one year and a pre- and post-operative measurement of intelligence quotient with the Wechsler Scales of Intelligence were eligible. Relevant data was extracted and summarized in a dataset. Study quality was addressed with the Newcastle-Ottawa Scale. A descriptive data synthesis was carried out to address each of the objectives and then a meta-analysis of random effects with the eight eligible articles was conducted. Standardized difference between post- and preoperative full-scale intelligence quotient was used for effect measurement. A meta-regression was performed to ascertain whether factors such as gender, age of onset of epilepsy, duration of epilepsy, age at surgery, etiology, type of surgery, Engel classification and affected hemisphere could influence post-operative intelligence quotient.

Results: The meta-analysis of the studies included found a mean difference between post-operative and preoperative full-scale intelligence quotient values of 1.014 standardized points ($p < 0.001$; 95%CI: 0.589 to 1.437). Among all the articles regarding curative surgeries, only three reported an overall significant improvement in intelligence quotient after surgery. Regarding palliative procedures, both studies with anterior corpus callosotomy reported a significant improvement in full-scale intelligence quotient values two years after surgery. The

meta-regression performed did not find any predictors of change in full-scale intelligence quotient.

Conclusions: Despite all the limitations, it appears that epilepsy surgery in pediatric age has an overall positive effect on intelligence quotient. This includes palliative procedures such as the anterior corpus callosotomy. No good predictors of post-operative intelligence quotient were found. More research in this area is needed to draw more solid conclusions.

Implications: Parents of refractory epilepsy children can be informed that significant negative outcomes in post-operative intelligence quotient are not expected. Additionally, a special education program for those children is unlikely to be required if it was not needed prior to surgery.

Keywords: Epilepsy, Surgery, Intelligence Quotient, Pediatric Age

Resumo

Referencial Teórico: Existe uma correlação bem estabelecida entre a epilepsia refratária em idade pediátrica e o desenvolvimento intelectual. Contudo, pouco se sabe sobre a influência dos procedimentos cirúrgicos utilizados no tratamento da epilepsia pediátrica no quociente de inteligência. Vários estudos referem subidas estatisticamente significativas no quociente de inteligência, enquanto outros não reportam alterações estatisticamente significativas. É objetivo de vários artigos identificar os fatores que possam influenciar o quociente de inteligência pós-operatório.

Objetivos: Avaliar a influência da cirurgia para tratamento da epilepsia pediátrica nos níveis do quociente de inteligência; averiguar se os resultados diferem entre procedimentos curativos e paliativos; analisar que fatores têm valor prognóstico para o quociente de inteligência pós-operatório.

Métodos: Foi realizada uma revisão sistemática com meta-análise com as palavras-chave "epilepsy", "epileptic", "surgery", "surgical", "Wechsler Scale" e "intelligence tests" nas bases de dados PubMed, the Cochrane Library, EMBASE e ClinicalTrials.gov. Foram eleitos apenas estudos em Inglês, Francês, Espanhol e Português, publicados desde 2000, com mais de 10 participantes (crianças com epilepsia submetidas a um procedimento cirúrgico para tratamento da epilepsia), um *follow-up* pós-operatório igual ou superior a um ano e uma medição do quociente de inteligência pré e pós-operatório, com uma Escala de Inteligência de Wechsler. Os dados relevantes foram extraídos e sumariados numa tabela. A qualidade dos estudos foi avaliada através da Escala de Newcastle-Ottawa. Foi realizada uma síntese descritiva dos dados para responder a cada um dos objetivos e, seguidamente, foi efetuada uma meta-análise de efeitos aleatórios com os oito artigos elegíveis. A medida de efeito utilizada foi a diferença estandardizada entre o quociente de inteligência pós-operatório e pré-operatório. Uma meta-regressão foi elaborada para averiguar se os seguintes fatores poderiam influenciar o quociente de inteligência pós-operatório: sexo, idade do início da epilepsia, duração da epilepsia, idade no momento da cirurgia, etiologia, tipo de cirurgia, classificação de Engel e hemisfério afetado.

Resultados: A meta-análise dos estudos incluídos mostrou uma diferença de médias entre o quociente de inteligência total pós e pré-operatório de 1,014 pontos estandardizados ($p < 0,001$; 95%CI: 0,589 a 1,437). De entre os estudos sobre cirurgias curativas, apenas três reportaram um aumento significativo do quociente de inteligência pós-operatório. Relativamente aos procedimentos paliativos, ambos os estudos com calosotomias anteriores

revelaram um aumento significativo dos valores do quociente de inteligência total, dois anos após a cirurgia. A meta-regressão realizada não encontrou nenhum preditor de mudança no quociente de inteligência total.

Conclusões: Apesar de todas as limitações, a cirurgia da epilepsia em idade pediátrica aparenta ter, no geral, um efeito positivo no quociente de inteligência. Isto inclui procedimentos paliativos tais como a calosotomia anterior. Não foram encontrados bons preditores do quociente de inteligência pós-operatório. Será necessária mais investigação nesta área para tirar conclusões mais sólidas.

Implicações: Podemos informar os pais das crianças com epilepsia refratária que não é expectável que existam resultados significativamente negativos no quociente de inteligência, no pós-operatório de cirurgia da epilepsia. Adicionalmente, é pouco provável que essas crianças necessitem de um programa de educação especial após a cirurgia, caso já não precisassem dele antes.

Palavras-chave: Epilepsia, Cirurgia, Quociente de Inteligência, Idade Pediátrica

Abbreviations

AED: Antiepileptic drug;

CC: Corpus callosotomy;

DQ: Development quotient;

FSIQ: Full-scale intelligence quotient;

ILAE: International League Against Epilepsy;

IQ: Intelligence quotient;

NOS: Newcastle-Ottawa Scale;

PIQ: Performance intelligence quotient;

RCT: Randomized control trial;

RE: Refractory epilepsy;

VCI: Verbal comprehension index;

VIQ: Verbal intelligence quotient;

WAIS: Wechsler Adult Intelligence Scale;

WASI: Wechsler Abbreviated Scale of Intelligence;

WIS: Wechsler Intelligence Scales;

WISC: Wechsler Intelligence Scale for Children;

WPPSI: Wechsler Pre-School Primary Scale of Intelligence.

1. Introduction

Rationale

Epilepsy is one of the most frequent chronic neurologic conditions in pediatric age and is the most common childhood brain disorder in the United States.¹ According to the latest estimates, epilepsy affects 4% of children from developed countries and 8% from underdeveloped countries. The incidence varies with age. The highest values reported occur in the first year of age, with 1 to 2 cases per 1000 children. On the other hand, the prevalence increases with age, with 4 to 6 cases per 1000 children at the age of 10.²⁻⁴

Although there are several treatment options for epilepsy, in some cases, seizures may not respond to medication. According to the International League Against Epilepsy (ILAE), patients who fail to achieve sustained freedom from seizures, despite adequate trials of two antiepileptic drugs – either as monotherapy or in combination – are considered to have a condition called refractory epilepsy (RE).⁵ In these cases, epilepsy surgery may be an option for freedom from seizures (curative procedures) or to reduce their severity (palliative procedures). Examples of curative procedures include lesionectomy/lesion resection, lobectomy/lobe resection and corticectomy, whereas disconnection procedures such as corpus callosotomy (CC) are palliative procedures. Hemispherectomy, hemispherotomy and multiple subpial transections can be curative or palliative.⁶⁻⁸

There is a well-established correlation between RE in pediatric age and intelligence development. Nevertheless, whether the previously mentioned surgical procedures can affect intelligence quotient (IQ) or not is still a matter of investigation. A recent meta-analysis about callosotomy which included both children and adults at the time of surgery⁹ showed no significant change on IQ from pre- to post-surgery. However, it was found that this palliative surgery had a negative effect in the performance IQ values of patients with average values before surgery. On the other hand, there was no significant modification in the performance IQ values of the patients with below-average performance IQ before surgery. In a recent study,¹⁰ it was found that five children who underwent hemispherectomy showed improvement in cognitive abilities across all subsets of the Wechsler Intelligence Scale for Children (WISC). Another study about hemispherectomy with nine children tested with the same intelligence test reported that all but one patient kept the same intellectual levels.¹¹ A number of studies about lobe resection surgery report significant IQ improvements^{12,13} while others report no significant modifications.^{14,15}

One way of measuring intelligence levels is by determining the IQ using intelligence tests. Nowadays, the Wechsler Intelligence Scales (WIS) are considered the gold standard tests for intelligence assessment.¹⁶⁻¹⁸

The WIS include the Wechsler Pre-School Primary Scale of Intelligence (WPPSI), the WISC, the Wechsler Adult Intelligence Scale (WAIS) and the Wechsler Abbreviated Scale of Intelligence (WASI). The WPPSI is used for ages ranging from 2 years and 6 months to 7 years and 7 months. The WISC is used for ages ranging from 6 years to 16 years and 11 months. The WAIS is used for ages ranging from 16 years to 90 years and 11 months. The WASI can be used for the same ages as the WISC and the WAIS. All of these tests have been revised and updated over the years to incorporate advances in the intelligence field as well as to better reflect the abilities of test-takers from different cultural environments. For example, the original WISC, the WISC-Revised (WISC-R) and the WISC-Third Edition (WISC-III) provided a verbal IQ (VIQ) and a performance IQ (PIQ) score. The WISC-Fourth Edition (WISC-IV) and the WISC-Fifth Edition (WISC-V) no longer provide these quotients. The WISC-III introduced four new index scores to represent more narrow domains of cognition, one of them being the Verbal Comprehension Index (VCI), which was designed to provide an overall measure of verbal acquired knowledge and verbal reasoning.¹⁹ All versions provide a full-scale intelligence quotient (FSIQ), with an average mean score of 100, which measures the individual overall level of general cognitive and intellectual functioning.^{18,20}

Objectives

Understanding whether IQ changes after epilepsy surgery in pediatric age is of great importance since children may require additional parental support or even special education in school. Therefore, this meta-analysis has three objectives. The main goal is to evaluate whether surgery for pediatric epilepsy treatment influences post-surgery IQ values or not. The secondary objectives are to ascertain whether these results differ between curative and palliative surgical procedures and which factors have prognostic value for post-operative IQ.

2. Methods

Protocol and Registration

The PRISMA guidelines were followed for this study methodology. A protocol was registered in PROSPERO on the second of December of 2020, with the code number [CRD42020216548]

and can be accessed at:
https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=216548.

Eligibility Criteria

The included studies had to meet the following inclusion criteria: 1) observational and experimental studies with more than 10 participants; 2) children (at most 18 years of age), with epilepsy, submitted to a surgical procedure for epilepsy treatment; 3) follow-up after surgery equal to or longer than one year. If the follow-up continued after the patient reached 18 years of age, that patient would still be included if the surgery had been performed in pediatric age; 4) a pre- and post-operative measurement of IQ with the WIS; 5) studies in English, French, Spanish or Portuguese published since 2000.

Studies that met the following criteria were excluded: 1) less than 10 participants; 2) adults (over 18 years of age) at the time of surgery; 3) children with follow-up of less than one year; 4) no reference to the type of epilepsy surgical procedure; 5) other intelligence tests; 6) no reference to the pre- and post-operative IQ values; 7) studies not in English, French, Spanish or Portuguese; 8) reviews or meta-analysis; 9) incomplete studies; 10) data present in a different format.

Information Sources and Search Strategy

The following electronic databases were searched, until the final analysis, for relevant literature: PubMed, the Cochrane Library, EMBASE and ClinicalTrials.gov. Only finished studies published in English, French, Spanish, Portuguese and that met the inclusion criteria were used. Only articles published since 2000 were used. The keywords used for this search included: "epilepsy", "epileptic", "surgery", "surgical", "Wechsler Scale" and "intelligence tests". Search terms were combined with operators, such as "AND" and "OR". In PubMed, the filters "human" species, "English, French, Spanish, Portuguese" language and "child: birth - 18 years" age were used. In PubMed, the Cochrane Library and EMBASE, the "year of publication" filter was used to rule out studies published before 2000. In the Cochrane Library and EMBASE the truncations "child*", "infan*" and "adolesce*" were used to cover root words that have multiple endings. In the Cochrane Library, only clinical trials were selected. In ClinicalTrials.gov, the filters "completed", "terminated" and "child (birth - 17)" were applied. A detailed search strategy for PubMed is shown in Appendix III.

Study Selection

One review author (ARA) and one collaborator (Dr. Helena Donato) independently screened titles and abstracts retrieved using the search strategy, as well as those from additional sources, to identify studies that would potentially meet the inclusion criteria stipulated. Duplicates were eliminated. Full texts of these potentially eligible studies were retrieved and two reviewers (ARA and BO PhD) independently applied eligibility criteria to select the appropriate articles.

Data Collection Process and Data Items

Two review authors (ARA and BO PhD) independently extracted relevant data regarding study participants' characteristics, interventions and outcomes, according to the previously stated inclusion criteria. Any uncertainties were resolved by discussion with a third reviewer (CP MD) until consensus was reached. Five study authors (Dr. Anne Vagner Jakobsen PhD, Dr. Christoffer Ehrstedt PhD, Dr. Martin M. Tisdall MD, Dr. Barry Sinclair MD and Dr. Shuli Liang PhD) were contacted to obtain and confirm data regarding their studies.

Data regarding the variables "gender", "age at epilepsy onset", "duration of epilepsy", "age at surgery", "seizure type", "epilepsy type", "etiology", "affected hemisphere", "epilepsy surgery type", "follow-up time", "Engel classification", "Wechsler Intelligence Scale", "pre-surgery IQ" and "post-surgery IQ" was extracted and summarized in a dataset. Since one of the aims of this study was to evaluate the effect of epilepsy surgery on IQ by analyzing preoperative *versus* post-operative IQ values and since these values must have been measured with the WIS, there was no necessity for a comparator/control. However, base values were considered as the comparator for the post-operative values.

Risk of Bias Assessment

The study quality was assessed by two authors (ARA and BO PhD) with the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies. Study heterogeneity was, firstly, analyzed by observing the funnel plot and then confirmed with the I^2 test and Cochran's Q test of heterogeneity. The publication bias was investigated with the Egger's test and the Begg and Mazumdar test after observing the forest and funnel plots.

Summary Measures

The measure of effect was the standardized difference between mean post-operative FSIQ values and mean preoperative FSIQ values (d) reported by individual studies. Since the included studies have reported standard deviations measured in both time points and not the standard deviations from the mean differences between time points, these were estimated according to the procedure reported by Wolfgang Viechtbauer, from the Maastricht University, in his lecture of 2019-02-07, assuming that the correlation between measures of both time points was constant and equal to the correlation measured between studies mean time points ($r = 0.985$).

Synthesis of Results

A descriptive data synthesis was performed to address each of the objectives, focusing on the population characteristics, type of intervention and different outcomes. Then, a meta-analysis of random effects with the eight eligible articles was conducted because of the limited number of studies and because there was a high level of heterogeneity between them.

The RStudio, version 1.3.1093, (©2009-2020 RStudio, PCB) of the R software,²¹ version 4.0.3, (2020-10-10) was used for handling data and conducting meta-analysis. The level of significance (α) considered was 0.05 (5%).

Additional Analysis

A meta-regression was conducted given possible factors or covariables that could influence the outcomes reported in the individual studies and, as such, have an impact in the estimated global effect and variability of IQ. These covariables included: gender (% of males), age of epilepsy onset, duration of epilepsy, age at surgery, etiology (% of dysplasias, % of mesial temporal sclerosis and % of tumors), type of surgery (% of curative surgery), Engel classification (% at grade I) and affected hemisphere (% left hemisphere). The measure of effect was the regression coefficients. Statistical significance was considered by a type I error of 0.05 (5%).

3. Results

Study Selection and Characteristics

A total of 383 articles were identified using the search strategy previously mentioned. Three additional records were identified via other sources. Then, 53 duplicates were removed. Of the remaining 333 articles, 246 were excluded after screening their titles and abstracts, since they did not meet the inclusion criteria. Eighty-seven studies were read in full to assess eligibility. Seventy-four full-text articles were then excluded since they met one or more of the exclusion criteria. The reasons for each exclusion are summarized in Figure 1. In the end, thirteen publications were included in the qualitative synthesis and eight in the meta-analysis. This process of selection is summarized in a flow of information diagram presented in Figure 1.

None of the included studies are randomized control trials (RCTs). Twelve studies are cohorts (ten retrospective and two prospective) and one is a case-control study. For each of these studies, data was extracted regarding study size (number of patients that underwent epilepsy surgery), participant characteristics (gender, age at epilepsy onset, duration of epilepsy, age at surgery, seizure type, etiology, affected hemisphere, Engel Classification, WIS used and pre-surgery IQ), interventions (type of epilepsy surgery), outcomes (post-surgery IQ) as well as the follow-up period (defined as the time from epilepsy surgery to post-surgery neuropsychological evaluation with the WIS). An overview of the extracted data for each study is shown in Table 1.

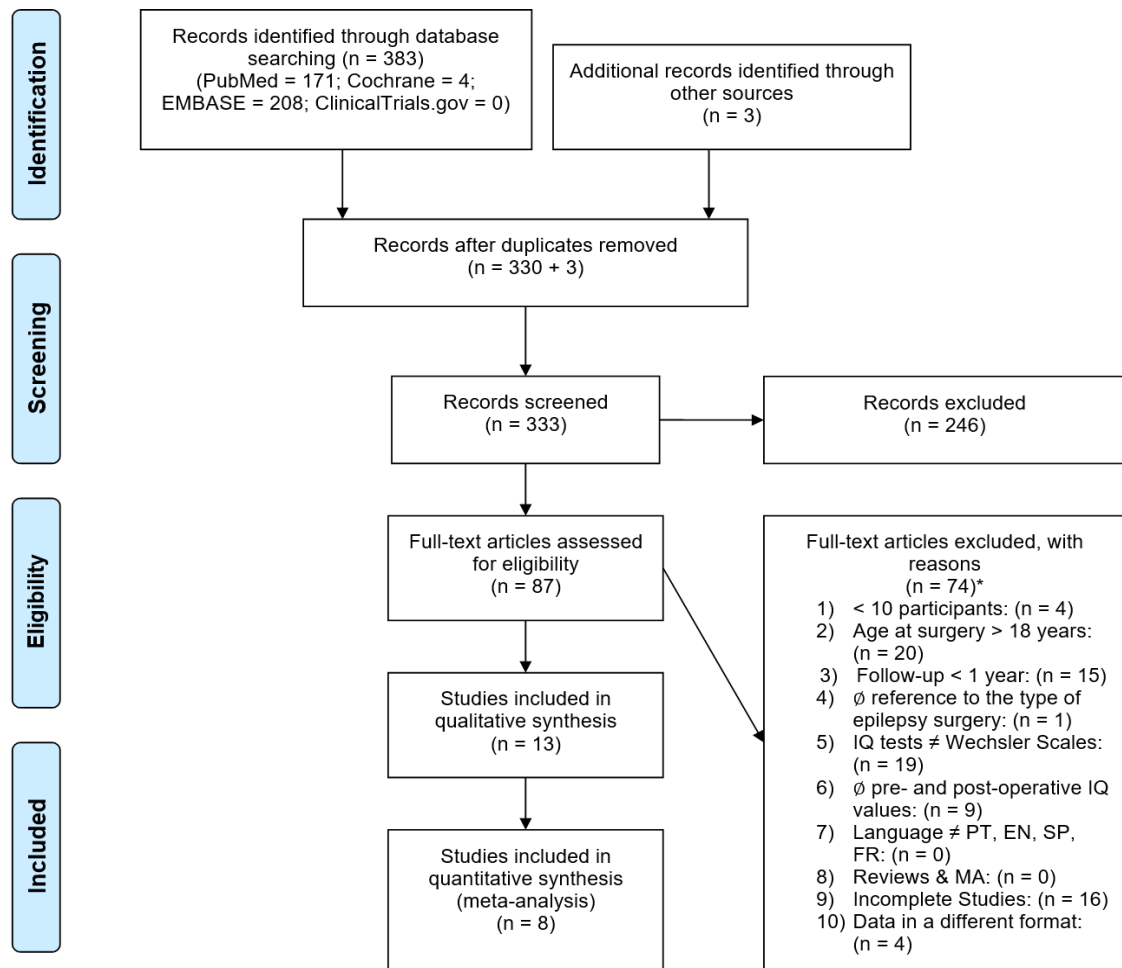


Figure 1 – Flow of information diagram for study selection

* Three studies met exclusion criteria 2) and 5); two studies met exclusion criteria 1) and 3); two studies met exclusion criteria 3) and 5); one study met exclusion criteria 3) and 6); one study met exclusion criteria 5) and 6); one study met exclusion criteria 2) and 6); one study met exclusion criteria 5) and 10); one study met exclusion criteria 2) and 3) and one study met exclusion criteria 3), 4) and 6).

Abbreviations: EN: English; FR: French; IQ: intelligence quotient; MA: meta-analysis; PT: Portuguese; SP: Spanish.

Table 1 – Characteristics of the included studies

Year	Author	Study Design	Study Size	Gender	Age of Epilepsy Onset; Mean (SD)	Duration of Epilepsy; Mean (SD)	Age at Surgery; Mean (SD)	Epilepsy/ Seizure Type	Etiology	Hemisphere	Epilepsy Surgery Type	Follow-up time; Mean (SD) [Range]	Engel Class.	WIS	Pre-surgery IQ; Mean (SD)	Post-surgery IQ; Mean (SD)
2020	Jakobsen AV <i>et al.</i> ²²	Retrospective	n = 43	(M) = 23 (F) = 20	4.4 (2.9)	NA	11.1 (3.3)	FE	Dys: 14 MTS: 13 Other: 15 #n = 42	(L) = 25 (R) = 18	<u>Resection</u> T: 28 EXT: 15	2 [1.9 – 2.4]	I = 28 II-IV = 12 #n = 40	WISC-III	FSIQ = 64.5 (21.2) #n = 28	FSIQ = 70.0 (23.1) #n = 28
2019	Skirrow C <i>et al.</i> ²³	Case Control	Surgery n = 39 Control n = 13	Surgery (M) = 21 (F) = 18 Control (M) = 7 (F) = 6	Surgery 6.3 (4.3) Control 3.9 (3.7)	Surgery 7.4 (4.5) Control* 6.8 (3.5)	Surgery 13.5 (3.2) Control* 10.7 (3.3)	FE	Surgery Dys: 11 MTS: 3 Tumor: 19 Other: 6 Control Dys: 1 MTS: 1 Tumor: 3 Other: 8	Surgery (L) = 23 (R) = 16 Control (L) = 9 (R) = 2 (NL) = 2	<u>Focal Resection</u> T: 17 P: 7 FR: 9 ML: 6	Surgery 7.2 [1.6 – 15.7] Control 5.9 (2.1)*	Surgery I = 28 II-IV = 11 Control I = 2 II-IV = 11	WPPSI-II WPPSI-R WISC-III WISC-IV WAIS-III WAIS-IV WASI	Surgery FSIQ = 86.6 (18.1) Control* FSIQ = 87.8 (14.3)	Surgery FSIQ = 91.3 (18.0) Control* FSIQ = 85.6 (17.1)
2018	Ehrstedt C <i>et al.</i> ²⁴	Retrospective	n = 11	NA	7.7 (5.1)	NA	13.2 (3.5)	FSZ GSZ	Tumor: 11	(L) = 3 (R) = 6 NA = 2	<u>Resection</u> T: 9 EXT: 2	[>2]	I = 9 II-IV = 2	WISC-IV WAIS-IV (Swedish Versions)	FSIQ = 84.1 (21.3)	FSIQ = 95.2 (14.8)
2017	Faramand AM <i>et al.</i> ²⁵	Retrospective Cohort	n = 121	NA	NA	4.2 (2.2 – 8)**	9.3 (6 – 14)**	FSZ	Tumor: 121	(L) = 52 (R) = 40 #n = 92	<u>Lesionectomy</u>	[1]	I = 74 II-IV = 18 #n = 92	WISC	FSIQ = 81 (71 – 95)** #n = 90	FSIQ = 86 (71 – 100)** #n = 41

Table 1 – Characteristics of the included studies (continued)

Year	Author	Study Design	Study Size	Gender	Age of Epilepsy Onset: Mean (SD)	Duration of Epilepsy: Mean (SD)	Age at Surgery: Mean (SD)	Epilepsy/Seizure Type	Etiology	Hemisphere	Epilepsy Surgery Type	Follow-up time: Mean (SD) [Range]	Engel Class.	WIS	Pre-surgery IQ: Mean (SD)	Post-surgery IQ: Mean (SD)
2015	Shurtleff HA <i>et al.</i> ²⁶	Retrospective Cohort	n = 15	NA	NA	1.3 (1.4)	4.9 (1.7)	FSZ	Dys: 2 Gliosis: 1 MTS: 2 Tumor: 10	(L) = 9 (R) = 6	Lesionectomy FR: 3 T: 2 ATL: 4 STL: 3 Superior and middle frontal gyrus: 2 Inferior frontal gyrus: 1	3.4 (1.9) [1.5 – 6.9]	I = 14 II = 1	WPPSI-III WPPSI-R WISC-III WISC-IV WASI	FSIQ = 100 (13.1) VIQ = 103 (18.3) PIQ = 99 (12.4) #n = 11	FSIQ = 106 (17.7) VIQ = 109 (17.2) PIQ = 103 (15.1) #n = 12
2015	Lee YJ <i>et al.</i> ²⁷	Retrospective Cohort	n = 20	(M) = 12 (F) = 8	7.3 (2.9)	6.6 (3.2)	12.8 (3.2)	NA	Dys: 2 MTS: 12 Tumor: 4 Other: 2	(L) = 8 (R) = 12	ATL+AH	3.6 (2.0) [2.5 – 4.8]	I = 14 II = 6	WPPSI WISC WAIS (Korean Versions)	FSIQ = 78.5 (25.0)	FSIQ = 81.5 (25.1)
2014	Liang S <i>et al.</i> ²⁸	Prospective Cohort	Surgery n = 23 Control n = 37	Surgery (M) = 16 (F) = 7 Control (M) = 22 (F) = 15	Surgery 5.1 (1.7) Control 5.4 (1.9)	Surgery 4.4 (2.1) Control* 4.3 (2.2)	Surgery 9.5 (2.2) Control* 9.7 (2.4)	FSZ GSZ	NA	NA	<u>Anterior CC</u>	[2]	Surgery I = 3 II-IV = 20 #n = 23 Control I = 2 II-IV = 32 #n = 34	WISC (Chinese Revision)	Surgery FSIQ = 56.1 VIQ = 57.0 PIQ = 56.2 #n = 23 Control* FSIQ = 55.3 VIQ = 55.4 PIQ = 56.8 #n = 37	Surgery FSIQ = 61.2 VIQ = 60.3 PIQ = 63.6 #n = 23 Control* FSIQ = 51.8 VIQ = 52.3 PIQ = 52.7 #n = 34

Table 1 – Characteristics of the included studies (continued)

Year	Author	Study Design	Study Size	Gender	Age of Epilepsy Onset: Mean (SD)	Duration of Epilepsy: Mean (SD)	Age at Surgery: Mean (SD)	Epilepsy/Seizure Type	Etiology	Hemisphere	Epilepsy Surgery Type	Follow-up time: Mean (SD) [Range]	Engel Class.	WIS	Pre-surgery IQ: Mean (SD)	Post-surgery IQ: Mean (SD)
2013	Lee YJ <i>et al.</i> ²⁹	Retrospective	n = 76	(M) = 54 (F) = 22	2.2 (2.9)	5.4 (3.1)	7.6 (3.7)	FSZ GSZ	Dys: 33 EM: 17 Other: 12 NA: 14	NA	<u>Lobar resection</u> Single lobar: 13 ML: 16 HSPQ: 10 CC: 37	[2]	I = 24 II = 6 III = 4 IV = 5 #n = 39	WISC WAIS (Korean Versions)	FSIQ = 40.4 (14.9) #n = 42	FSIQ = 46.1 (19.0) #n = 27
2012	Liang S <i>et al.</i> ³⁰	Retrospective	n = 206	(M) = 112 (F) = 94	NA	7.7	11.3 (2.4)	FSZ GSZ FE	Dys: 111 EM/ Gliosis: 36 MTS: 38 TS: 4 Tumor: 10 Other: 7	NA	EZR: 107 ATL: 60 SAH: 11 <u>Combined Anterior</u> CC: 28	[2]	I = 149 II = 32 III-IV = 25	WISC (Chinese Version)	FSIQ = 78.0	FSIQ = 84.9
2011	Skirrow C <i>et al.</i> ¹³	Retrospective	Surgery n = 42 Control n = 11	Surgery (M) = 21 (F) = 21 Control (M) = 4 (F) = 7	Surgery 4.0 (4.0) Control 3.7 (3.2)	NA	13.3 (3.1)	FSZ	Surgery MTS: 26 Tumor: 16 Control MTS: 5 NA: 6	Surgery (L) = 25 (R) = 17 Control (L) = 7 (R) = 5	<u>Resection</u> T: 42	[≥5]	Surgery I = 36 II-IV = 6 Control I = 4 II-IV = 7	WISC-R WISC-III WAIS-R WAIS-III	Surgery FSIQ = 82.5 (19.8) Control* FSIQ = 77.1 (18.3)	Surgery FSIQ = 88.5 (20.3) Control* FSIQ = 78.5 (16.5)
2011	Datta AN <i>et al.</i> ³¹	Retrospective	n = 57	(M) = 29 (F) = 28	0.1 – 16	0.5 (0.3)	11.7 (3.9)	NA	Dys: 7 MTS: 11 Tumor: 19 TS: 5 Vascular: 2 Other: 3 NA: 10	(L) = 29 (R) = 27 CC = 1	<u>Resection</u> AT: 30 FR: 11 P: 7 O: 3 ML: 9 CC: 1	[≥1]	I = 38 II = 10 III = 4 IV = 5	WPPSI WISC WAIS	FSIQ = 89.0 VIQ = 89.5 PIQ = 89.6	FSIQ = 89.0 VIQ = 89.9 PIQ = 91.0

Table 1 – Characteristics of the included studies (continued)

Year	Author	Study Design	Study Size	Gender	Age of Epilepsy Onset; Mean (SD)	Duration of Epilepsy; Mean (SD)	Age at Surgery; Mean (SD)	Epilepsy/Seizure Type	Etiology	Hemisphere	Epilepsy Surgery Type	Follow-up time; Mean (SD) [Range]	Engel Class.	WIS	Pre-surgery IQ; Mean (SD)	Post-surgery IQ; Mean (SD)
2009	Lee YJ <i>et al.</i> ³²	Retrospective	n = 19	(M) = 11 (F) = 8	8.3 (3.1)	6.4 (4.0)	14.6 (2.8)	FSZ	Dys: 9 Tumor: 5 MTS: 11 DP: 6	NA	ATL+AH: 14 ATL without AH: 2 Subtotal temporal lobectomy: 3	2.1 [1.2 – 3.5]	I = 12 II = 5 III = 2 IV = 0	Age-appropriate WIS (Korean Version)	FSIQ = 78.1 (25.0) VIQ = 81.7 (24.7) PIQ = 78.1 (23.2)	FSIQ = 78.0 (25.5) VIQ = 80.1 (25.2) PIQ = 78.9 (26.3)
2005	Korkman M <i>et al.</i> ³³	Prospective	n = 38	(M) = 21 (F) = 17	NA	NA	11.6 (4.2)	NA	GC: 19 Tumor: 9 MTS: 5 TS: 1 Other: 4	(L) = 19 (R) = 19	<u>Resection</u> T: 23 EXT: 3 ML: 5 HSPE/HSPO: 7	2 [1.8 – 2.4]	I = 29 II = 3 III = 3 IV = 3	WPPIS-R WISC-R WISC-III WAIS-R	VIQ = 79.3 (20.6) PIQ = 81.3 (20.8)	VIQ = 80.7 (21.9) PIQ = 82.8 (26.0)

The unit of time is year. **Study Size** represents the number of children that underwent epilepsy surgery in each study. **Follow-up time** was defined as the time from epilepsy surgery to the post-operative neuropsychological evaluation with the Wechsler Intelligence Scale. **Surgery** refers to the Surgery Group and **Control** refers to the Control Group. #Represents the number of participants whose data was available. *Baseline values used for Control Groups. **Median (IQR) values.

Abbreviations: AH: amygdalohippocampectomy; AT: anterior temporal; ATL: anterior temporal lobectomy; CC: corpus callosotomy; DP: dual pathology; Dys: dysplasia; EM: encephalomalacia; EXT: extratemporal; EZR: epileptogenic zone resection (including lesion resection); F: female; FE: focal epilepsy; FR: frontal; FSIQ: full-scale intelligence quotient; FSZ: focal seizures; GC: gliotic change; GSZ: generalized seizures; HSPE: hemispherectomy; HSPO: hemispherotomy; L: left; M: male; ML: multilobar; MTS: mesial temporal sclerosis; NA: not available; NL: non-localizing; O: occipital; P: parietal; PIQ: performance intelligence quotient; R: right; SAH: selective amygdalohippocampectomy; SLT: selective temporal lobectomy; T: temporal; TS: tuberous sclerosis; VIQ: verbal intelligence quotient; WAIS: Wechsler Adult Intelligence Scale; WASI: Wechsler Abbreviated Scale of Intelligence; WIS: Wechsler Intelligence Scale; WISC: Wechsler Intelligence Scale for Children; WPPIS: Wechsler Preschool and Primary Scale of Intelligence.

Risk of Bias Assessment

None of the included articles were considered of poor quality. Overall, no selection bias was identified. The quality assessment for each cohort and case-control study is reported in Table 2 and Table 3, respectively.

By observing the funnel plot (Appendix IV), the studies included in the meta-analysis appeared to have a high level of heterogeneity which was later confirmed by the I^2 and Cochran's Q test of heterogeneity ($I^2 = 85.52\%$; $Q(7) = 43.70$ ($p < 0.001$)). We may assume that there is no publication bias as the effect size is not correlated with its variance (Begg-Mazumdar test: Kendall tau = 0.143; $p = 0.720$) and is independent from study precision (Egger regression: $b = -0.034$; $p = 0.868$).

Table 2 – Quality assessment for cohort studies with the Newcastle-Ottawa Scale

	Selection	Comparability	Outcome	Total (in 9*)
<i>Jakobsen AV, 2020</i> ²²	***	**	*	6*
<i>Ehrstedt C, 2018</i> ²⁴	***	*	**	6*
<i>Faramand AM, 2017</i> ²⁵	***	**	*	6*
<i>Shurleff HA, 2015</i> ²⁶	***	**	**	7*
<i>Lee YJ, 2015</i> ²⁷	***	**	**	7*
<i>Liang S, 2014</i> ²⁸	***	**	**	7*
<i>Lee YJ, 2013</i> ²⁹	***	**	*	6*
<i>Liang S, 2012</i> ³⁰	**	*	**	5*
<i>Skirrow C, 2011</i> ¹³	****	**	**	8*
<i>Datta AN, 2011</i> ³¹	***	*	**	6*
<i>Lee YJ, 2009</i> ³²	***	**	**	7*
<i>Korkman M, 2005</i> ³³	***	**	**	7*

Table 3 – Quality assessment for case-control studies with the Newcastle-Ottawa Scale

	Selection	Comparability	Exposure	Total (in 9*)
<i>Skirrow C, 2019</i> ²³	***	**	**	7*

Results of Individual Studies

- Overall effect of epilepsy surgery on post-operative IQ values

Overall, none of the publications included reported a significant decline in IQ values after surgery, regardless of the surgical procedure. However, since different follow-up periods were reported among these studies, three subgroups were made for a more accurate analysis: a short follow-up group (one year), a medium follow-up group (two years) and a long follow-up group (three or more years).

Three studies^{25,29,31} reported that the effect of surgery was not significant in post-operative IQ after one year of follow-up. Two studies^{32,33} with a two-year follow-up period reported no significant post-operative IQ changes. On the other hand, three studies^{22,28,29} reported an overall significant improvement. Finally, in the long follow-up group, two studies^{26,27} reported that the effect of surgery was not significant in the post-surgical IQ values whereas two studies^{13,24} reported a significant improvement and one study²³ reported a modest improvement. These results are shown in Table 4.

At an individual level, in Jakobsen AV,²² 35% of the sample had their FSIQ improved more than 10 points, 56% were unchanged and 9% underwent a decrease of more than 10 points. In Faramand AM,²⁵ 61% had a median gain of eight points in FSIQ, 2.5% had no change and 36.5% had a median decline of six points. Skirrow C, 2019²³ reported a gain in FSIQ of at least 10 points in 39% of the surgery patients.

Table 4 – Overall effect of epilepsy surgery in post-operative IQ values

	Short follow-up	Medium follow-up	Long follow-up
<i>Jakobsen AV, 2020</i> ²²	-----	Significant improvement	-----
<i>Skirrow C, 2019</i> ²³	-----	-----	Improvement
<i>Ehrstedt C, 2018</i> ²⁴	-----	-----	Significant improvement
<i>Faramand AM, 2017</i> ²⁵	No significant effect	-----	-----
<i>Shurleff HA, 2015</i> ²⁶	-----	-----	No significant effect
<i>Lee YJ, 2015</i> ²⁷	-----	-----	No significant effect
<i>Liang S, 2014</i> ²⁸	-----	Significant improvement	-----
<i>Lee YJ, 2013</i> ²⁹	No significant effect	Significant improvement	-----
<i>Liang S, 2012</i> ³⁰	-----	Improvement	-----
<i>Skirrow C, 2011</i> ¹³	-----	-----	Significant improvement
<i>Datta AN, 2011</i> ³¹	No significant effect	-----	-----
<i>Lee YJ, 2009</i> ³²	-----	No significant effect	-----
<i>Korkman M, 2005</i> ³³	-----	No significant effect	-----

- Effect of curative vs palliative surgical procedures in post-operative IQ values

In eleven studies, a curative surgical procedure (lesionectomy, lobectomy, selective amygdalohippocampectomy) was used for epilepsy treatment, whereas two studies^{28,30} reported IQ changes after palliative interventions (CC). Hemispherectomy/hemispherotomy was reported in one study.³³ In one study with 76 Lennox-Gastaut syndrome patients,²⁹ the surgical approaches included lobar resections, hemispherotomies and CCs. However, changes in IQ outcome regarding each type of surgery were not analyzed.

Considering all the studies with curative surgeries, only three^{13,22,24} reported an overall significant improvement in IQ after surgery. Two of them^{13,24} were also the ones with a longer follow-up period. Two studies^{23,30} also reported an increase in IQ values.

Both studies with CC^{28,30} reported a significant improvement in IQ values two years after surgery. In one of these studies,³⁰ CC was used combined with a curative procedure in 28 patients whereas the remaining 178 patients underwent a curative procedure (169 had a normal IQ and nine had a low IQ before surgery). It was found that the participants with

preoperative low IQ (FSIQ = 60.2) who underwent CC significantly improved their IQs (a +9.6 change; $p < 0.05$) when compared with those with normal (FSIQ = 81.8) or low (FSIQ = 62.1) preoperative IQs that did not undergo CC (a +6.4 and +7.4 change respectively). In the other study,²⁸ it was found that the surgery group (with 23 participants) had a +5.1 change in FSIQ after CC ($p < 0.01$) whereas the medicine group (with 37 participants) had a -3.6 change. It was also reported that both VIQ and PIQ significantly improved in the surgical group (+3.3 and +7.1 change; $p < 0.01$). On the other hand, the medicine group VIQ and PIQ values declined in the same follow-up time (-3.1 and -4.0 change respectively).

In one study,³³ the IQ outcome of the hemispherectomy group (seven patients) was compared with the post-surgical IQ of the temporal lobe resection group (23 participants) and the extratemporal/multilobar resection group (8 participants) after two years of follow-up. A significant between groups effect of type of surgery was found ($p < 0.001$), where the hemispherectomy group had a significant lower VIQ and PIQ than the other groups ($p < 0.01$). Both VIQ and PIQ changed from a mean of 60.9 to 55.1 and from 61.4 to 51.3, respectively, after two years of follow-up. These conclusions can be seen in Table 5.

Table 5 – Effect of curative vs palliative surgical procedures in post-operative IQ values

	Curative Surgery	Corpus Callosotomy	Hemispherectomy/ Hemispherotomy
<i>Jakobsen AV, 2020</i> ²²	Significant improvement	-----	-----
<i>Skirrow C, 2019</i> ²³	Improvement	-----	-----
<i>Ehrstedt C, 2018</i> ²⁴	Significant improvement	-----	-----
<i>Faramand AM, 2017</i> ²⁵	No significant effect	-----	-----
<i>Shurleff HA, 2015</i> ²⁶	No significant effect	-----	-----
<i>Lee YJ, 2015</i> ²⁷	No significant effect	-----	-----
<i>Liang S, 2014</i> ²⁸	-----	Significant Improvement	-----
<i>Lee YJ, 2013</i> ²⁹	Not analyzed	Not analyzed	Not analyzed
<i>Liang S, 2012</i> ³⁰	Improvement	Significant Improvement	-----
<i>Skirrow C, 2011</i> ¹³	Significant improvement	-----	-----
<i>Datta AN, 2011</i> ³¹	No significant effect	-----	-----
<i>Lee YJ, 2009</i> ³²	No significant effect	-----	-----
<i>Korkman M, 2005</i> ³³	No significant effect	-----	Decline

- Factors with prognostic value for post-operative IQ

Lee YJ, 2015²⁷ and Korkman M³³ analyzed the possible relation between gender and FSIQ change but no correlation was reported.

Age of epilepsy onset did not significantly influence post-operative FSIQ in two studies (Skirrow C, 2011¹³ and Faramand AM²⁵). Lee YJ, 2015²⁷ found that later onset of epilepsy was a good predictor of post-operative FSIQ ($p = 0.046$) and children with declines over five negative points in FSIQ and VIQ were of early age at onset. Skirrow C, 2019²³ also reported a similar significant correlation ($p = 0.001$), although later age at epilepsy onset did not correlate with FSIQ change ($p = 0.88$).

Shorter duration of epilepsy was associated with higher gains in FSIQ in three studies (+13 points in Shurleff HA;²⁶ $\geq +5$ points in Lee YJ, 2015²⁷ and +9.5 points vs +0.9 points in Lee YJ, 2013²⁹) when compared with longer durations. However, these differences were only statistically significant in the Lee studies.^{27,29} Lee YJ, 2015²⁷ also reported that shorter epilepsy duration was a good predictor of PIQ after surgery (a gain over five points). In three different studies (Jakobsen AV;²² Faramand AM²⁵ and Skirrow C, 2011¹³) no correlation between post-operative FSIQ and duration of epilepsy was found. In Skirrow C, 2019,²³ it was reported that post-operative FSIQ was inversely correlated with a longer duration of epilepsy but there was no correlation with FSIQ change between pre- and post-surgery.

Age at surgery was not correlated with FSIQ change in four studies (Skirrow C, 2019;²³ Faramand AM;²⁵ Lee YJ, 2015²⁷ and Liang S, 2014²⁸). Liang S, 2012³⁰ mentioned that early age of surgery might prevent long-term impairment of intelligence and Korkman M³³ reported that children who underwent interventions at younger ages had poorer IQ outcome.

Regarding Engel classification, four studies (Jakobsen AV;²² Lee YJ, 2015;²⁷ Lee YJ 2013²⁹ and Liang S, 2012³⁰) reported that Engel classification I was a good predictor of post-operative FSIQ since seizure-free patients had significantly higher FSIQ gains when compared with the non-seizure-free. On the other hand, Skirrow C, 2019;²³ Liang S, 2014;²⁸ Skirrow C, 2011¹³ and Korkman M³³ found no significant association between post-operative seizure status and FSIQ change.

When it comes to the affected hemisphere, the four studies that studied a possible association between intervened hemisphere and FSIQ change^{22,23,26,27} found no significant association. On the other hand, Jakobsen AV²² reported that VCI statistically improved in right-handed children with left hemisphere surgery and that all children with left-sided temporal surgery maintained

or improved their VCI values. Skirrow C, 2011¹³ found VIQ improvements only in the left hemisphere surgery group. Korkman M³³ reported that the left hemisphere group tended to have poorer VIQ outcome although not statistically significant. This could be due to the fact that there were more left hemispherectomy patients in this study and this surgery is usually performed in patients with lower base IQ values.

Skirrow C, 2019²³ and Lee YJ, 2015²⁷ reported no correlation between etiology and FSIQ change.

Skirrow C, 2019²³ mentioned that longer duration of follow-up was associated with greater IQ improvement.

Four studies (Jakobsen AV;²² Lee YJ, 2015;²⁷ Lee YJ 2013²⁹ and Skirrow C, 2011¹³) reported that antiepileptic drugs (AED) reduction after surgery was a good predictor of post-operative FSIQ. Furthermore, Skirrow C, 2011¹³ mentioned that maintaining AED, mainly topiramate, was a bad predictor for FSIQ outcome. However, Skirrow C, 2019²³ found no correlation between AED cessation and IQ change.

Synthesis of Results

By observing the forest plot (Figure 2), the meta-analysis of the eight included studies found a mean difference between post-operative and preoperative FSIQ values of 1.014 standardized points ($p < 0.001$; 95%CI: 0.589 to 1.437).

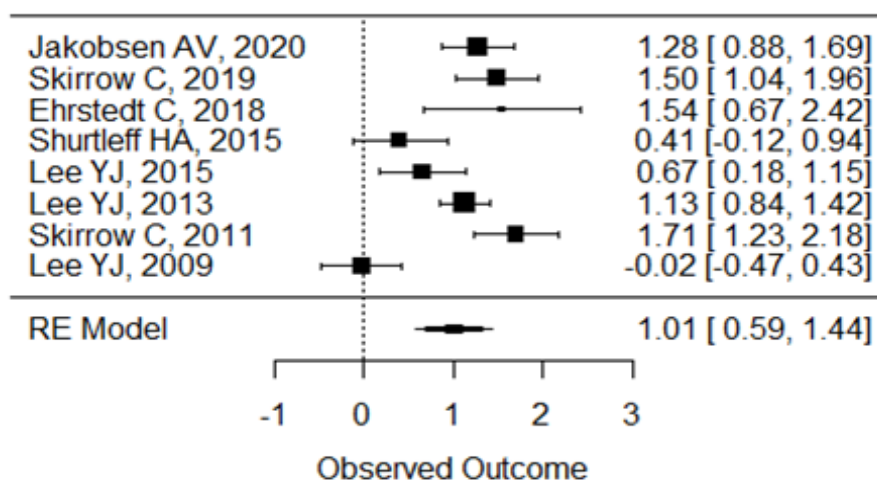


Figure 2 – Forest plot

Additional Analysis

The meta-regression conducted, considering each one of the moderators described in Table 6, did not find any predictors of FSIQ change, which indicates that the effect of surgery is independent of gender, age of epilepsy onset, duration of epilepsy, age at surgery, etiology (at least from dysplasias, MTS and tumors since only these were analyzed), type of surgery (curative vs palliative surgery), Engel classification, affected hemisphere and follow-up duration ($p > 0.05$ for all).

Table 6 – Meta-regression coefficients using each of the listed variables as moderators

Variable	Coefficient b (p value)
Gender (% Males)	-2.3811 (0.5917)
Age of Epilepsy Onset	-0.1983 (0.1103)
Duration of Epilepsy	0.0969 (0.5747)
Age at Surgery	0.0269 (0.7606)
% Dysplasias	-0.0442 (0.9814)
% MTS	-0.4621 (0.7335)
% Tumor	0.9573 (0.4192)
Type of Surgery (% Just curative surgery)	-0.2203 (0.8410)
Engel Classification (% Engel Class. = I)	0.9692 (0.6576)
Affected Hemisphere (% Left hemisphere)	1.4831 (0.9577)
Follow-up Duration (years)	0.0897 (0.5167)

4. Discussion

Summary of Evidence

The first conclusion to be drawn is that none of the publications included reported a significant decline in IQ values after surgery, regardless of the surgical procedure. Moreover, the meta-analysis of the eight included studies found a mean difference between post-operative and preoperative FSIQ values of +1.014 standardized points. This is of great importance since parents concerned with possible adverse effects of epilepsy surgery on their children's intelligence³¹ can be reassured that this is not expected to happen. Furthermore, children with RE who were not in a special education program before surgery are unlikely to require one for intellectual disability after surgery.^{34,35}

Another major finding of this work is that palliative procedures – mainly CC – which are used in epileptic syndromes associated with RE, such as the Lennox-Gastaut Syndrome, have a positive effect on IQ in the studies analyzed. In one of these studies, (Liang S, 2014²⁸), FSIQ, VIQ and PIQ significantly improved in the surgical group when compared with the medicine group (whose three quotients declined in the same follow-up time). These results are in contrast to the findings of a meta-analysis about CC with both children and adult patients.⁹ It should be noted that only studies from 1969 to 2011 with a patient's age at surgery of at least 10 years met the inclusion criteria for that meta-analysis. This means that studies such as Liang S, 2014²⁸ were not included. Furthermore, both partial and complete CC were included in that meta-analysis, while in both of Liang's studies the surgical procedure used was an anterior CC. Although the type of CC (partial vs complete) was not statistically correlated with any of the IQ changes, two studies^{36,37} reported positive correlations between callosal morphology and intelligence measures, mainly in posterior callosal sections. This means that posterior regions of the corpus callosum might be important in explaining the anatomical substrates of intelligence. Selective removal of these regions could have a more negative impact on IQ change when compared with selective anterior CC. Therefore, further investigation in this area is required to draw more robust conclusions.

On the other hand, after analyzing possible predictors of post-operative IQ improvement such as gender, age of epilepsy onset, duration of epilepsy, age at surgery, etiology, Engel Classification, affected hemisphere and follow-up duration, this meta-analysis did not find any statistically significant differences. Since RE is associated with neurocognitive impairment, it was expected that a shorter duration of epilepsy and a post-operative seizure-free status would have a significant impact on IQ. A study about unknown onset epilepsy (previously referred to

as cryptogenic localization epilepsy)³⁸ also reported no significant IQ differences (addressed with the WISC-R) regarding epilepsy duration and seizure frequency. A longer follow-up duration was expected to positively correlate with post-operative IQ improvement since several studies with shorter follow-up duration did not find any intellectual gains.¹³ This was one of the reasons why only studies with at least one year of follow-up were included in this work.

Finally, the meta-regression coefficient of the variable “type of surgery” should be interpreted with caution because almost all of the included studies used curative procedures and most of them did not significantly influence IQ at an individual study level. Hemispherectomy and hemispherotomy were not part of this variable since they can be both curative and palliative. Because of the limited number of articles regarding these procedures, no solid conclusions could be drawn on how they might impact post-operative IQ.

Limitations

This study had several limitations. Firstly, no RCTs met the inclusion criteria. Because of this, only cohorts and one case-control study were included. Furthermore, most of these studies had a retrospective design, which has the disadvantage of having to rely on accurate recordkeeping and, as a result, limited the available data for further analysis. Secondly, the limited number of studies reporting IQ outcome after palliative surgeries in pediatric age significantly restricted the possibility of drawing solid conclusions regarding how these procedures might affect intelligence in children with RE. Thirdly, since only studies with IQ assessment with WISs were included and since these scales are not available for children with less than three years, this age group was not the focus of study in the articles included. Moreover, in some papers, children with severe cognitive impairment were excluded since they were not able to complete the WIS questionnaires. This is one of the reasons why there were so few articles regarding hemispherectomy/hemispherotomy, since these procedures are usually performed in children whose condition is related to intellectual disability. One way of studying the two previous groups would be to include articles where the post-operative developmental quotient (DQ) was compared with the preoperative DQ. This quotient can be addressed with development scales, such as the Bayley Scales and the Griffiths Scales of Development.^{39,40} Another way would be to include articles where DQ was considered equivalent to IQ, since this would reduce heterogeneity.⁴⁰ However, this would create a bias because developmental tests do not measure the same functions as IQ tests. Although some authors state that DQ and later IQ are highly correlated,^{41,42} DQ tests should not be considered as alternative assessments to measure IQ.

Conclusions

In spite of all the limitations of this meta-analysis and the high level of heterogeneity between studies, epilepsy surgery in pediatric age seems to have an overall positive impact on IQ. Parents of children with refractory epilepsy can be reassured that significant post-operative intellectual declines are not expected. It is not expected that a special education program for intellectual disability after surgery will be required. Anterior corpus callosotomy also appears to have a positive effect on IQ, although whether this improvement differs from the one obtained with curative procedures could not be accurately inferred with the available studies. No good predictors of post-operative IQ were found. Further research in these fields is required to draw more solid conclusions.

5. Funding

No funding was provided for this study.

6. Acknowledgements

Firstly, I would like to express my sincere gratitude to my advisors, Professor Dr. Bárbara Oliveiros and Professor Cristina Duarte Pereira, for their guidance and advice throughout this work and for their profound belief in my capacities.

I would also like to acknowledge Professor Helena Donato for helping with the article screening and her assistant, Maria Elvira Mendes Rafael, for providing some of the full-text articles required.

Finally, I am deeply grateful to my parents, grand-parents and closer friends for their constant support and never-ending patience, to whom I dedicate this thesis.

7. References

1. Aaberg KM, Gunnes N, Bakken IJ, Lund Søråas C, Berntsen A, Magnus P, *et al.* Incidence and Prevalence of Childhood Epilepsy: A Nationwide Cohort Study. *Pediatrics*. 2017 May; 139(5): e20163908. doi: 10.1542/peds.2016-3908. Epub 2017 Apr 5. PMID: 28557750.
2. Pereira C, Robalo C. Capítulo 40. Fenómenos paroxísticos, crises epiléticas e epilepsias. In Oliveira G, Saraiva J, Mota HC, Canha J, editors. *Lições de Pediatria*. Coimbra: Imprensa da Universidade de Coimbra, 2017: Vol. II, p. 271.
3. Camfield P, Camfield C. Incidence, prevalence and aetiology of seizures and epilepsy in children. *Epileptic Disord*. 2015 Jun; 17(2): 117-23. doi: 10.1684/epd.2015.0736. PMID: 25895502.
4. Maia C, Moreira AR, Martins C. Epilepsia em idade pediátrica: casuística da consulta de pediatria de um hospital distrital. *Nascer e Crescer*. 2017 Jun; 26(2): 109-13. ISSN 2183-9417.
5. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, *et al.* Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2010 Jun; 51(6): 1069-77. doi: 10.1111/j.1528-1167.2009.02397.x. Epub 2009 Nov 3. Erratum in: *Epilepsia*. 2010 Sep; 51(9):1922. PMID: 19889013.
6. Engel J Jr. Approaches to refractory epilepsy. *Ann Indian Acad Neurol*. 2014 Mar; 17(Suppl 1): S12-7. doi: 10.4103/0972-2327.128644. PMID: 24791078; PMCID: PMC4001229.
7. Bromfield EB. Chapter 4, Epilepsy Surgery. In Bromfield EB, Cavazos JE, Sirven JI, editors. *An Introduction to Epilepsy* [Internet]. West Hartford (CT): American Epilepsy Society, 2006. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK2514/>.
8. Baumgartner JE, Ajmal FQ. Palliative Surgical Techniques (VNS, Callosotomy). In Di Rocco C, Pang D, Rutka J, editors. *Textbook of Pediatric Neurosurgery* [Internet]. Springer: Cham, 2018: 1-24. Available from: doi.org/10.1007/978-3-319-31512-6_101-1.
9. Westerhausen R, Karud CMR. Callosotomy affects performance IQ: A meta-analysis of individual participant data. *Neurosci Lett*. 2018 Feb 5; 665: 43-47. doi: 10.1016/j.neulet.2017.11.040. Epub 2017 Nov 22. PMID: 29174639.

10. Tay TT, Reed DR, Josan VJ, Rust SR, Tan JT. Seizure, developmental and cognitive outcomes in children post hemispherotomy. *Developmental Medicine and Child Neurology*. Mac Keith Press, 2020. 62 (Suppl. 1), 18. doi.org/10.1111/dmcn.14411.
11. Silva JR, Sakamoto AC, Thomé Ú, Escorsi-Rosset S, Santos MV, Machado HR, *et al*. Left hemispherectomy in older children and adolescents: outcome of cognitive abilities. *Childs Nerv Syst*. 2020 Jun; 36(6): 1275-1282. doi: 10.1007/s00381-019-04377-9. Epub 2019 Dec 3. PMID: 31797069.
12. de Knecht VE, Hoei-Hansen CE, Knudsen M, Jakobsen AV, Müller E, Thomsen KM, *et al*. Increase in cognitive function is seen in many single-operated pediatric patients after epilepsy surgery. *Seizure*. 2020 Oct; 81: 254-262. doi: 10.1016/j.seizure.2020.08.002. Epub 2020 Aug 28. PMID: 32911236.
13. Skirrow C, Cross JH, Cormack F, Harkness W, Vargha-Khadem F, Baldeweg T. Long-term intellectual outcome after temporal lobe surgery in childhood. *Neurology*. 2011 Apr; 76(15): 1330–1337. doi: 10.1212/WNL.0b013e31821527f0. PMCID: PMC3090063. PMID: 21482948.
14. Puka K, Khattab M, Kerr EN, Smith ML. Academic achievement one year after resective epilepsy surgery in children. *Epilepsy Behav*. 2015 Jun; 47: 1-5. doi: 10.1016/j.yebeh.2015.04.062. Epub 2015 May 15. PMID: 25988982.
15. Kuehn SM, Keene DL, Richards PMP, Ventureyra ECG. Are There Changes in Intelligence and Memory Functioning Following Surgery for the Treatment of Refractory Epilepsy in Childhood?. *Childs Nerv Syst*. 2002 Jul; 18(6-7): 306-10. doi: 10.1007/s00381-002-0599-7. Epub 2002 May 25. PMID: 12172937.
16. Stepien KM, McCarthy P, Treacy EP, O'Byrne JJ, Pastores GM. Neurocognitive assessments and long-term outcome in an adult with 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency. *Mol Genet Metab Rep*. 2018 Jun; 16: 31-35. doi: 10.1016/j.ymgmr.2018.06.005. eCollection 2018 Sep. PMCID: PMC6019692. PMID: 30013934.
17. Mungketklang C, Crewther SG, Bavin EL, Goharpey N, Parsons C. Comparison of Measures of Ability in Adolescents with Intellectual Disability. *Front Psychol*. 2016 May; 7: 683. doi: 10.3389/fpsyg.2016.00683. eCollection 2016. PMCID: PMC4868842. PMID: 27242597.

18. The Wechsler Family of Gold Standard Assessments. Be part of the future, by building on the past [Internet]. Pearson; 2017. Available from: <https://www.pearsonclinical.co.uk/Sitedownloads/Catalogues/2018-wechsler-family-brochure.pdf>.
19. Lange RT. Verbal Comprehension Index. In Kreutzer JS, DeLuca J, Caplan B, editors. *Encyclopedia of Clinical Neuropsychology*. Springer: New York, 2011: 193.
20. Efficacy Research Report WISC-V [Internet]. Pearson; 2017. Available from: <https://www.pearson.com/content/dam/one-dot-com/one-dot-com/global/Files/efficacy-and-research/reports/WISC-V-Research-Report-2016.pdf>.
21. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; 2020.
22. Jakobsen AV, Müller E, Uldall PV. A methodological perspective on the cognitive outcome of epilepsy surgery in children and adolescents. *Epilepsy Behav*. 2020 Oct; 111:107330. doi: 10.1016/j.yebeh.2020.107330. Epub 2020 Jul 23. PMID: 32759075.
23. Skirrow C, Cross JH, Owens R, Weiss-Croft L, Martin-Sanfilippo P, Banks T, *et al*. Determinants of IQ outcome after focal epilepsy surgery in childhood: A longitudinal case-control neuroimaging study. *Epilepsia*. 2019 May; 60(5): 872-884. doi: 10.1111/epi.14707. Epub 2019 Apr 10. PMID: 30968956.
24. Ehrstedt C, Rydell AM, Hallsten MG, Strömberg B, Ahlsten G. Cognition, health-related quality of life, and mood in children and young adults diagnosed with a glioneuronal tumor in childhood. *Epilepsy Behav*. 2018 Jun; 83: 59-66. doi: 10.1016/j.yebeh.2018.03.026. Epub 2018 Apr 11. PMID: 29654937.
25. Faramand AM, Barnes N, Harrison S, Gunny R, Jacques T, Tahir MZ, *et al*. Seizure and cognitive outcomes after resection of glioneuronal tumors in children. *Epilepsia*. 2018 Jan; 59(1): 170-178. doi: 10.1111/epi.13961. Epub 2017 Nov 26. PMID: 29178251.
26. Shurtleff HA, Barry D, Firman T, Warner MH, Aguilar-Estrada RL, Saneto RP, *et al*. Impact of epilepsy surgery on development of preschool children: identification of a cohort likely to benefit from early intervention. *J Neurosurg Pediatr*. 2015 Oct; 16(4): 383-92. doi: 10.3171/2015.3.PEDS14359. Epub 2015 Jul 3. PMID: 26140458.

27. Lee YJ, Kang HC, Kim HD, Kim DS, Shim KW, Eom S, *et al.* Neurocognitive function in children after anterior temporal lobectomy with amygdalohippocampectomy. *Pediatr Neurol.* 2015 Jan; 52(1): 88-93. doi: 10.1016/j.pediatrneurol.2014.09.006. Epub 2014 Sep 18. PMID: 25439484.
28. Liang S, Zhang S, Hu X, Zhang Z, Fu X, Jiang H, *et al.* Anterior corpus callosotomy in school-aged children with Lennox–Gastaut syndrome: A prospective study. *Eur J Paediatr Neurol.* 2014 Nov; 18(6): 670-6. doi: 10.1016/j.ejpn.2014.05.004. Epub 2014 May 22. PMID: 24912732.
29. Lee YJ, Lee JS, Kang HC, Kim DS, Shim KW, Eom S, *et al.* Outcomes of epilepsy surgery in childhood-onset epileptic encephalopathy. *Brain Dev.* 2014 Jun; 36(6): 496-504. doi: 10.1016/j.braindev.2013.06.010. Epub 2013 Jul 11. PMID: 23850002.
30. Liang S, Wang S, Zhang J, Ding C, Zhang Z, Fu X, *et al.* Long-term outcomes of epilepsy surgery in school-aged children with partial epilepsy. *Pediatr Neurol.* 2012 Oct; 47(4): 284-90. doi: 10.1016/j.pediatrneurol.2012.06.014. PMID: 22964443.
31. Datta AN, Snyder TJ, Wheatley MB, Jurasek L, Ahmed NS, Gross DW, *et al.* Intelligence quotient is not affected by epilepsy surgery in childhood. *Pediatr Neurol.* 2011 Feb; 44(2): 117-21. doi: 10.1016/j.pediatrneurol.2010.10.011. PMID: 21215911.
32. Lee YJ, Kang HC, Bae SJ, Kim HD, Kim JT, Lee BI, *et al.* Comparison of temporal lobectomies of children and adults with intractable temporal lobe epilepsy. *Childs Nerv Syst.* 2010 Feb; 26(2): 177-83. doi: 10.1007/s00381-009-1015-3. Epub 2009 Nov 10. PMID: 19902220.
33. Korkman M, Granström ML, Kantola-Sorsa E, Gaily E, Paetau R, Liukkonen E, *et al.* Two-year follow-up of intelligence after pediatric epilepsy surgery. *Pediatr Neurol.* 2005 Sep; 33(3): 173-8. doi: 10.1016/j.pediatrneurol.2005.04.006. PMID: 16139731.
34. Ojeda ABB, Carugno P. Special Education. [Updated 2020 Nov 21]. In StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK499857/>.
35. Sec. 300.8 Child with a disability. [Updated 2018 May 25]. In IDEA Individuals with Disabilities Education Act [Internet]. Available from: <https://sites.ed.gov/idea/regs/b/a/300.8>.

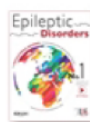
36. Alaei A, Zarei R, Farnia S, Khademloo M. Relationship Between Anterior Commissure and Corpus Callosum Size and Human Intelligence in Brain MRI of Healthy Volunteers, *Iran J Radiol.* 2020 Jan; 17(1):e66706. [Online ahead of Print]. doi: 10.5812/iranjradiol.66706.
37. Luders E, Narr KL, Bilder RM, Thompson PM, Szeszko PR, Hamilton L. *et al.* Positive correlations between corpus callosum thickness and intelligence. *Neuroimage.* 2007 Oct 1; 37(4): 1457-64. doi: 10.1016/j.neuroimage.2007.06.028. Epub 2007 Jul 12. PMID: 17689267; PMCID: PMC2754582.
38. van Mil SGM, Reijs RP, van Hall MHJA, Aldenkamp AP. The effect of duration of epilepsy on IQ in children with CLRE; a comparison to SLRE and IGE. *Seizure.* 2008 Jun; 17(4): 308-13. doi: 10.1016/j.seizure.2007.10.001. Epub 2007 Nov 19. PMID: 18023367.
39. Stein MT, Lukasik MK. Chapter 79 - Developmental Screening and Assessment: Infants, Toddlers, and Preschoolers. In Carey WB, Crocker AC, Coleman WL, Elias ER, Feldman HM, editors. *Developmental-Behavioral Pediatrics (Fourth Edition)*. W.B. Saunders, 2009: 804.
40. Viggedal G, Olsson I, Carlsson G, Rydenhag B, Uvebrant P. Intelligence two years after epilepsy surgery in children. *Epilepsy Behav.* 2013 Dec; 29(3): 565-70. doi: 10.1016/j.yebeh.2013.10.012. Epub 2013 Nov 5. PMID: 24201119.
41. Kurita H, Osada H, Shimizu K, Tachimori H. Validity of DQ as an estimate of IQ in children with autistic disorder. *Psychiatry Clin Neurosci.* 2003 Apr; 57(2): 231-3. doi: 10.1046/j.1440-1819.2003.01106.x. PMID: 12667172.
42. Eun JJ, Lee HJ, Kim JK. Developmental profiles of preschool children with delayed language development. *Korean J Pediatr.* 2014 Aug; 57(8): 363-9. doi: 10.3345/kjp.2014.57.8.363. Epub 2014 Aug 25. Erratum in: *Korean J Pediatr.* 2016 Sep;59(9):386. PMID: 25210524; PMCID: PMC4155181.

Appendices

Intelligence Quotient outcome following epilepsy surgery in pediatric age - a Systematic Review and Meta-Analysis

From	To	Date	Subject
CRD-REGISTER	"am_roid@hotmail.com"	Fri, 26 Mar 2021 09:51:48 +0000	PROSPERO Registration message [216548]
CRD-REGISTER	"am_roid@hotmail.com"	Sat, 6 Feb 2021 01:08:24 +0000	PROSPERO acknowledgement of receipt [216548]
CRD-REGISTER	am_roid@hotmail.com	Tue, 01 Dec 2020 22:00:52 -0800 (PST)	PROSPERO Registration message [216548]
CRD-REGISTER	"am_roid@hotmail.com"	Sun, 1 Nov 2020 14:39:48 +0000	PROSPERO acknowledgement of receipt [216548]

Appendix I – PROSPERO protocol information



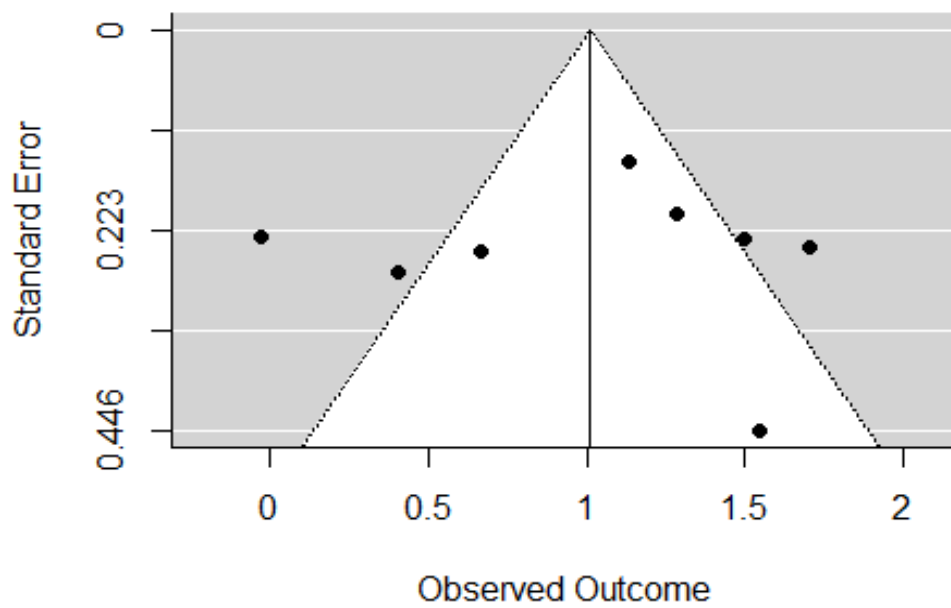
Intelligence quotient outcome following epilepsy surgery in pediatric age – a Systematic Review and Meta-Analysis

Journal:	<i>Epileptic Disorders</i>
Manuscript ID	ED-2021-03-0083
Manuscript Type:	Review Article
Date Submitted by the Author:	12-Mar-2021
Complete List of Authors:	Roldão Alferes, Alexandre; University of Coimbra Faculty of Medicine, Faculty of Medicine Oliveiros, Bárbara; University of Coimbra Faculty of Medicine, Laboratory of Biostatistics and Medical Informatics Pereira, Cristina; Centro Hospitalar e Universitario de Coimbra, Coimbra, Portugal, Centro Hospitalar e Universitario de Coimbra
Key Words:	Epilepsy, Surgery, Intelligence Quotient, Pediatric Age

Appendix II – Epileptic Disorders manuscript information

Search	Actions	Details	Query	Results
#1	...	>	Search: (epilepsy OR epileptic) AND (Surgery OR Surgical) AND (Wechsler Scale* OR Intelligence Tests) Filters: Humans, English, French, Portuguese, Spanish, Child: birth-18 years, from 2000 - 2021 Sort by: Most Recent	171 Date: 3/9/2021

Appendix III – PubMed search strategy



Appendix IV – Funnel plot

