



The influence of disease course and surgery on quality of life in children with focal cortical dysplasia and long-term epilepsy-associated tumours: A systematic review and meta-analysis

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ABSTRACT

Introduction: Carefully selected patients with lesional epilepsy, including focal cortical dysplasia (FCD) and long-term epilepsy-associated tumours (LEAT), can benefit from epilepsy surgery. The influence of disease course and subsequent epilepsy surgery on quality of life (QoL) and intelligence quotient (IQ) is not well understood.

Methods: A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Studies reporting QoL or IQ measures in paediatric patients with FCD and LEAT at epilepsy onset, at establishment of drug resistance (pre-operative/non-surgically managed) and post-operatively were included. To evaluate the "effect size" and clinical significance of surgery, a meta-analysis of the data was conducted using fixed effects models for weighted mean differences, 95% confidence intervals and sensitivity analyses.

Results: Nineteen eligible studies (911 patients) were included, 17 assessing IQ and 2 evaluating QoL. Twelve studies reported preoperative and postoperative IQ measures and five reported IQ in non-surgically managed cohorts after drug resistance was established; no papers reported IQ at epilepsy onset. No significant IQ/DQ changes were detected after surgery (pre-operative pooled mean 69.32; post-operative pooled mean 69.98; $p = 0.32$). Age at epilepsy surgery, type of surgery and epilepsy-related pathology did not influence the post-operative IQ. QoL was reported in 2 studies with the pooled mean estimates for pre- and post-operative QoL being 42.52 and 55.50, respectively.

Conclusions: The present study demonstrated no statistical change in IQ and QoL following surgery in paediatric patients with FCD and LEAT. There was no data on IQ and QoL at disease onset. Attempting to understand the impact of epilepsy, ongoing seizures and surgery on IQ and QoL will facilitate planning of future studies that aim to optimise quality of life and developmental outcomes in these children. Studies assessing children at epilepsy onset with longitudinal follow-up are required to optimise the timing of epilepsy surgery on QoL and IQ.

1. Introduction

Epilepsy affects 1% of the global population. The combination of recurrent seizures and associated cognitive, behavioural and psychological comorbidities can result in reduced quality of life (Bell and Sander, 2001). In a quarter of patients with drug-resistant epilepsy

(DRE), surgery is an established treatment option, with the aim of reducing or stopping the seizures. Whilst rates of seizure freedom following resective epilepsy surgery are well established at around 60–70% (Rugg-Gunn et al., 2020), the impact of surgery on developmental outcomes and quality of life is less well understood.

Many children undergoing epilepsy surgery have clearly identifiable

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lesions on MRI scans including malformations of cortical development (MCD), focal cortical dysplasia (FCD), hippocampal sclerosis, or long-term epilepsy-associated tumours (LEATs) (Cascino, 2008). While the presence of these lesions has been found to be the most significant factor associated with DRE (Jobst BC, Cascino GD. 2015), it also increases the odds of attaining Engel class I outcomes following epilepsy surgery (Téllez-Zenteno et al., 2010; Berkovic et al., 1995). Natural history studies have shown that the vast majority of these lesional epilepsies will become drug resistant and be considered for surgical intervention, albeit sometimes years after the initial diagnosis of epilepsy. There is potential that this delay results in poorer outcomes with duration of epilepsy being an important prognosticator of post-operative seizure outcomes (Braun KPJ. 2020; Cloppenborg et al., 2001; Skirrow et al., 2019).

The relationship between epilepsy and cognition has been hypothesised to be bidirectional. On the one hand, the brain abnormalities that result in cognitive dysfunction may be part of the aetiology of epilepsy, and on the other hand, it may be exacerbated by recurrent seizure activity (Helmstaedter, et al., 2017). A study evaluating the long-term influence of DRE seizures on intellectual function revealed that in paediatric patients, seizure recurrence was associated with a decrease in standardised intelligence quotient (IQ) scores, not necessarily correlating to a decrease in functional level (Bjørnaes et al., 2001). This suggests that recurrent seizure may contribute to intellectual decline. However, it remains possible that the aetiology is a major predictor of cognitive outcomes and that seizures contribute little to those outcomes.

Quality of life (QoL) and IQ in paediatric epilepsy patients undergoing surgical intervention have not been extensively studied and are further limited by short follow-up (Williams et al., 1998; Gleissner et al., 2006; Korkman et al., 2005; Westerveld et al., 2000). A retrospective study of 42 paediatric epilepsy patients who underwent temporal lobe surgery demonstrated that IQ changes become apparent after an extensive follow-up period (Skirrow et al., 2011). The authors posit that significant improvement in IQ and QoL may become evident 5 years postoperatively, attributable to the cessation of anti-seizure medication (ASM).

Despite epilepsy surgery representing a disease-modifying treatment (Engel et al., 2003; Spencer et al., 2003), trialling multiple ASMs may delay referral for surgical intervention, possibly contributing to further exacerbation of the epileptogenic network and the associated deterioration in QoL and cognitive abilities. The persistence of epilepsy from childhood into adulthood has been associated with long-term neurodevelopmental trajectory alterations, and cognitive and psychosocial comorbidities (Baxendale et al., 2010; Wilson et al., 2012). Earlier surgical intervention in carefully selected lesional epilepsy patients may have the potential to improve cognition and QoL in those achieving seizure freedom postoperatively (Cross and Duchowny, 2014; Jacoby et al., 2008).

We conducted this systematic review and meta-analysis of cognitive and QoL outcomes in children undergoing surgery for FCD and LEAT with two specific aims. First, we aimed to establish whether IQ and QoL were affected by ongoing epilepsy and epilepsy surgery by assessing them at the point of diagnosis, pre surgery and post-surgery. Secondly, we wanted to assess the factors that contribute to the effect of surgery using meta-regression.

2. Methods

This systematic review has been conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P 2015) and the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2011; Moher et al., 2015; Shamseer et al., 2015). The systematic review has been registered with PROSPERO (International Prospective Register of Systematic Reviews) in advance of the initiation of the data collection phase (Reference number: CRD42021293304).

2.1. Search strategy and information sources

Information was retrieved from Pubmed on the 1st of August 2022. The search was conducted by two independent investigators, employing the following search strategy parametrization: “epilepsy” AND (“focal cortical dysplasia” or “fcd” or “malformation of cortical development” or “long-term epilepsy associated tumour” or “leat” or “ganglioglioma” or “dnet” or “dysembryoplastic neuroepithelial tumour”) AND (“quality of life” or “qol” or “development” or “IQ” or “neuropsychology” or “DQ” or “intelligence quotient” or “developmental quotient”). The search period spanned 1980–2021 and results were restricted by two filters: (i) English language and (ii) human subjects only.

2.2. Study records and data management

Literature search results were imported into EndNote 20 reference manager software (Team, 2013) for article selection and deduplication.

2.3. Eligibility criteria

Studies included in the analysis were original clinical studies, specifically evaluating paediatric epilepsy patients (<18 years old) diagnosed with lesional epilepsy (MCD, FCD, LEATs) and who had undergone epilepsy surgery and for whom either QoL or IQ measures had been reported at any of 3 timepoints: (Bell and Sander, 2001) at diagnosis of epilepsy, (Rugg-Gunn et al., 2020) at drug resistance (or pre-operatively in surgical series) and (Cascino, 2008) post-epilepsy surgery. – as individual patient values, as mean and standard deviation, or as median and interquartile range. Articles reporting any QoL and IQ measures were eligible for inclusion in the study.

Excluded studies had the following characteristics: (i) were focused purely on adult populations (>18 years old); (ii) were only reporting Engel outcomes, but no QoL or IQ measures; (iii) were not published in English language; (iv) were reviews, systematic reviews or meta-analyses; (v) were conferring a low level of evidence, such as case reports, letters to the editor, commentaries or conference abstracts.

2.4. Selection process

The title and abstract of the retrieved studies were independently screened by 2 authors (AMV, AW), based on the inclusion and exclusion criteria. The results were pooled and the full text of the selected studies was reviewed. Any conflict regarding the suitability of particular papers has been resolved with consensus and with input from a third author (AC).

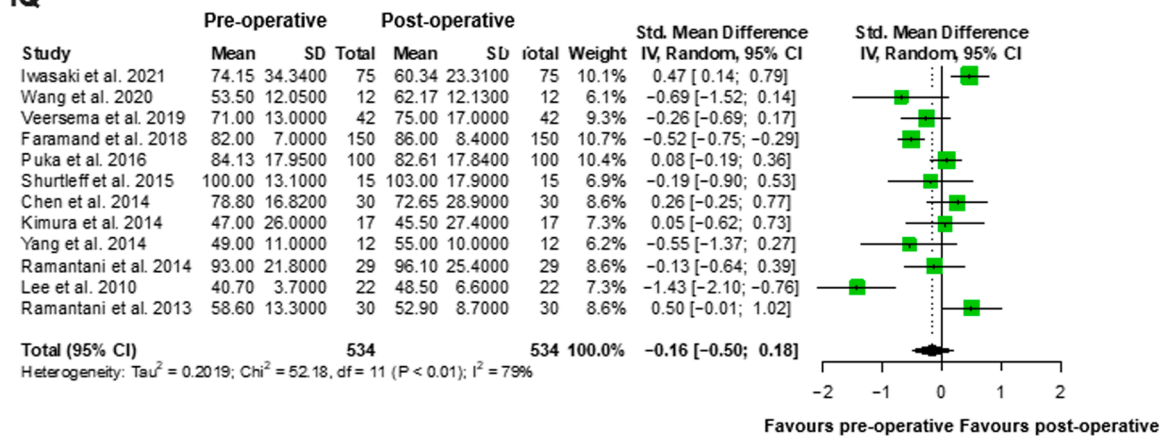
2.5. Data items

Extracted relevant data were tabulated in a Microsoft Excel spreadsheet (Microsoft Excel, Microsoft Corporation, 2010) and data items included were as follows: title, authors, year of publication, type of study, number of patients included in the study, type of cohorts (paediatric, mixed – paediatric and adult), mean age at seizure onset, type of surgery (resection, disconnection, mixed cohort), mean age at epilepsy surgery, pathology (FCD, LEAT, mixed cohort) type of QoL outcome measure used (if applicable), preoperative and postoperative QoL scores, preoperative and postoperative IQ scores, percentage of patients exhibiting postoperative Engel I outcome, follow up time, any other comments.

2.6. Outcomes and prioritisation

The primary outcome of this systematic review was to provide an assessment of the clinical impact of surgical intervention on IQ and QoL in paediatric lesional epilepsy patients, and to compare that with effects exhibited by cohorts of children with lesional epilepsy who have not

IQ



IQ/DQ

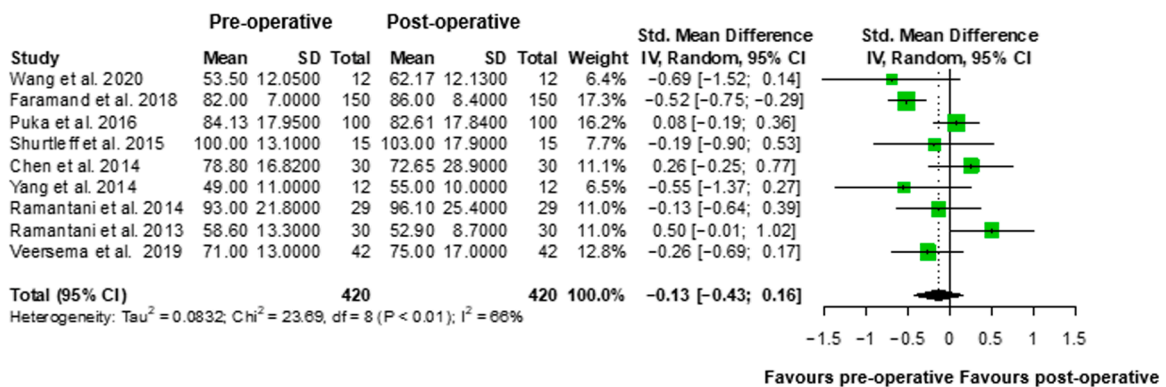


Fig. 1. - Forest plot for standardised mean difference in pre-operative versus post-operative IQ/DQ measures and purely IQ measures, respectively. The bold vertical line represents the line of null effect. The horizontal lines represent the 95% confidence interval corresponding to each study and the dots in the green squares are the estimated standardised mean difference of the study result. The black diamond at the bottom of the forest plot represents the overall IQ difference and the associated confidence interval.

been surgically managed.

The secondary outcomes referred to the influence exerted by pre-operative IQ on postoperative IQ and to the relationship between IQ and postoperative seizure freedom.

2.7. Critical appraisal

Assessment of bias across studies has been performed using the Risk of bias in non-randomised studies of interventions (ROBINS-I) tool (Sterne et al., 2016). Two researchers independently assessed the parameters across each study, in the case of a disagreement, this was settled by third reviewer.

2.8. Statistical analysis

Categorical variables were reported as percentages, while continuous variables were reported as means and standard deviations (SD). Means and standard deviations for each parameter (pre-operative IQ, post-operative IQ, age at epilepsy onset, age at epilepsy surgery) were calculated.

To uniformly analyse data from the included studies, several data conversions have been required. For studies reporting IQ in multiple ranges with associated numbers of patients, the weighted mean and SD have been calculated using the following formulae:

$$\bar{x} = \frac{x_1 v_1 + x_2 v_2 + \dots + x_n v_n}{v_1 + v_2 + \dots + v_n}$$

$$s = \sqrt{\frac{(x_1 - \bar{x})^2 v_1 + (x_2 - \bar{x})^2 v_2 + \dots + (x_n - \bar{x})^2 v_n}{v_1 + v_2 + \dots + v_n - 1}}$$

where x_1, x_2, \dots, x_n are the IQ group values, v_1, v_2, \dots, v_n are the patient numbers corresponding to each IQ group, \bar{x} is the mean and s is the SD.

For studies reporting median and IQR, conversion to mean and SD has been performed using the following formulae (Hozo et al., 2005):

$$\bar{x} = \frac{a + 2m + b}{4}$$

$$s = \sqrt{\frac{1}{12} \left(\frac{(a - 2m + b)^2}{4} + (b - a)^2 \right)}$$

where m =median, a =lower value of IQR, b =higher value of IQR, \bar{x} is the mean and s is the SD.

2.9. Meta analysis

In order to assess the impact of surgery on IQ, standardised mean difference (SMD; Hedges g) were used with associated 95% confidence intervals (95% CI) to quantify the pooled effect size. Meta analyses reporting pooled means were also presented separately for pre and post operative scores for IQ and QOL. All meta-analyses were visually presented as a forest plot.

All meta analyses employed a random effects model for two reasons (Bell and Sander, 2001) there were more than five studies and

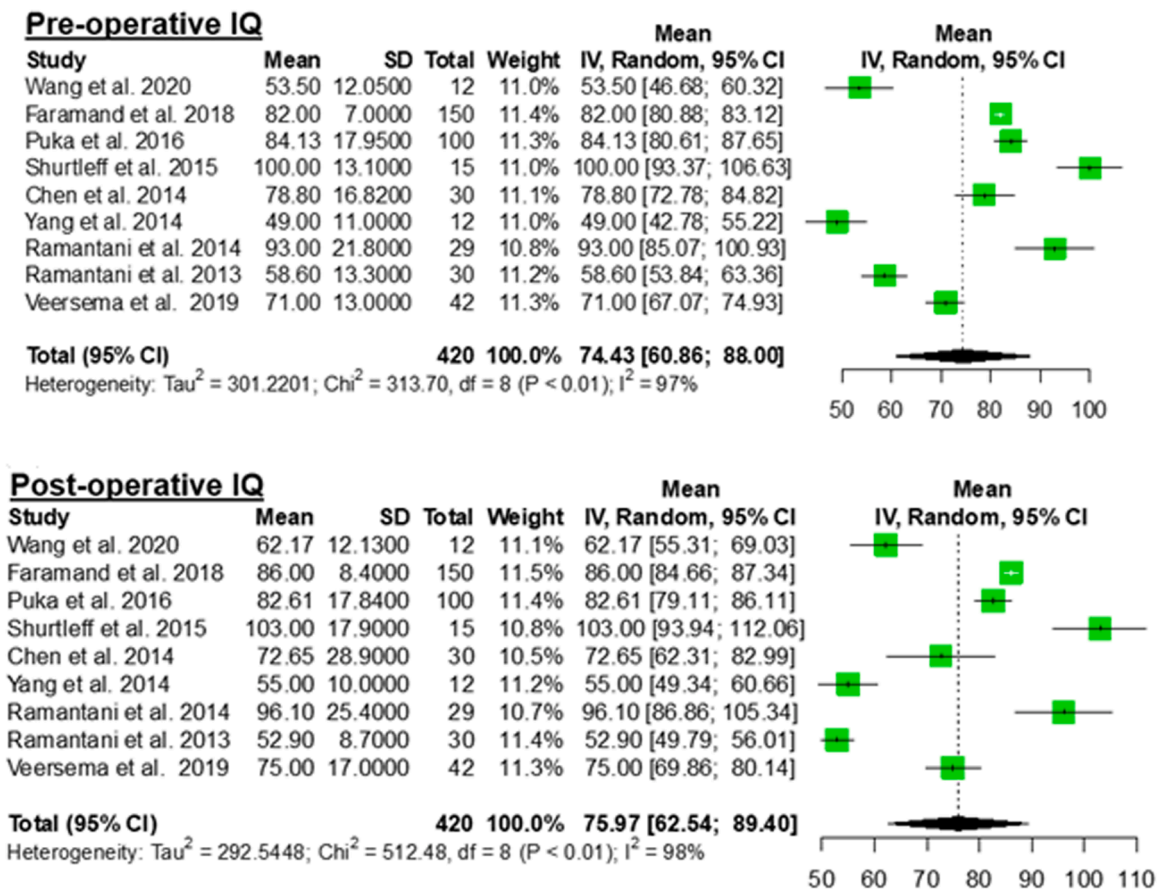


Fig. 2. - Forest plot for pre-operative and post-operative IQ pooled means. The horizontal lines represent the 95% confidence interval corresponding to each study and the dots in the green squares are mean pre-operative IQ values of each study. The black diamond at the bottom of the forest plot represents the overall pre-operative mean IQ and the associated confidence interval.

(Rugg-Gunn et al., 2020) homogeneity between the studies could not be assumed due to difference in measurement tools (Tufanaru et al., 2015). The restricted maximum likelihood estimator (Viechtbauer, 2005) was used to estimate the variance in between study heterogeneity.

The statistical significance of the inter-study heterogeneity of the analysis was evaluated by employing Cochran's Q, and heterogeneity values were categorised using Higgins I². The degree of the I² was grouped as follows: 0% (no heterogeneity), 25% (small heterogeneity), 50% (moderate heterogeneity) and 75% (large heterogeneity) (Higgins et al., 2003).

To further explore potential sources of heterogeneity subgroup analyses and meta regression analyses were conducted for categorical and continuous variables respectively using mixed effect models. Subgroup analysis was used to assess differences in IQ among type of pathology and type of surgery. In addition, meta regression analyses were used to assess the impact of age at epilepsy surgery, age at seizure freedom, rate of post-operative seizure freedom and influence of pre-operative IQ on SMD of IQ. Choice of variables was decided a priori. Meta regressions were visually represented with the use of bubble plots.

Risk of publication bias was visually assessed with the use of a funnel plot and was statistically verified with an Eggers test (Egger et al., 1997).

Statistical analyses were performed in R (version 4.1.2) and R studio (R Development Core Team. The R Project for Statistical Computing. <http://www.R-project.org>) using the 'meta' and 'metafor' packages (Viechtbauer, 2010; Schwarzer, 2007). Statistical significance was considered at p < 0.05.

3. Results

3.1. Study characteristics

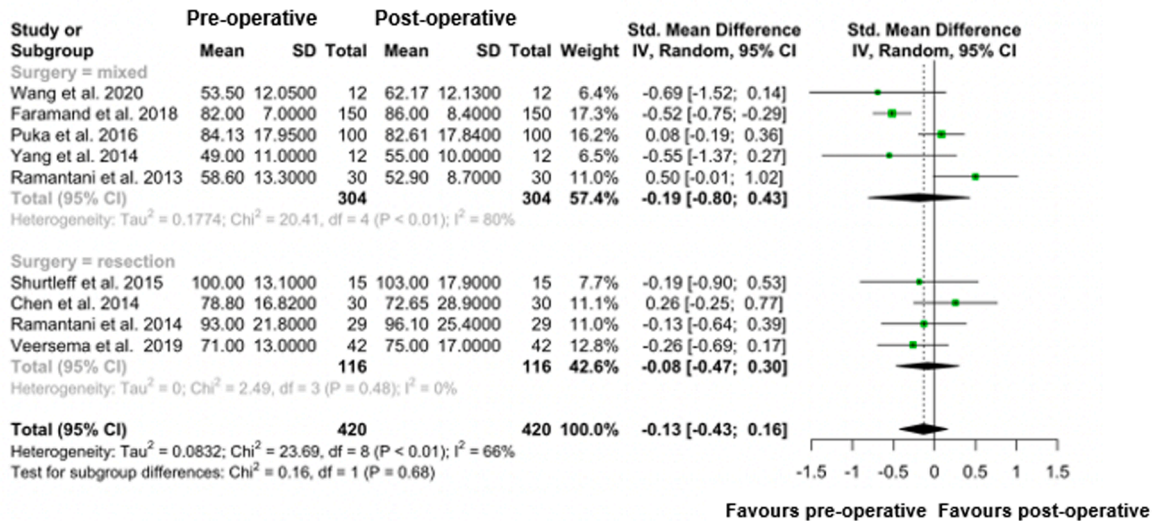
The database search retrieved 1145 articles in Pubmed on 1st August 2022. Deduplication resulted in a total of 1141 articles which were screened by title and abstract. A total of 19 articles met all the inclusion criteria and have been included in the meta-analysis. The article selection process is summarised in the PRISMA Flow Diagram (Fig. A1, Appendix).

The characteristics of these studies were tabulated, as follows: 12 studies (Iwasaki et al., 2021; Wang et al., 2020; Veersema et al., 2019; Faramand et al., 2018; Puka et al., 2016; Shurtleff et al., 2015; Chen et al., 2014; Kimura et al., 2014; Yang et al., 2014; Ramantani et al., 2014; Lee et al., 2010; Ramantani et al., 2013) focused on reporting pre- and post-operative IQ/DQ measures (Table B1, Appendix), 5 studies (Palmini et al., 1991; Korman et al., 2013; Krsek et al., 2009; Mrelashvili et al., 2015; Vasconcellos et al., 2008) reported only pre-operative IQ measures (Table B2, Appendix), and 2 studies (Landazuri et al., 2020; Chaturvedi et al., 2018) reported QoL measures pre- and post-operatively (Table B3, Appendix). No studies reported IQ or QoL at diagnosis of epilepsy.

3.2. Pre- vs post-operative IQ and DQ comparison

The 12 studies reporting both pre- and post-operative IQ and DQ measures evaluated a total of 534 patients, displaying a pre-operative mean IQ/DQ of 69.32 and a post-operative IQ/DQ of 69.98 (SMD = -0.16; 95% CI [-0.50; 0.18]; p = 0.32, see Fig. 1). The random effects

A



B

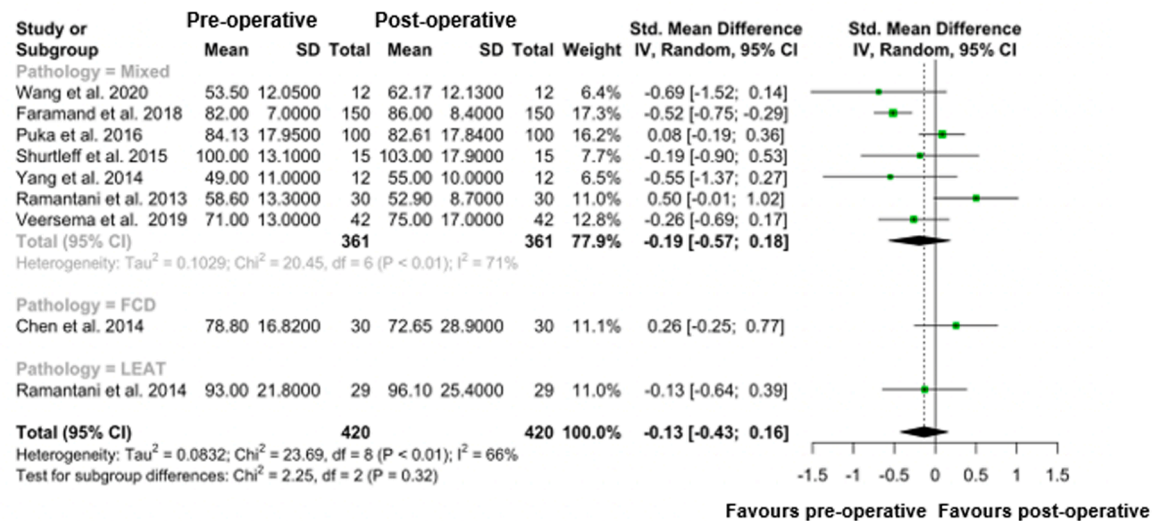


Fig. 3. - A. Forest plot for the subgroup analysis relating surgery type to the post-operative IQ values. Included studies were categorised based on the surgery type that the reported patient cohort underwent - either resective surgery or mixed (studies collectively reporting resective and disconnection surgery). B. Forest plot for the subgroup analysis relating pathology type to the post-operative IQ values. Included studies were categorised based on the pathology type that was reported in the patient cohort - either FCD, LEATs, or mixed (studies collectively reporting FCD and LEATs). The bold vertical line represents the line of null effect. The horizontal lines represent the 95% confidence interval corresponding to each study and the dots in the green squares are the estimated standardised mean difference of the study result. The black diamond at the bottom of the forest plot represents the overall IQ difference and the associated confidence interval.

model revealed no significant difference in IQ between the two time points. Substantially high heterogeneity levels were detected among included studies ($Q=52.18$; $I^2=78.90\%$; $p < 0.01$).

3.3. Pre- vs post-operative IQ only comparison

The 9 studies reporting both pre- and post-operative IQ measures evaluated a total of 420 patients, displaying a pre-operative mean IQ of 74.45 and a post-operative IQ of 76.16 (SMD = -0.13 ; 95% CI $[-0.43; 0.16]$; $p = 0.32$; see Fig. 1). The random effects model revealed no significant difference between the pre-operative and the post-operative IQ. Substantially high heterogeneity levels were detected among included studies (IQ=23.69; $I^2=66.20\%$; $p < 0.01$).

Separate random effects models were conducted for pooled mean estimates for pre-operative and post-operative IQ. These were 74.43 (95% CI $[60.86; 88.00]$; $I^2=97.40\%$; $p < 0.001$, Fig. 2) and 72.96 (95% CI $[57.46; 88.47]$, $I^2=98\%$, $p < 0.01$, Fig. 2), respectively.

3.4. Purely pre-operative IQ analysis

The 5 studies reporting non-surgical, purely pre-operative IQ evaluated a total of 265 patients with DRE, but no surgical intervention. The mean IQ was 74.90 (95% CI $[57.15; 92.66]$, $I^2=96.9$, $p < 0.01$, $Q=127$, Fig. A2, Appendix).

3.5. Subgroup and meta-regression analyses of the effect of covariates on IQ

Subgroup analyses were conducted to explore the effect of various covariates on the standardised mean difference of IQ change. Subgroup analysis for categorical variables indicated that the type of surgery (SMD = -0.13 ; 95% CI $[-0.43; 0.16]$; $p = 0.68$, $Q=0.16$, see Fig. 3A) and the epilepsy-related pathology (SMD = -0.13 ; 95% CI $[-0.43; 0.16]$; $p = 0.32$, $Q=2.25$, see Fig. 3B) did not influence the IQ change.

Meta regression analyses (see Fig. 4) for continuous variable found

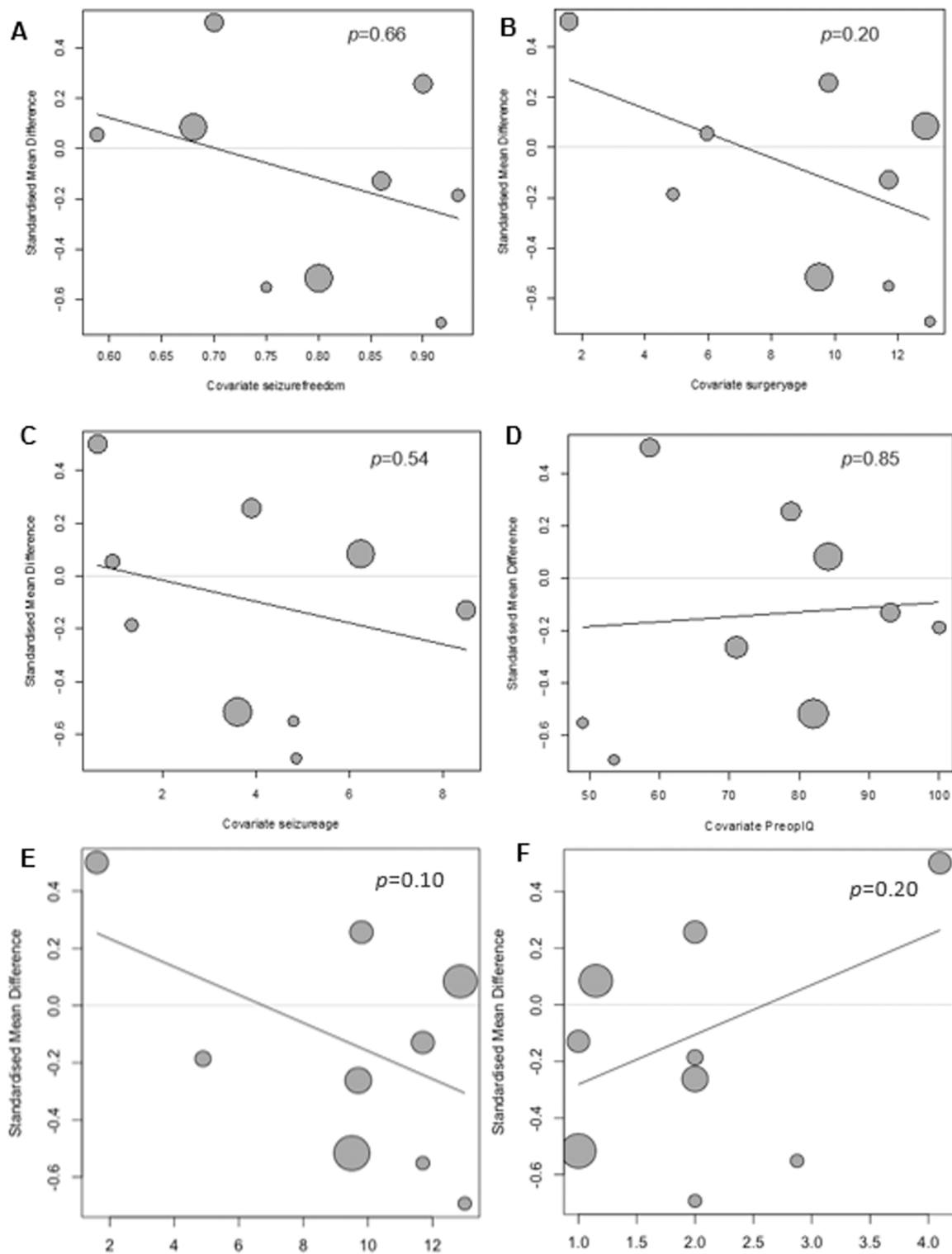


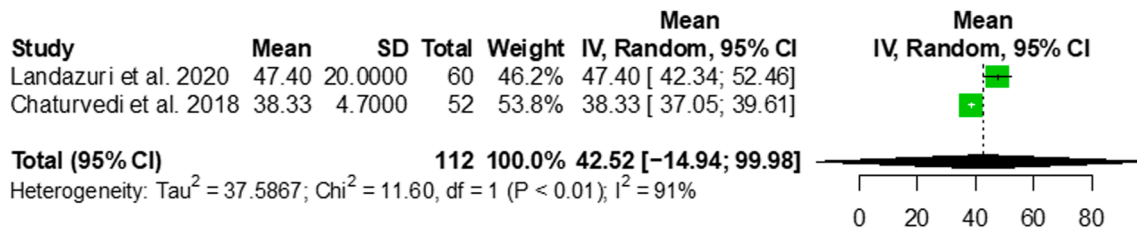
Fig. 4. – Bubble plot for meta-regression analyses, representing the influence of (A) Rate (%) of post-operative seizure freedom (B) Age at epilepsy surgery (C) Age at seizure freedom and (D) Pre-operative IQ (E) Duration of epilepsy and (F) Duration of follow up in years acting as a covariate for the standardised mean difference. Size of bubbles represent weighting of the study.

no significant associations between IQ change and rate of seizure freedom ($p = 0.66$, $R^2 = 0\%$), age at surgery ($p = 0.20$, $R^2 = 0\%$), age at first seizure ($p = 0.54$, $R^2 = 0\%$), pre-operative IQ ($p = 0.85$, $R^2 = 0\%$), duration of epilepsy ($p = 0.10$, $R^2 = 18.32\%$) and duration of follow up ($p = 0.20$, $R^2 = 24.36\%$).

3.6. Pre- vs post-operative quality of life comparison

A thematic analysis was conducted on the small number of retrieved studies focusing on QoL changes following surgical intervention. There was high variability with regards to the QoL measures employed in the included studies: one study reported data based on QOLIE-31

Pre-operative



Post-operative

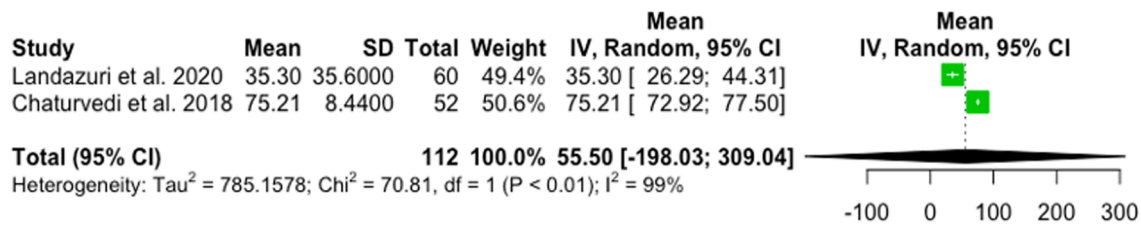


Fig. 5. - Forest plot for pre-operative and post-operative QOL pooled means. The horizontal lines represent the 95% confidence interval corresponding to each study and the dots in the green squares are the mean pre-operative QOL values of each study. The black diamond at the bottom of the forest plot represents the overall pre-operative mean QOL and the associated confidence interval.

Table 1
Risk of bias for included studies.

Paper	Baseline confounding	Selection of participants	Classification of intervention	Deviation from intended intervention	Missing data	Measurement of outcomes	Selection of reported results	Overall risk of bias
Landazuri et al 2020	Low	Low	NI	NI	Low	Low	Low	Low
Chaturvedi et al 2018	Low	Low	NI	NI	Low	Low	Low	Low
Iwasaki et al 2021	Low	Low	NI	NI	Moderate	Low	Low	Low
Wang et al 2020	Low	Low	NI	NI	Low	Low	Low	Low
Veersema et al 2019	Low	Low	NI	NI	Low	Low	Low	Low
Faramand et al 2018	Low	Low	NI	NI	Moderate	Low	Low	Low
Puka et al 2016	Low	Low	NI	NI	Low	Low	Low	Low
Shurtleff et al 2015	Low	Low	NI	NI	Low	Low	Low	Low
Chen et al 2014	Low	Low	NI	NI	Moderate	Low	Low	Low
Yang et al 2014	Low	Moderate	NI	NI	Low	Low	Low	Low
Ramantani et al 2014	Low	Moderate	NI	NI	Moderate	Low	Low	Low
Lee et al 2010	Low	Low	NI	NI	Low	Low	Low	Low
Ramantani et al 2013	Low	Low	NI	NI	Low	Low	Low	Low
Palmini et al 1991	Low	Low	NI	NI	Low	Low	Low	Low
Korman et al 2013	Low	Low	NI	NI	Low	Low	Low	Low
Krsek et al 2009	Low	Low	NI	NI	Low	Low	Low	Low
Mrelashvili et al 2015	Low	Low	NI	NI	Low	Low	Low	Low
Vasconcellos et al 2008	Low	Low	NI	NI	Low	Low	Low	Low

questionnaire, while data from the second study emerged from the QOLIE-89 test. The results of the studies were similarly variable: while one study describing a patient group with mixed pathology reported a slight decrease in QoL (Landazuri et al.,2020), the other study evaluating a cohort of pure FCD patients demonstrated a large increase in QoL (Chaturvedi et al., 2018).

Separate random effects models were conducted for pooled mean estimates for pre-operative and post-operative QOL. These were 42.52

(95% CI [-14.94; 99.98]; I² =91.4%; p < 0.001; Q=11.60, Fig. 5) and 55.50 (95% CI [-198.03; 309.04]; I² =98.6%; p < 0.001; Q=70.81, Fig. 5), respectively, on a scale on which the increase in value indicates an increased QoL.

3.7. Publication bias

From visual inspection of the funnel plot, there did not appear to be a

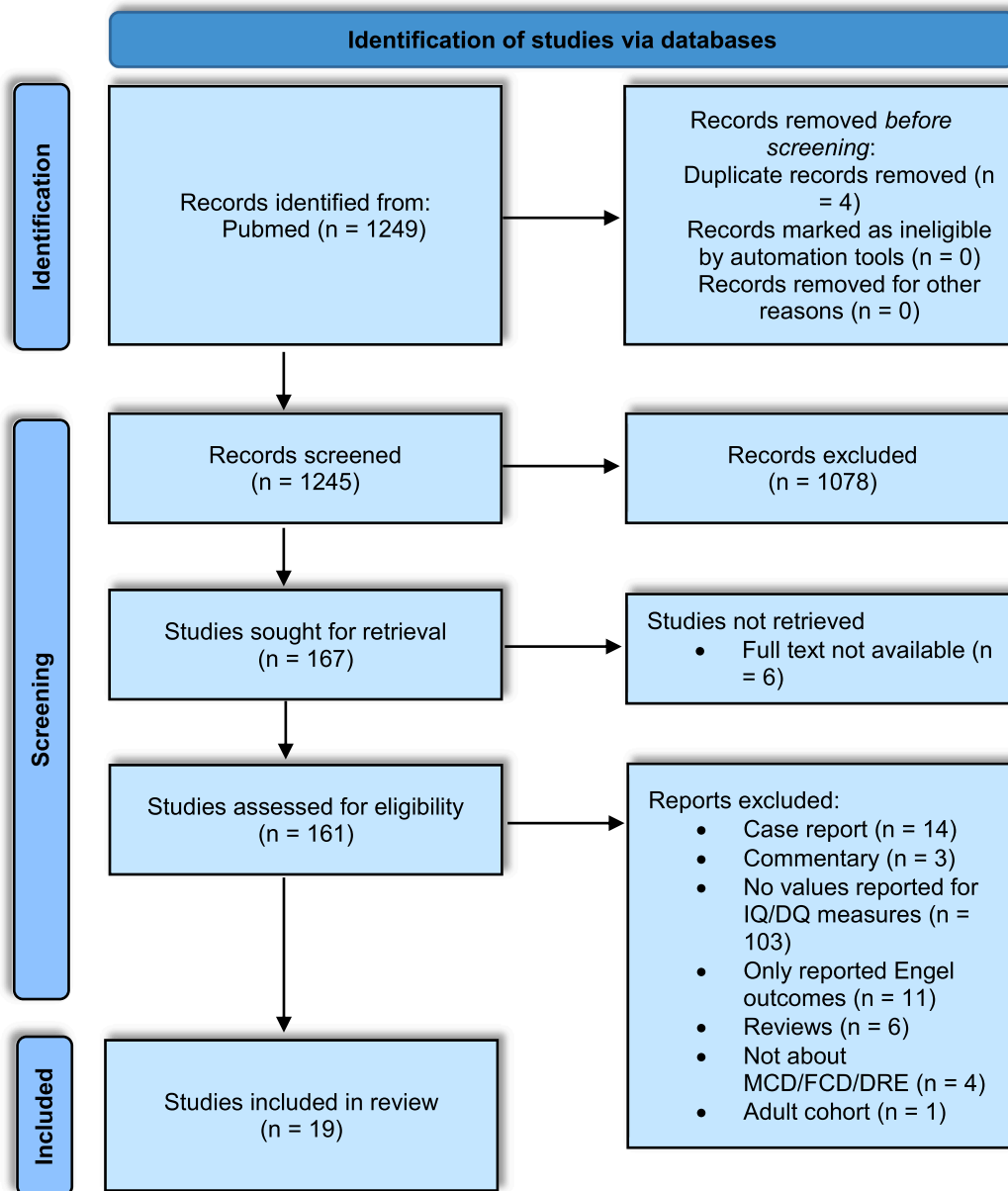


Fig. A1. PRISMA Flow Chart.

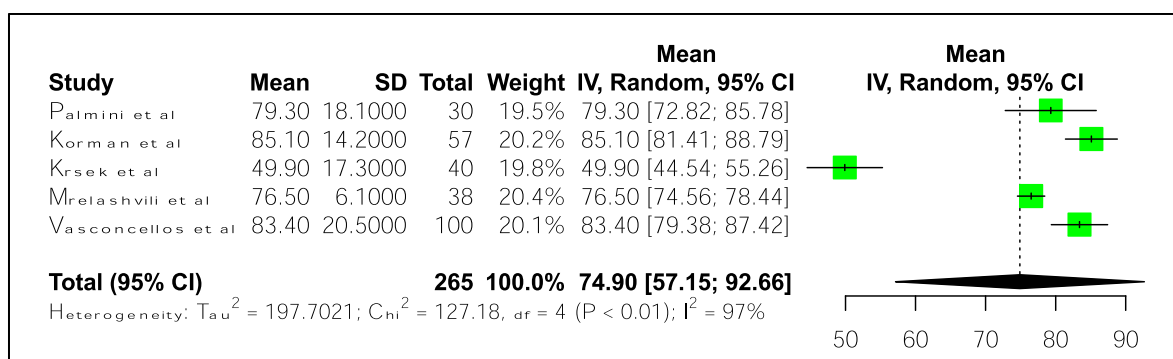


Fig. A2. Forest plot for pre-operative IQ pooled means for drug resistant epilepsy group only. The horizontal lines represent the 95% confidence interval corresponding to each study and the dots in the green squares are the mean pre-operative QOL values of each study. The black diamond at the bottom of the forest plot represents the overall pre-operative mean QOL and the associated confidence interval.

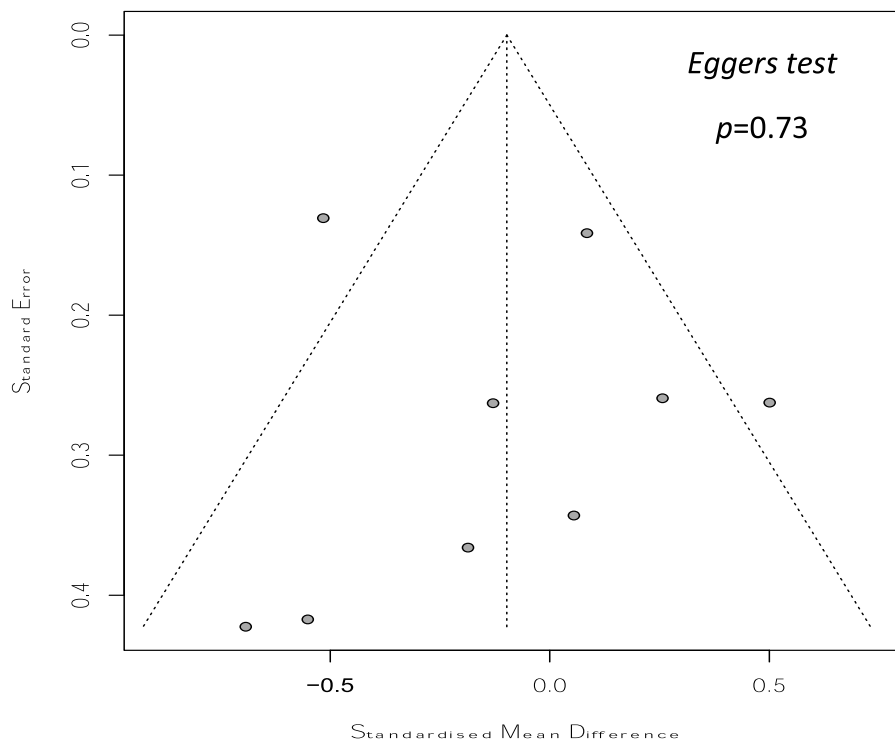


Fig. A3. Funnel plot for meta-analysis reporting the impact of epilepsy surgery on IQ change.

Table B1

Study characteristics for papers focused on pre- and post-operative IQ/DQ measures.

Study	Sample Size	Age group	Pathology	Mean age at seizure onset (years) (mean ± SD)	Mean age at surgery (years) (mean ± SD)	Type of surgery	Pre-operative IQ/DQ (mean ± SD)	Post-operative IQ/DQ (mean ± SD)	Seizure freedom (%)	Seizure freedom timepoint (years)
Iwasaki et al. 2021	75	Paeds	Mixed	0.31 ± 0.52	0.99 ± 0.9	Mixed	74.15 ± 34.34	60.34 ± 23.31	82.70	1
Wang et al. 2020	12	Paeds	Mixed	4.86 ± 2.12	13 ± 1.83	Disconnection	53.5 ± 12.05	62.17 ± 12.13	91.70	2
Veersema et al. 2019	42	Mixed (paeds + adults)	Mixed	4.2 ± 3.6	9.7 ± 5.3	Resection	71 ± 13	75 ± 17	59	2
Faramand et al. 2018	150	Paeds	Mixed	3.6 ± 1.7	9.5 ± 2.3	Mixed	82 ± 7	86 ± 8.4	80	1
Puka et al. 2016	100	Paeds	Mixed	6.24 ± 4.8	12.86 ± 4.17	Mixed	84.13 ± 17.95	82.61 ± 17.84	68	1.15
Shurtleff et al. 2015	15	Paeds	Mixed	1.33 ± 1.43	4.89 ± 1.74	Resection	100 ± 13.1	103 ± 17.9	93.33	2
Chen et al. 2014	30	Paeds	FCD	3.9 ± 2.6	9.8 ± 4.6	Resection	78.8 ± 16.82	72.65 ± 28.9	90	2
Kimura et al. 2014	17	Paeds	FCD	0.92 ± 0.83	6.0 ± 2.7	Mixed	47 ± 26	45.5 ± 27.4	58.80	3.2
Yang et al. 2014	12	Paeds	Mixed	4.8 ± 3.1	11.7 ± 4.1	Disconnection	49 ± 11	55 ± 10	75	2.875
Ramantani et al. 2014	29	Paeds	LEAT	8.5 ± 5.2	11.7 ± 5.4	Resection	93 ± 21.8	96.1 ± 25.4	86	1
Lee et al. 2010	22	Paeds	Mixed	2.0 ± 2.8	7.8 ± 3.7	Mixed	40.7 ± 3.7	48.5 ± 6.6	59.30	2.76
Ramantani et al. 2013	30	Paeds	Mixed	0.6 ± 0.5	1.6 ± 0.7	Mixed	58.6 ± 13.3	52.9 ± 8.7	70	4.1

clear asymmetry, which was also consistent with the findings from the Eggers test ($p = 0.73$, Fig. A3, Appendix). Therefore, it can be inferred that no publication bias exists.

3.8. Risk of bias assessment

The risk of bias of the included studies has been assessed using the ROBINS-I tool, as detailed in Table 1. Overall, the risk of bias was low

across all studies.

4. Discussion

4.1. Summary of findings

Poor quality of life and intellectual difficulties are frequently recognised in the paediatric population affected by FCD and LEAT, yet the

Table B2
Study characteristics for papers reporting only pre-operative IQ in drug-resistant epilepsy.

Study	Sample Size	Age group	Pathology	Mean age at seizure onset (years) (mean ± SD)	Pre-operative IQ/DQ (mean ± SD)
Palmini et al. 1991	30	Mixed	Mixed	5.7 ± 6.2	79.3 ± 18.1
Korman et al. 2013	57	Paeds	FCD	6.6 ± 4.3	85.1 ± 14.2
Krsek et al. 2009	40	Paeds	FCD	3.1 ± 2.5	49.9 ± 17.3
Mrelashvili et al. 2015	38	Paeds	FCD	1.5 ± 1.3	76.5 ± 6.1
Vasconcellos et al. 2008	100	Paeds	Mixed	4.9 ± 3.8	83.4 ± 20.5

relationships between these factors and the effect of epilepsy surgery in this patient group remains underdefined.

Our analysis did not reveal any significant changes in IQ or QoL following epilepsy surgery. Additionally, none of the factors assessed as part of the meta-analysis exerted an influence on IQ or QoL in this patient population. This equates with a lack of an identifiable effect of epilepsy surgery on post-surgical IQ measures. One explanation is that there may be no important relationship between seizures and cognition given that termination of seizures with surgery does not result in a measurable cognitive improvement. It is increasingly accepted that aetiology is a major predictor of cognitive outcomes in patients with epilepsy (Zhu et al., 2020).

An alternative explanation of the results is related to the fact that in a large proportion of patients the pre-operative trajectory can be adverse, with aspects such as baseline cognition, functional plasticity level and level of seizure control being relevant in establishing this (Cloppenborg et al., 2001; Helmstaedter et al., 2020). In these individuals a null change between the pre- and post-operative IQ score equates with a successful surgical outcome, potentially leading to an improved trajectory compared to no surgical treatment.

In our analysis, 8 of the 12 included studies assessing pre- and post-operative IQ changes reported a mean pre-operative IQ value below 75, and only two studies (Shurtleff et al., 2015; Ramantani et al., 2013) exhibited a value close to 100, suggesting that a substantial proportion of patients had severe cognitive impairment (Table B1). Whether these individuals start with a low IQ (supporting the former hypothesis of a common aetiology leading to seizures and cognitive dysfunction) or normal IQ that deteriorates over time (supporting the latter hypothesis of seizure-induced decline) remain to be elucidated. Importantly, from this review, we are unable to establish what the normal distribution of patients with FCD and LEAT are and whether the patients evaluated in the included studies represent biased samples.

A current dilemma which requires elucidation lies in the exact timing of offering epilepsy surgery in patients with clear lesions such as FCD and LEAT, as there is not yet clear evidence supporting a positive association between earlier provision of surgical intervention and better

Table B3
Study characteristics for papers reporting Quality of Life measures pre- and post-operatively.

Study	QoL Measure Used	Sample Size	Age group	Pathology	Mean age at seizure onset (years) (mean ± SD)	Mean age at surgery (years) (mean ± SD)	Type of surgery	Pre-operative QoL (mean ± SD)	Post-operative QoL (mean ± SD)	Seizure freedom (%)	Seizure freedom timepoint (years)
Landazuri et al. 2020	QOLIE-31	60	Mixed	Mixed	16.4 ± 15.2	35.1 ± 17.7	Mixed	47.4 ± 20	35.3 ± 35.6	64.3	1
Chaturvedi et al. 2018	QOLIE-89	52	Paeds	FCD	7.9 ± 3.6	20.9 ± 7.2	Mixed	38.33 ± 4.7	75.21 ± 8.44	70	2

IQ measures post-operatively, particularly because of the lack of understanding regarding the decline in these outcomes proportionally with the duration of epilepsy (Bjørnaes et al., 2001; Laguitton et al., 2021). Therefore, future scientific endeavours should aim to diagnose and recruit patients earlier, to ensure IQ evaluations are performed at diagnosis, pre- and post-operatively, and at every follow-up encounter, and to offer a longer follow-up period.

With regards to the QoL analysis, the number of studies which were retrieved by the designed search strategy was small, which prevented a more detailed statistical analysis of their results. Moreover, their results were discordant, potentially attributable to the usage of distinct QoL questionnaires and the evaluation of either purely FCD or mixed patient cohorts. The scarcity of QoL studies on lesional epilepsy patients should prompt towards an increased research interest in this particular area. Additionally, hospitals evaluating and treating patients with drug resistant lesional epilepsy should incorporate regular QoL assessments as part of their pre- and post-surgical evaluations.

4.2. Strengths and limitations

The present systematic review and meta-analysis employed a pre-defined search strategy and strict inclusion and exclusion criteria for the selection of included studies. We focused the analysis specifically on FCD and LEAT, including mixed cohorts and those who did not have both pre- and post-operative data to maximise the available data.

The majority of the included studies pooled patient information regarding lesional epilepsy type, resulting in patient cohorts for whom the stratification by pathology type was impossible, so they were defined in the analysis as “mixed pathology”. Therefore, after subdividing the studies, a very small number of these were assessed as part of the subgroup analysis relating pathology type to the post-operative IQ results. In addition, some included studies failed to separate the patients into age groups (purely paediatric, purely adult, mixed) and patients in these cohorts were regarded as “mixed cohort” in the analysis. This was particularly problematic when attempting to stratify IQ measures according to age group – either paediatric or adult.

A critical evaluation of the IQ measures employed in the various studies emphasised that for the tests which rely on language capacities the performance of children originating from immigrant families, who have not yet acquired fluency in the national language, is potentially lower. Additionally, the IQ values could be underestimated under circumstances whereby testing is not conducted by a specialised child neuropsychologist.

Another significant factor to consider is the short follow-up duration across all the included studies. Longer follow-up periods in children affected by focal epilepsy have been found to positively correlate with IQ improvements post-operatively, being particularly observed after 5 years following surgical intervention (Skirrow et al., 2011). Importantly, previous studies demonstrated relationships between shorter epilepsy duration and better preserved pre-surgical cognitive function (Ramantani et al., 2013), and improved seizure control over longer-term (Simasathien et al., 2013). Additionally, considering the marked difference in pre-operative scores between included studies, we suspect that the patient cohorts differed in composition in relation to their pathology and surgical intervention (resection, disconnection).

Nonetheless, the small number of studies included in this analysis does not offer the power to observe these effects with certainty.

5. Conclusion

This systematic review and meta-analysis reveals that there is currently a lack of correlation between epilepsy surgery and improvements in IQ or QoL in paediatric lesional epilepsy patients. This could be because there is no causative relationship between seizures and cognitive decline and therefore no recovery happens after seizures are terminated with surgery. Alternatively, it is possible that follow up has not been long enough for significant cognitive gains to be identified. At present, the mean follow-up time is not long enough to allow an accurate appreciation of the long-term effects of surgical intervention on IQ and QoL. Thus, we propose a minimum follow-up duration of 5–10 years for paediatric patients undergoing epilepsy surgery. The present findings encourage the conduction of further longitudinal studies with extended follow-up periods, aiming to thoroughly understand the impact of epilepsy, ongoing seizures, epilepsy surgery and the timing of this intervention on developmental trajectories and overall QoL.

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Declaration of Competing Interest

none.

Appendix A

See Figs. A1–A3.

Appendix B

See Table B1–B3.

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