Seizure and non-seizure outcomes after epilepsy surgery in selected patient groups

Jesper Reinholdsson

Department of Clinical Neuroscience

Institute of Neuroscience and Physiology

Sahlgrenska Academy, University of Gothenburg

2023

UNIVERSITY OF GOTHENBURG

Cover illustration by Siri Larsson, inspired by an electroencephalographic recording of an absence seizure.

Seizure and non-seizure outcomes after epilepsy surgery in selected patient groups

jesper.reinholdson@gu.se / jesper.reinholdsson@skane.se

ISBN: 978-91-8069-243-4 (PRINT)

ISBN: 978-91-8069-244-1 (PDF)

http://hdl.handle.net/2077/75203

Printed by Stema Specialtryck AB, Borås, Sweden 2023

To Siri

ABSTRACT

This thesis addresses some understudied aspects of epilepsy surgery with special emphasis on children and adolescents. The specific aims were to analyse educational and employment outcomes after epilepsy surgery in childhood or adolescence (Paper I), to analyse long-term seizure outcomes after resective epilepsy surgery in patients with IQ <70 (Paper II) and in infants and young children operated before four years of age (Paper III), and to develop a protocol for prospective collection of non-seizure outcome data in children who undergo rare epilepsy surgery procedures (Paper IV). Papers I-III are based on prospective data from the population-based Swedish National Epilepsy Surgery Register.

Out of 134 patients with baseline IQ ≥70 operated on before the age of 19 years, about 80% had at least high school education and about 70% were employed 10-20 years after surgery. Seizure-free patients showed rates of full-time employment on par with the general population. Most patients with IQ <70 had special education and were on social benefits at follow-up (Paper I).

Out of 51 patients with baseline IQ <70 who had focal resective surgery at age ≥4 years, 6% had sustained seizure freedom at long-term (10-20 years) follow-up, while another 24% were seizure-free the year preceding follow-up and 45% had a ≥75% reduction in seizure frequency. Compared to those with IQ ≥70, patients with IQ <70 had an adjusted relative risk for persisting seizures at long-term follow-up of 1.68 (95% CI 1.13-2.51) (Paper II).

Out of 47 children who had resective epilepsy surgery at age <4 years, 45% were seizure-free and 26% had a ≥75% reduction in seizure frequency two years after surgery. Out of 32 with long-term (5- or 10-year) follow-up data, 50% were seizure-free and 44% had been so since surgery. At long term, 69% of the seizure-free children were off anti-seizure medication (ASM) (Paper III).

Children and adolescents who undergo hemispherotomy, callosotomy or procedures for hypothalamic hamartoma or have resective surgery at age <4 years constitute rare clinical subgroups. Many have severe forms of epilepsy and neurodevelopmental co-morbidity. A protocol for a prospective Nordic follow-up study of these subgroups is presented, and methodological aspects are discussed in relation to previous literature (Paper IV).

In conclusion, the long-term vocational outcome after paediatric epilepsy surgery is favourable for those with intellectual functioning within the normal range before surgery. Intellectual disability is independently associated with low chances of long-term seizure freedom, but resective surgery may reduce seizure frequency substantially. Resective surgery in the very young makes it possible to stop ASM in those who become seizure-free. Comprehensive studies of seizure and non-seizure outcomes after rare procedures necessitate multi-centre studies.

SAMMANFATTNING

Epilepsi är en av de vanligaste kroniska neurologiska sjukdomarna hos barn såväl som hos vuxna. I Sverige finns det ungefär 70 000 personer med epilepsi, varav drygt 10 000 är barn. Risken för att insjukna är som högst under det första levnadsåret. Epilepsi innebär en benägenhet att få upprepade epileptiska anfall. De bakomliggande orsakerna är många; epilepsi kan bland annat orsakas av en skada eller tumör i hjärnan liksom av genetiska faktorer. Hos barn som insjuknar tidigt dominerar genetiska orsaker, medfödda missbildningar samt skador som uppkommit före eller i nära anslutning till förlossningen. I det senare fallet är epilepsin ofta förenad med cerebral pares. Många barn med epilepsi som debuterat tidigt har utvecklingsrelaterade funktionsnedsättningar. Exempelvis kan det röra sig om intellektuell funktionsnedsättning eller autism. Epilepsi innebär också negativa konsekvenser för skolgång, arbetsliv och socialt liv, framför allt om epilepsin visar sig vara svårbehandlad.

Epilepsi behandlas vanligtvis med läkemedel. Upp till en tredjedel blir dock inte anfallsfria genom läkemedelsbehandling och för vissa av dessa personer är kirurgisk behandling ett alternativ. Epilepsikirurgiska ingrepp innebär antingen att det område i hjärnan där anfallen har sitt ursprung opereras bort eller att förbindelser i hjärnan som är nödvändiga för att anfallet ska kunna spridas skärs av. På så sätt kan epilepsikirurgi leda till att anfallen helt upphör eller att de uppkommer mer sällan och/eller att de inte blir lika allvarliga, något som i sin tur kan medföra positiva effekter på skolgång, arbetsliv och socialt liv. Dessutom kan personer som blir helt anfallsfria ofta sluta med läkemedel och därmed slippa biverkningar.

Syftet med denna avhandling var att beskriva och analysera behandlingsresultat på lång sikt efter epilepsikirurgi med avseende på såväl anfall som icke-anfallsrelaterade utfallsmått, med fokus på dem som opererats under barndomen eller i tonåren, av vilka många har intellektuell funktionsnedsättning, här definierat som IQ <70.

Avhandlingen består av fyra delarbeten. De tre första är observationsstudier som bygger på data från det nationella svenska epilepsikirurgiregistret. Det fjärde delarbetet utgörs av ett studieprotokoll och en metoddiskussion inför ett nytt nordiskt samarbetsprojekt som syftar till att följa upp barn som genomgår en grupp ovanliga epilepsikirurgiska ingrepp.

I den första studien undersöktes utbildning och sysselsättning i vuxen ålder hos personer som genomgått epilepsikirurgi under barndomen eller tonårstiden. Uppföljningstiden sträckte sig upp till 20 år efter operation och är därmed betydligt längre än i många tidigare studier. Vid samtliga uppföljningstillfällen arbetade mer än tre fjärdedelar av de med IQ ≥70 vid tiden för operationen

antingen heltid eller deltid, alternativt studerade. En motsvarande andel, ca 80%, hade klarat gymnasiet eller högre utbildning. Bland dem som var anfallsfria vid uppföljningen var andelen personer i heltidsarbete liksom andelen med eftergymnasial utbildning lika stor som hos befolkningen i stort, med hänsyn tagen till ålder och kön. Personer med IQ <70 före operationen var i hög utsträckning i behov av bidrag för sin försörjning och hade i de flesta fall gått i särskola. Resultaten talar för att personer som opereras i barndomen eller under tonåren har en gynnsam prognos vad gäller utbildning och arbete i vuxen ålder under förutsättning att de har en IQ inom normalområdet vid tiden för operationen. Andelen i förvärvsarbete var högre än i många tidigare studier av personer som opererats i vuxen ålder. Detta talar för att negativa psykosociala effekter av långvarig svårbehandlad epilepsi kan förhindras genom tidigare operation.

I den andra studien analyserades behandlingsresultatet med avseende på anfallsfrekvens i en grupp personer med IQ <70, som genomgått resektiv kirurgi efter fyra års ålder. Med resektiv kirurgi menas att man vid operationen avlägsnar det område i hjärnan som orsakar epilepsin. Uppföljningstiden var upp till 20 år. Resultaten från gruppen med IQ <70 jämfördes med resultaten från en grupp personer som hade IQ ≥70. Personer med IQ <70 hade en nästan dubbelt så hög risk att inte vara anfallsfria vid långtidsuppföljningen. Denna skillnad kvarstod, om än något mindre uttalad, efter att hänsyn tagits till viktiga skillnader mellan grupperna vad gäller exempelvis orsak till epilepsin. Även om endast ett fåtal i IQ <70-gruppen blev fullständigt anfallsfria uppnådde en majoritet antingen längre perioder av anfallsfrihet trots enstaka kvarstående anfall alternativt en kraftig minskning av anfallsfrekvensen. Resultaten talar för att personer med intellektuell funktionsnedsättning och svårbehandlad epilepsi bör erbjudas epilepsikirurgisk utredning. De och deras anhöriga bör dock under beslutsprocessen som föregår operation informeras om den låga sannolikheten för anfallsfrihet för att säkerställa att förväntningarna på ingreppets effekter är realistiska.

I den tredje studien undersöktes behandlingsresultat med avseende på både anfallsfrekvens och läkemedelsbehandling i en grupp barn som opererats med resektiv kirurgi före fyra års ålder. De flesta barnen hade flera anfall per dag i genomsnitt och hade utöver epilepsin även en motorisk eller intellektuell funktionsnedsättning. Komplikationer efter operationen var ovanliga och förekom inte i högre utsträckning än hos äldre barn eller vuxna. Två år efter operation var knappt hälften av barnen anfallsfria och ytterligare en fjärdedel hade en kraftigt minskad anfallsfrekvens. Bäst anfallsresultat sågs hos de barn som opererats i tinningloben eller med så kallad hemisfärotomi. Det senare ingreppet innebär att den ena hjärnhalvan kopplas bort från resten av hjärnan och utförs bara när det finns mycket utbredda skador i en av hjärnhalvorna som i sin tur orsakar epilepsin. Vid långtidsuppföljningen fem eller tio år efter operation var hälften av barnen fortsatt anfallsfria och de allra flesta av dessa hade helt kunnat sluta ta medicin mot epilepsi. Av barnen som vid långtidsuppföljningen fortfarande

hade anfall var anfallsfrekvensen betydligt lägre än före operationen hos de allra flesta. Resultaten från studien illustrerar att epilepsikirurgi kan bota eller påtagligt lindra epilepsin även hos mycket unga barn. Barn med svårbehandlad epilepsi bör därför remitteras tidigt för utredning i syfte att ta reda på om kirurgi är ett lämpligt behandlingsalternativ.

Epilepsikirurgi är en förhållandevis ovanlig behandling och när det gäller vissa operationstyper kan det röra sig om några enstaka ingrepp per år i hela Sverige. Det medför att kunskapen om behandlingsresultat för vissa patientgrupper bygger på små studier som ofta även har metodologiska brister. En del av dessa svårigheter kan överbryggas genom att ett gemensamt uppföljningsprotokoll används i flera länder. Det fjärde delarbetet i avhandlingen beskriver ett sådant protokoll för uppföljning av barn i hela Norden, d.v.s. Sverige, Danmark, Finland och Norge, som genomgår ett antal ovanliga epilepsikirurgiska ingrepp. Dessa är resektiv kirurgi före fyra års ålder samt hemisfärotomi, callosotomi och ingrepp mot hypotalamushamartom upp till 18 års ålder. Utöver uppgifter om epilepsin innehåller uppföljningsprotokollet strukturerade bedömningar av kognitiv nivå samt hälsorelaterad livskvalitet hos såväl barnen som deras föräldrar. Samtliga bedömningar kommer att utföras såväl före som två och fem år efter operationen. Resultaten från uppföljningsstudien förväntas kunna bidra till att öka kunskapen om hur kognitiv utveckling och livskvalitet påverkas på lång sikt efter ett antal ovanliga epilepsikirurgiska ingrepp. Denna kunskap är viktig för att kunna ge korrekt och individanpassad information till barn och föräldrar som står inför beslutet att acceptera eller avböja erbjudande om operation.

LIST OF PAPERS

The thesis is based on the following papers:

I. Reinholdson J, Olsson I, Edelvik Tranberg A, Malmgren K. Long-term employment outcomes after epilepsy surgery in childhood. *Neurology.* 2020; 94(2): e205-e216.

II. Reinholdson J, Olsson I, Edelvik Tranberg A, Malmgren K. Low IQ predicts worse long-term seizure outcome after resective epilepsy surgery – A propensity score matched analysis. *Epilepsy Research.* 2023; 191: 107110.

III. Reinholdson J, Olsson I, Edelvik A, Hallböök T, Lundgren J, Rydenhag B, Malmgren K. Long-term follow-up after epilepsy surgery in infancy and early childhood – a prospective population based observational study. *Seizure.* 2015; 30: 83-89.

IV. Reinholdson J, Malmgren K, Chaplin J, Olsson I, Hallböök T. Method considerations and study protocol for a Nordic multi-centre prospective study on outcomes in rare paediatric epilepsy surgery subgroups. *Acta Paediatrica.* 2023; 112(5): 924-930.

ABBREVIATIONS

ASD: autism spectrum disorder

ASM: anti-seizure medication

DBS: deep brain stimulation

DQ: developmental quotient

DRE: drug-resistant epilepsy

EEG: electroencephalography

ELDQOL: Epilepsy and Learning Disability Quality of Life

FBTCS: focal-to-bilateral tonic-clonic seizure

FCD: focal cortical dysplasia

FLR: frontal lobe resection

HRQoL: health-related quality of life

HS: hippocampal sclerosis

ID: intellectual disability

ILAE: International League Against Epilepsy

IQ: intelligence quotient

LEAT: low-grade epilepsy associated tumour

LiTT: laser interstitial thermotherapy

MCD: malformation of cortical development

MLR: multilobar resection

MTLE: mesial temporal lobe epilepsy

mTOR: mammalian target of rapamycin

MRI: magnetic resonance imaging

PET: positron emission tomography

QOLCE: Quality of Life in Childhood Epilepsy

QOLIE: Quality of Life in Epilepsy

RCT: randomised controlled trial

RNS: responsive neurostimulation

SEEG: stereo-electroencephalography

SEEG-guided RF-TC: stereo-EEG guided radiofrequency thermocoagulation

SNESUR: Swedish National Epilepsy Surgery Register

SPECT: single-photon emission computed tomography

TLR: temporal lobe resection

TSC: tuberous sclerosis complex

VNS: vagus nerve stimulation

CONTENTS

1: INTRODUCTION 1
Definition and classification of epileptic seizures and epilepsies 1
Causes of epilepsy 1
Epidemiology of epilepsy 2
Neurodevelopmental co-morbidity in childhood onset epilepsy 2
Pharmacological treatment of epilepsy 3
Epilepsy surgery: basic concepts and overview of clinical applications 4
Adverse effects of epilepsy surgery 6
Seizure outcome after epilepsy surgery – methodological aspects 7
Seizure outcome after resective surgery 9
Seizure outcome after callosotomy 11
Non-seizure outcomes of epilepsy surgery 11
Non-seizure outcomes – cognition 12
Non-seizure outcomes – educational attainment and employment 13
Non-seizure outcomes – health-related quality of life 13
2: AIM 15
3: PATIENTS AND METHODS 16
The Swedish National Epilepsy Surgery Register 16
Paper I 19
Paper II 23
Paper III 25
Ethical approval 27
RESULTS AND DISCUSSION 28
4: EDUCATIONAL AND EMPLOYMENT OUTCOMES AFTER EPILEPSY SURGERY IN CHILDHOOD OR ADOLESCENCE (PAPER I) 28
Description of the population included in Paper I 28
Educational attainment of patients with IQ ≥70 28
Employment outcome of patients with IQ ≥70 32
Educational attainment and full-time employment in patients with IQ ≥70 compared to the general population 33
Educational attainment and employment outcome of patients with IQ <70 35
Predictors of employment 35
Strengths and limitations 36
Conclusions 37
5: SEIZURE OUTCOME AFTER RESECTIVE EPILEPSY SURGERY IN PATIENTS WITH LOW IQ (PAPER II) 38

Description of the population included in Paper II 38
Long-term seizure outcome of the full cohort of patients with IQ <70 38
Predictors of seizure outcome in patients with IQ <70 39
Low IQ as a predictor of seizure outcome 41
Strengths and limitations 42
Conclusions 42
6: SEIZURE OUTCOME AFTER RESECTIVE EPILEPSY SURGERY IN INFANCY AND EARLY CHILDHOOD (PAPER III) 44
Description of the population included in Paper III 44
Seizure outcome two years after surgery 44
Two-year seizure outcome in relation to type of surgery 45
Two-year seizure outcome in relation to histopathology 47
Long-term seizure outcome 47
Medication outcome 48
Complications 48
Strengths and limitations 49
Conclusions 49
7: METHODOLOGICAL ISSUES IN THE STUDY OF RARE PAEDIATRIC EPILEPSY SURGERY PROCEDURES (PAPER IV) 51
Study design and cohort size – general considerations 51
Methodological issues in the assessment of health-related quality of life outcome 52
Methodological issues in the assessment of cognitive and developmental outcome 55
A Nordic multi-centre study of rare paediatric epilepsy surgery procedures 56
Choice of health-related quality of life instruments for the Nordic study 57
Conclusions 58
8: CONCLUSIONS IN SUMMARY 59
9: FUTURE PERSPECTIVES 60
ACKNOWLEDGEMENTS 61
BIBLIOGRAPHY 63
ORIGINAL PUBLICATIONS 75

1: INTRODUCTION

Epilepsy is a chronic neurological disorder characterised by recurrent unprovoked seizures. [1,2] In addition to the direct effects of seizures in terms of physical injury and loss of control over body functions, epilepsy is associated with an increased risk of cognitive and psychological disturbances, educational underachievement and unemployment, and a decreased health-related quality of life (HRQoL). For a subset of people with drug-resistant epilepsy (DRE), surgical treatment is an important therapeutic option. [3,4] This thesis addresses some understudied aspects of outcomes after epilepsy surgery with special emphasis on children and adolescents.

Definition and classification of epileptic seizures and epilepsies

The International League Against Epilepsy (ILAE) defines epilepsy as "a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures". [1] In clinical practice, the diagnosis of epilepsy usually requires at least two unprovoked seizures more than 24 hours apart. [2] Rather than a homogenous entity, epilepsy can be seen as an umbrella term denoting a heterogeneous group of diseases with widely varying underlying causes. In the current framework adopted by the ILAE in 2017, two main pillars upon which epilepsy classification rests are seizure type and aetiology. [5,6]

An epileptic seizure is a transient phenomenon caused by excessive, synchronous neuronal discharges in the cerebral cortex. Seizure classification aims to categorise seizures according to mode of onset which can be focal or generalised. The classification builds upon information about the clinical manifestation of the seizure, commonly known as seizure semiology, and inter-ictal or ictal electroencephalography (EEG) data. In the case of generalised-onset seizures, seizure activity starts in widespread, bilaterally distributed neuronal networks and are generally manifested by loss of consciousness and bilateral convulsions, myoclonic jerks or general loss of muscular tone. In contrast, a focal-onset seizure first develops in a discrete cortical area from which it may or may not spread. The semiology depends on the cortical area affected and may include focal motor symptoms or isolated sensory or cognitive disturbances. In some cases, focal-onset seizure activity can spread to bilateral networks and give rise to symptoms identical to those of a generalised-onset seizure.

Causes of epilepsy

Epilepsy can be caused by a very large number of underlying disorders or alterations of neuronal functioning which can be congenital or acquired. In the current classification scheme, epilepsies are categorised aetiologically as either structural, genetic, metabolic, infectious, immune or unknown. [6] Structural aetiology implies an alteration of brain morphology that correlates with abnormal neuronal functioning in the form of an increased propensity to generate seizures. The morphological

abnormalities are often detectable by means of standard neuroimaging techniques but can also be restricted to subtle aberrations of cortical cellular architecture that are only noticeable upon microscopic tissue examination. Common examples of structural aetiology are central nervous system tumours and malformations or glial scars secondary to cerebrovascular disease. Seizures of structural aetiology often, but not always, have a focal onset. The genetic category includes both monogenic disorders such as Dravet syndrome and epilepsies with a presumed polygenic origin, for example self-limiting epilepsies of childhood. [7,8] Genetic variants implicated have been shown to affect, for example, the function of ion channels and proteins essential for synapse formation. [9] Patients with genetic epilepsies can have seizures with both focal and generalised onset. In many cases, epilepsies belong to more than one aetiological category. An example is the group of genetic-structural epilepsies caused by mutations affecting the mammalian target of rapamycin (mTOR) signalling pathway. Depending on the affected gene, alterations in mTOR signalling can be associated with isolated cortical malformations as well as the multi-system disease tuberous sclerosis complex (TSC) which is characterised by tumour-like growths in multiple organs including the brain. [10,11]

Epidemiology of epilepsy

Epilepsy is one of the most common neurological disorders in people of all ages; according to the World Health Organisation, about 50 million people worldwide have epilepsy. [12] A global systematic review of population-based studies estimated the point prevalence of active epilepsy to be approximately 0.5-0.7%. Studies from low-income countries typically yield higher figures, presumably due to a higher prevalence of epilepsy caused by central nervous system infections. [13] In Europe, the prevalence of active epilepsy has been estimated at 0.5% in children, 0.6% in adults aged 20-65 and 0.7% in the elderly. [14] The age-specific incidence rate of epilepsy is highest during the first year of life, predominantly due to genetic factors, congenital malformations and pre- or perinatal brain injury. [15-17]

Neurodevelopmental co-morbidity in childhood onset epilepsy

Children with early onset epilepsy have a high risk of impaired cognitive functions as well as behavioural and psychiatric co-morbidity. [18-24] The risk is even higher if the epilepsy turns out to be drug-resistant, which is often the case when seizures start early in life. A recent population-based study from Scotland of children diagnosed with epilepsy before three years of age showed that 36% of the children were classified as having DRE two years after diagnosis. The study also demonstrated the strong interdependence of early onset, DRE, and adverse developmental outcome as 83% of the children with DRE and 49% in the full cohort showed global developmental delay. The strongest predictor for an unfavourable cognitive outcome was the presence of a determined epilepsy aetiology

which in turn was genetic, structural or combined genetic-structural in an absolute majority of cases. [17] Studies of older children with epilepsy have shown that 20-25% have intellectual disability (ID) of varying degrees in incidence cohorts [18,25] while as many as 40% fulfilled ID criteria in a prevalence cohort of school-aged children with active epilepsy. [26] Furthermore, symptoms indicative of neuropsychiatric disorders are estimated to occur in over 50% of children with epilepsy. [26,27] Although prevalence estimates vary between studies, autism spectrum disorder (ASD) is clearly overrepresented in children with epilepsy and the occurrence of ID is a strong risk factor for ASD. [27,28] Notably, in the population-based prevalence cohort of school-aged children with active epilepsy referred to above, 21% of all children and 61% of those with ID fulfilled criteria for ASD. [26]

The increased risk of adverse neurodevelopmental outcome in children with epilepsy is explained by several factors including (a common underlying) aetiology, the effects of frequent epileptiform discharges on normal neuronal function and synapse formation, and anti-seizure medication (ASM) side effects. The relative importance of the first two factors differs depending on aetiology and epilepsy type. [29,30] In a number of genetic syndromes and neurometabolic diseases, impaired cognitive and psychomotor development is apparent before epilepsy onset, indicating a central role of aetiology in determining developmental outcome. In other cases, developmental slowing or even regression may be temporally linked to the onset of seizures, a pattern that suggests a significant deleterious effect of the epileptic activity as such. Consequently, prompt treatment of seizures can lead to improved neurodevelopment in some of these children. [31,32]

Pharmacological treatment of epilepsy

The first line of treatment for epilepsy consists of ASMs, substances that act to inhibit seizure generation by decreasing neuronal excitability. Common molecular targets include voltage-gated sodium and calcium channels and chloride-permeable $GABA_a$-receptors. [33,34] Importantly, ASMs are seizure prophylaxis and there is no solid evidence that the medications have any persistent effect on the risk for seizures after treatment cessation. As ASMs act by altering neuronal excitability, it is not surprising that they are associated with cognitive and behavioural adverse effects. [35,36] Nonspecific central nervous system symptoms including fatigue, tiredness and memory problems are reported by many patients. [37] Furthermore, several studies have demonstrated an inverse correlation between the number of ASMs taken and executive functioning, processing speed and episodic memory as measured by standardised neuropsychological tests. [38,39] The adverse effect profiles differ between ASMs. While a number of old drugs such as phenobarbital and phenytoin are known for their dose dependant depressant effect on cognitive functioning, some newer compounds such as levetiracetam and lamotrigine are better tolerated. [40] Even if cognitive adverse effects of ASMs are generally assumed to

be reversible, animal studies and research on intrauterine ASM exposure have caused concern regarding potential detrimental neurodevelopmental effects of ASM treatment during early childhood. [41,42] For ethical and practical reasons, the effect of postnatal ASM exposure on long-term neurodevelopmental outcome is difficult to study. Specifically, all observational studies of pharmacologically treated children with epilepsy are confounded by the developmental impact of epilepsy as such and its underlying aetiology. This being said, there is general consensus that the benefits of treating early onset seizures outweigh the neurodevelopmental risks of ASM exposure. Accordingly, the current ILAE guidelines for treatment of early onset epilepsy emphasise the importance of quick achievement of seizure control although adverse effects of ASMs should be monitored closely in the very young. [43]

About two in three patients achieve freedom from seizures by means of ASMs. Studies of both children [44,45] and adults [46] have shown that most patients who become seizure-free respond to the first or the second ASM tried; treatment response to successive drug regimens after the failure of first and second line treatments remains rare despite the introduction of a number of new ASMs during the last two-three decades. [47] In line with this evidence, DRE is defined by the ILAE as "[the] failure of adequate trials of two tolerated and appropriately chosen and used anti-epileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom". [48]

Epilepsy surgery: basic concepts and overview of clinical applications

Epilepsy surgery is a neurosurgical treatment modality suitable for a subset of patients with DRE. [3,4] Schematically, the surgical procedures entail resection or disconnection of epileptogenic lesions or cortical areas that are instrumental to seizure generation or propagation. If seizures originate in a discrete brain region, as is the case in focal-onset epilepsy, this region is commonly referred to as the epileptogenic zone. In order to determine if a patient is a surgical candidate or not, and to accurately inform patients about probable benefits and risks of surgery in his/her individual case, the decision to operate is preceded by a thorough evaluation by a multidisciplinary team. The aim of the workup is to delineate the epileptogenic zone and determine whether it can be safely resected without causing unacceptable neurological deficits. The corner stones of epilepsy surgery evaluations are in-hospital ictal video-EEG and high-resolution magnetic resonance imaging (MRI) of the brain. The aim of the former investigation is to determine the area of seizure onset by correlating seizure semiology to changes in the ictal EEG. This information is then compared to imaging data in order to determine if the electrographic seizure onset zone corresponds to any structural abnormality. When needed, functional imaging methods are used. These include SPECT (single-photon emission computed tomography) which measures blood flow and PET (positron emission tomography) which measures

glucose consumption. The functional imaging data are co-registered to the patient's MRI images and may render information valuable for the planning of further investigations with surgically implanted intracranial EEG electrodes. The purpose of using intracranial electrodes is to obtain a high-resolution electrographic representation of the seizure onset and spread and/or to allow for EEG recording of deeply located cortical areas, e.g. the insula. A neuropsychological assessment is also part of the presurgical evaluation. Its purpose is to assess both the global cognitive level and specific neuropsychological functions in order to better predict the risk for certain cognitive side effects of surgery, for example postoperative memory impairment. The preoperative cognitive evaluation is also important in establishing a baseline reference that allows for accurate identification of postoperative cognitive gains as well as adverse effects.

Epilepsy surgery procedures have long been dichotomised into resective or palliative operations. Resective surgery aims to eliminate seizures and is thus the only potentially curative treatment of epilepsy available to date. Only focal-onset epilepsies are amenable to resective surgery. The operations range from small lesionectomies and cortical resections of varying extent to hemispheric procedures. The latter type of operation, which is usually referred to as (total) hemispherotomy or functional hemispherectomy, is strictly speaking a disconnective procedure as the affected cerebral hemisphere is left in place with its blood supply intact. This is done to avoid the long-term sequelae associated with the original anatomical hemispherectomy technique, namely chronic superficial cerebral hemosiderosis and hydrocephalus. [49] Hemispherotomy is reserved for patients with widespread hemispheric pathology who usually have preoperative neurological deficits. In addition to open surgery, a number of minimally invasive ablative procedures including stereo-EEG-guided radiofrequency thermocoagulation (SEEG-guided RF-TC) and MRI-guided laser interstitial thermotherapy (LiTT) have emerged during the last decades. These modalities can potentially bring seizure freedom although available evidence points toward lower efficacy compared to traditional resective surgery. [50-52] As SEEG-guided RF-TC and LiTT have only recently been introduced into routine clinical practice, they are not included in this thesis which focuses on long-term outcomes.

Resective operations constitute a majority of all epilepsy surgery procedures. In adults, resections in the temporal lobe (TLR) have long predominated. [53,54] This reflects the fact that mesial temporal lobe epilepsy (MTLE), an acquired condition of multifactorial origin characterised by seizures originating in mesial temporal structures including the hippocampus, is one of the most common types of drug-resistant structural focal-onset epilepsy from adolescence and onwards, even though its prevalence in surgical series has declined during later decades. [55,56] In children, and especially in those operated on at a younger age, the distribution of surgical procedures performed is more diverse. Extratemporal resections, mostly in the frontal lobe (FLR), are comparatively more common in paediatric cohorts and

the most extensive resective operations, i.e. multilobar resections (MLR) and hemispherotomy, are mostly undertaken in young children. [54,57,58] The difference in distribution of surgical procedures between adults and children is mostly explained by the high prevalence of malformations of cortical development (MCD) causing DRE of structural aetiology in the younger age groups. The MCDs can be of varying types and sizes and affect different cortical regions, in turn necessitating different surgical approaches. [59,60]

From a surgical perspective, intractable epilepsy caused by hypothalamic hamartoma constitutes a special case. The condition, which has its onset during infancy or early childhood, is characterised by gelastic seizures, focal-to-bilateral tonic-clonic seizures (FBTCSs), endocrine abnormalities and cognitive and behavioural impairments. [61] The causative lesion is a non-neoplastic mass that is often difficult to resect in its entirety due to the close proximity to the hypothalamus, optic chiasm and major blood vessels. Depending on the size and growth pattern, partial disconnective or ablative techniques including LiTT are therefore employed in the surgical treatment. [62]

In contrast to resective surgery, palliative procedures are not undertaken with the aim to eliminate seizures. Rather, the goal is to reduce the frequency and severity of seizures through the section of neural pathways that are essential for seizure activity propagation. In practice, the operations are usually reserved for patients with multifocal structural pathology who have frequent generalised seizures incurring a high risk of physical harm. The most common palliate procedure is callosotomy, an operation that entails the partial or full-extent section of the corpus callosum. [63] In addition to traditional palliative procedures, different neurostimulation techniques including vagus nerve stimulation (VNS), deep brain stimulation (DBS) and responsive neurostimulation (RNS) have been introduced since the 1990s. While VNS can be considered a less efficacious alternative to callosotomy with the benefit of fewer adverse effects [64], the clinical utility of DBS and RNS remains to be fully determined although both are considered to be palliative interventions. [65,66]

Adverse effects of epilepsy surgery

Like all neurosurgical procedures, epilepsy surgery carries a risk for bleeding, venous thrombosis, postoperative infection and cerebrospinal fluid leakage. Such general neurosurgical complications occur in about 5% of all epilepsy surgery procedures. In a minority of these cases, i.e. approximately 1% of all procedures, further surgery including for example abscess drainage or cranioplasty is required. [67] Surgical mortality is rare; in a systematic review of resective procedures the perioperative mortality was estimated at 0.6%. [67] Furthermore, no perioperative deaths were reported in a number of large cohort studies including altogether over 3700 procedures both palliative and resective. [68-70]

In addition to general surgical complications, resection of cortical tissue entails risks of postoperative neurological deficits. These risks are higher when resections are performed in close proximity to eloquent cortex or major visual, somatosensory or motor tracts. Some postoperative deficits including verbal memory impairment after dominant medial TLR, contralateral upper quadrantanopia after TLR and worsening of hemiparesis after hemispherotomy are common after the respective types of surgery. Hence, these deficits are not always considered to be complications but rather expected adverse effects which are discussed with patients prior to surgery as part of the decision-making process. [71] Unexpected neurological deficits persisting beyond three months is observed after about 3% of all epilepsy surgery operations. [67,68]

Seizure outcome after epilepsy surgery – methodological aspects

Postoperative seizure status, *seizure outcome,* is for self-evident reasons the most extensively studied outcome domain in the epilepsy surgery literature. Although the ultimate aim of epilepsy surgery, i.e. seizure freedom, may seem straight-forward, a universally applied definition of seizure outcome remains elusive. The main reasons are differences in outcome categorisation and the temporal aspect of outcome assessment; measurements of seizure outcome in an individual need to take into account the preoperative situation as well as the time passed since surgery. The most common outcome assessment scales, namely the Engel scale and the ILAE scale, are presented below in Table 1. [72,73]

One common categorisation of seizure outcome in the literature is the simple dichotomisation of seizure-free versus not seizure-free. However, the definitions of seizure freedom vary. Both the Engel and the ILAE classification schemes recognise patients who have had sustained freedom from all seizures since surgery, including sensory seizures without impaired awareness (auras). These patients fall into the Engel class I A/ILAE class 1a and comprise the most homogenous and well-defined category from a methodological point of view. However, many studies do not distinguish class I A/1a outcomes from the broader seizure-free category and seizure freedom may in these cases be defined as Engel classes I, I A-B, ILAE class 1 or 1-2. For outcomes other than class I A/1a, the older Engel scale takes into account the whole postoperative period whereas the ILAE outcome categories refer to the year preceding follow-up. For patients with persisting seizures at the time of follow-up, both scales aim to measure change relative to the baseline seizure situation. While the ILAE scheme gauges the number of days with seizures per year and relates the figures to baseline data, the Engel scale employs a more qualitative or, as some critics argue, subjective approach in using labels such as “worthwhile improvement”, “significant reduction”, and “rare disabling seizures”. [73] Although such labels may constitute a correct description of the outcome of an individual patient, the ambiguously defined

categories complicate comparisons across different studies. It can also be noted that clinicians, and not patients, often have defined what constitutes a worthwhile improvement.

In addition to the different categorisation schemes, assessments of seizure outcome are also complicated by varying follow-up times within as well as between studies. A majority of all studies published are cross-sectional, a circumstance that could partly be explained by the fact that epilepsy surgery is a comparatively rare treatment. As a consequence, appropriately sized longitudinal cohorts take a long time to recruit, especially in single-centre settings, and require an extensive follow-up period. Nevertheless, longitudinal studies are needed to provide comprehensive knowledge about long-term outcomes.

Table 1: The Engel and ILAE epilepsy surgery outcome classifications

Engel Classification, 1993 [72]		**ILAE Classification, 2001** [73]	
Outcome category	**Definition**	**Outcome category**	**Definition**
Class I	Free of disabling seizures	Class 1	Completely seizure-free; no auras
IA	Completely seizure-free since surgery	1a	Completely seizure-free since surgery, no auras
IB	Non-disabling simple partial seizures only since surgery	Class 2	Only auras, no other seizures
IC	Some disabling seizures after surgery, but free from disabling seizures for at least 2 years	Class 3	1-3 seizure days per year; with or without auras
ID	Generalised convulsions with antiepileptic drug withdrawal only	Class 4	4 seizure days per year to 50% reduction of baseline seizure frequency; with or without auras
Class II	Rare disabling seizures ("almost seizure-free")	Class 5	Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; with or without auras
IIA	Initially free of disabling seizures but has rare seizures now	Class 6	More than 100% increase of baseline seizure days; with or without auras
IIB	Rare disabling seizures since surgery		
IIC	More than rare disabling seizures since surgery, but rare seizures for the last 2 years		
IID	Nocturnal seizures only		
Class III	Worthwhile improvement		
IIIA	Worthwhile seizure reduction		
IIIB	Prolonged seizure-free intervals amounting to greater than half the followed-up period, but not <2 years		
Class IV	No worthwhile improvement		
IVA	Significant seizure reduction		
IVB	No appreciable change		
IVC	Seizures worse		

Seizure outcome after resective surgery

Three randomised-controlled trials (RCTs) have provided unambiguous evidence of the efficacy of surgery in inducing short-term (one[74,75] or two[76] years of follow-up) seizure freedom as compared to pharmacological therapy only. In two of the trials, the intervention studied was TLR in patients with

MTLE. Participants were predominantly adults although a few adolescents were also included. At follow-up, 58% and 73% in the surgical groups were free from consciousness-impairing seizures compared to 8% and 0% in the medication groups, respectively. [75,76] In the only paediatric RCT published to date, different surgical procedures appropriate for each patient's specific type of epilepsy were studied in a diverse group of children and adolescents ≤18 years of age. Most patients underwent resective procedures although a few had palliative surgery in the form of callosotomy. At one year, 77% of the operated children and 7% of those receiving only ASMs were seizure-free defined as ILAE class 1. [74]

In observational studies of resective surgery, the proportions of seizure-free patients vary considerably, typically between 40% and 80%. The heterogeneity is explained by differences in the distribution of surgical procedures and aetiologies across studies but also by variations in follow-up times and definitions of seizure freedom. Furthermore, small sample sizes contribute to uncertainty of point estimates. [77] With regard to aetiology, low-grade epilepsy associated tumours (LEATs) and hippocampal sclerosis (HS) are predictive of favourable seizure outcomes in patients of all ages. Hippocampal sclerosis is a common pathological substrate for MTLE, and the resection is often standardised and defined by anatomical borders. Among patients operated for LEATs or HS, 60-75% are estimated to be free from consciousness-impairing seizures five years after surgery. [53,54,77,78] In adults and children, reported rates of seizure freedom are consistently higher for TLR compared to extratemporal focal resections. [53,54,57,79-83] In part, this pattern is explained by the high prevalence of HS in TLR series. The probability of seizure freedom after resective surgery for MCD varies between different types of malformations; focal cortical dysplasia (FCD) type II has been shown to be associated with better outcomes compared to FCD type I and neuronal heterotopia/microdysgenesis. [78] Hemispherotomy, which is the most extensive type of resective surgery, is highly effective in controlling seizures; most studies show that over 70% are seizure-free one year after surgery. [84] In the largest hemispherotomy series published to date, 62% were completely seizure free since surgery (Engel class IA) after five years. [85]

Longitudinal cohort studies consistently show that the proportion of patients with sustained seizure-freedom declines over time. [54,58,79,85,86] Most studies also show that relapses are most frequent during the first few years after surgery, i.e. with longer sustained seizure freedom, the relapse risk diminishes. [58,79,85] Seizure recurrence as a binary outcome is however an insufficient measure as the clinical course of patients who do relapse has been shown to vary considerably. [87] For example, in a large study of adults having undergone mostly TLR with follow-up data up to 19 years after surgery, only a minority of the patients who relapsed had persistent seizures during the rest of the follow-up period. Instead,

most had prolonged intervals of seizure freedom at some point during the study. [79] Similar results have also been demonstrated in children. [86,87]

As implied by the discussion above, epilepsy aetiology and the anatomical localisation of resection are major determinants of seizure outcome. Presumably, this is because these two factors determine the prospects of complete removal of the epileptogenic zone. In addition to aetiology and localisation, a host of other presurgical variables predictive of seizure outcome have been identified. These include a high preoperative seizure frequency [54,88], a history of FBTCSs [53,89,90], a long duration of epilepsy before surgery [54,91,92], normal or non-focal brain MRI findings [53,54], and a preoperative diagnosis of ID/low intelligence quotient (IQ) [53,93]. All these characteristics have been associated with lower chances of seizure freedom and can, with the exception of epilepsy duration and seizure frequency, be seen as indicators of multifocal or diffuse brain dysfunction.

Seizure outcome after callosotomy

Callosotomy is primarily indicated in cases of frequent drop attacks (tonic or atonic seizures), i.e. generalised seizures which cause the patient to fall and thereby incur a high risk of physical harm. Patients with drop attacks often have severe epilepsy syndromes with multiple seizure types, e.g. Lennox-Gastaut syndrome, and although drop attacks can cease entirely after surgery, complete seizure freedom is not a realistic aim. Therefore, seizure outcome after callosotomy is usually reported in terms of freedom from drop attacks instead of according to the Engel or ILAE scales. About 50% of patients have been estimated to become free from drop attacks after surgery, although estimates vary due to small sample sizes. [94-96]

Non-seizure outcomes of epilepsy surgery

Just as epilepsy has consequences for patients beyond the direct effects of seizures, epilepsy surgery may have beneficial effects in a number of domains other than seizure relief. Such secondary effects include, for example, increased independence and employment prospects, improved cognition, or freedom from ASMs and their side effects. The relative priorities of non-seizure outcome domains vary between different patient groups. In an interview study of adults undergoing presurgical evaluation, the ability to work, to hold a driver's licence, and increased independence and social abilities were frequently cited as aims for surgery. [97] Parents of children, on the other hand, may preoperatively express hopes for improved development after surgery as well as beneficial effects on attention, mood and sleep. [98] Compared to the relatively prolific literature on seizure outcome, non-seizure outcome domains have been less frequently explored in epilepsy surgery studies. This holds true especially when it comes to long-term evaluations. [99]

Non-seizure outcomes – cognition

The term cognitive outcome includes both overall cognitive ability, which is usually measured by means of IQ tests, and level of functioning within specific neuropsychological domains such as working memory, verbal memory, and processing speed. Cognitive outcomes, with a special emphasis on memory functions, have been most extensively studied in adults and older children/adolescents undergoing TLR. [100] In part, this is attributable to the high prevalence of memory impairment in non-operated MTLE patients as well as the risk of adverse effects on primarily verbal memory associated with resections involving the hippocampus. [101,102] On group level, overall cognitive ability appears to be stable in operated patients, especially in studies with shorter follow-up. [100,103] As for long-term studies, improvements of full-scale IQ have been shown in a substantial proportion of children followed up at least five years after TLR. Positive IQ change was associated with ASM discontinuation. [104] Postoperative verbal memory impairment is observed in up to 40% of adults and has been found to be associated with resection in the dominant temporal lobe and with persisting seizures after surgery. Adverse effects on memory after TLR are less pronounced in children as demonstrated by a longitudinal study in which children regained early postoperative losses in verbal learning capacity whereas adults did not. This finding indicates greater neuronal plasticity in younger patients. [105]

Paediatric studies of cognitive outcomes have predominantly focused on overall cognitive level in the form of IQ or, in the very young, developmental quotient (DQ). A meta-analysis including both short-term (<4 years of follow-up) and long-term (>4 years) studies of different surgical procedures in children aged <18 years found IQ to be stable in a majority when pre- and postoperative scores were compared. An increase of at least 10 points was seen in 21% of children whereas 14% showed a negative change of equal magnitude. Furthermore, an association between seizure freedom and positive IQ change was found in about half of the included studies. [106] Finally, the authors found some indices of an association between increasing length of follow-up and improved cognitive outcomes. This suggests that cognitive effects of surgery may take time to develop and highlights the need for long-term studies.

Preoperative developmental delay is very common in children who undergo epilepsy surgery during the first few years of life. Formal pre- and postoperative neuropsychological assessments have been reported in a few studies, mostly of limited size. [107-112] Cognitive catch-up after surgery, defined as a significant increase in IQ/DQ, has been found to be rare. [110,112] Instead, most children with moderate-severe developmental delay before surgery can be expected to have significant impairments also at follow-up in spite of seizure freedom. This being said, more subtle improvements in domains such as attention and social behaviour have been noted by parents in one study and successful surgery has

also been found to allow for accelerated cognitive development, albeit still at a slower speed than healthy peers. [109]

Non-seizure outcomes – educational attainment and employment

In addition to seizure freedom, enhanced postoperative employment prospects are considered important by adults undergoing presurgical evaluation. [97,113] Like other outcome domains, employment has been most extensively studied after TLR and, to a lesser extent, after extratemporal focal resections. Most cross-sectional studies have shown improved employment rates after surgery on group level, although estimates vary widely. [114-117] Other studies have yielded conflicting results in the form of fewer patients being employed after surgery. [118-120] Furthermore, the few longitudinal studies available show some evidence of declining employment rates with prolonged follow-up when patients approach upper middle age. [121,122] This pattern can be seen also in the general population reference figures included in one study but appears to be more pronounced in epilepsy surgery patients, also in those who are seizure-free. [122] As for predictors, seizure freedom and presurgical employment have not surprisingly been found to be major determinants of postoperative employment. [114,115,122]

All research into educational and vocational outcomes is highly dependent on the age of the participants as the findings have to be related to the phases in life during which people typically acquire an education, are part of the labour force, and finally retire. This aspect complicates the interpretation of cross-sectional studies. When it comes to studies on children, a long follow-up time is required in order to allow for a meaningful analysis of vocational outcome. As a consequence, such studies are relatively scarce. In accordance with studies in adults, there is some evidence of better educational attainment and higher employment rates in individuals who become seizure-free after surgery in childhood compared to those with persisting seizures. [123,124]

Non-seizure outcomes – health-related quality of life

Health-related quality of life has emerged as an important adjunct outcome measure in clinical epilepsy research over the last decades. [125] It is a loosely defined construct that is usually meant to denote the aspects of an individual's general well-being or life satisfaction that can be attributed to the presence, absence or treatment of disease. [126] Just like the broader term quality of life, HRQoL is inherently subjective and its measurement for scientific or comparative purposes relies on the use of valid instruments in the form of questionnaires. Although HRQoL is ideally assessed using self-report questionnaires, proxy questionnaires designed to be filled out by parents, close relatives or carers have to be used for young children and people with ID.

In the context of epilepsy surgery, HRQoL has been most thoroughly investigated in intellectually able adults and higher HRQoL has consistently been reported in seizure-free patients compared to surgical and non-surgical controls with persisting seizures. [127-136] An increasing number of studies have shown similar outcomes in children. [137-144] Furthermore, there is some evidence, both from adult [145] and paediatric studies [146,147], of improved HRQoL also in patients with persisting seizures. In these studies, improvements have been seen in patients with a large reduction in seizure frequency relative to baseline [145] and in those with at least "worthwhile improvement" (Engel II-III/ILAE 3). [146,147] Paediatric HRQoL studies published to date have predominantly covered outcomes after focal resections and the children included have had an IQ in the lower normal range. In one previous paper on HRQoL outcomes one year after focal resections, children with and without ID were compared. HRQoL was found to improve after surgery and while the children with ID were found to have lower overall scores, the magnitude of improvement was similar across the two groups. When it comes to studies on hemispherotomy, few report HRQoL outcomes. Although there is evidence of satisfactory post-surgery HRQoL on group level in retrospective analyses, most studies lack preoperative assessments and sample sizes are small, limiting comparisons of clinical subgroups. [130,148-151] Only in one study, which was restricted to adults, baseline and postoperative HRQoL scores were compared. The study showed a small but statistically significant increase at group level. [148] Studies on HRQoL after callosotomy come with limitations similar to those of the hemispherotomy literature. Retrospective HRQoL as reported by parents or caregivers has been found to be favourable in small surgical series. [152-156] Reduced frequency of drop attacks and improved alertness and attention after callosotomy have been mentioned as instrumental for improved HRQoL. [156-159]

2: AIM

The overarching aim of this thesis was to advance the knowledge about long-term outcomes after epilepsy surgery in a number of patient groups in which the current evidence is insufficient. These patient groups, which consist predominantly of patients operated during childhood or adolescence, are characterised by early epilepsy onset and a high prevalence of neurodevelopmental co-morbidity.

The aims of the individual papers were:

I: To describe and analyse long-term social outcomes in the form of educational attainment and employment status of adults who underwent epilepsy surgery in childhood or adolescence.

II: To describe long-term seizure outcomes after resective epilepsy surgery in patients with preoperative intellectual disability and to test the hypothesis that intellectual disability is a risk factor for having persisting seizures after surgery.

III: To describe and analyse outcomes with respect to seizures and ASM treatment after resective epilepsy surgery in children operated on before four years of age.

IV: To describe methodological considerations and a study protocol for a Nordic population-based follow-up programme covering seizure as well as non-seizure outcomes in children aged <4 years undergoing resective epilepsy surgery and children aged ≤18 years undergoing hemispherotomy, callosotomy or surgery for hypothalamic hamartoma.

3: PATIENTS AND METHODS

Paper I, II and III are prospective, population-based observational studies which all build upon data from the Swedish National Epilepsy Surgery Register (SNESUR). In this chapter, the general structure of the SNESUR is presented followed by separate descriptions of the methods used in Paper I-III. Paper IV is a study protocol and will be discussed in Chapter 7.

The Swedish National Epilepsy Surgery Register

Since 1990, all patients in Sweden who undergo neurosurgical treatment for epilepsy have been followed up through the SNESUR, a register initiated by the Swedish National Board of Health and Welfare for the purpose of quality control. Epilepsy surgery in Sweden is presently performed at the six university hospitals in Gothenburg, Linköping, Lund, Stockholm, Umeå and Uppsala. The multidisciplinary epilepsy surgery teams at these hospitals all contribute to the register which ensures population-based inclusion of patients. During the first years while establishing the register, some operations were included retrospectively. Since 1995, the data collection has been entirely prospective. A prerequisite for inclusion in the register is that the primary surgical indication is seizures, i.e. patients having tumour resections motivated by oncological considerations or mass effect symptoms are not included, even though they also may have seizures.

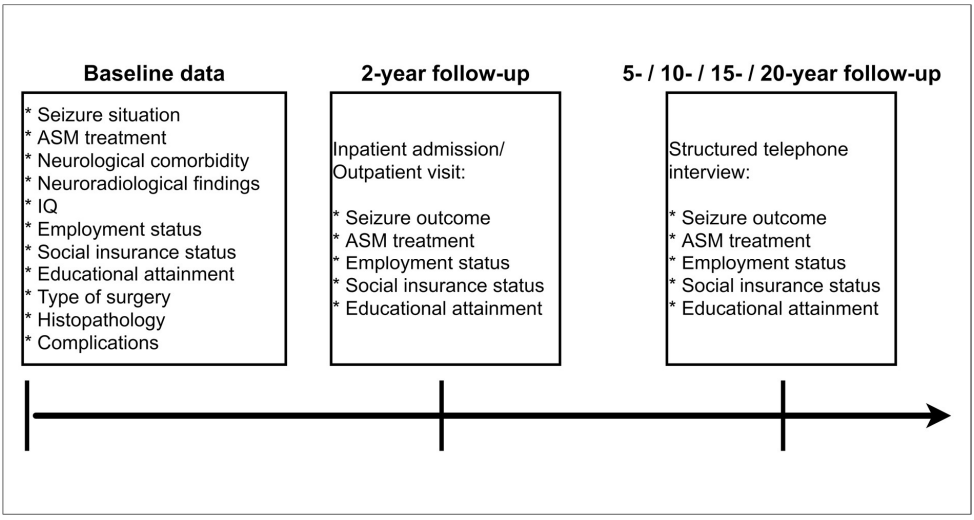

Figure 1: *Data collection in the SNESUR at each time point.*

All data entered into the register are reported according to a structured protocol. An overview of baseline and follow-up data in the register is presented in Figure 1. Preoperative data are reported at the end of the presurgical evaluation when the decision to proceed to surgery has been made by the treating clinicians together with the patient or his/her parents/caregivers. The preoperative variables include seizure frequency, seizure types, ASM treatment, neurological co-morbidity, IQ and neuroradiological findings. Social data encompassing employment status, educational attainment and social insurance status are also ascertained. Preoperative seizure frequency is defined as the mean monthly number of seizures of all types per month during the year preceding surgery. The information about preoperative as well postoperative seizure status is based on reports from patients and/or parents or caregivers. Intelligence quotient is reported to the register categorised as ≥70, 50-69 or <50. An IQ <70 is used as a cut-off for ID. [160] Assessments of IQ are made by means of age-appropriate Wechsler scales. In young children, DQ as measured with mental development scales including Griffiths and Bayley is used instead of IQ. Three months after the operation, surgical data are reported. These encompass type of surgery, histopathological diagnosis and complications. Complications are categorised as minor or major. [71] The former category is defined as complications resolving within three months whereas the latter includes all complications that persist beyond three months and result in an impact on the activities of daily living of the patient. Persisting unexpected neurological deficits are considered major complications regardless of their impact on activities of daily living. In this thesis preoperative and surgical data, with the exception of complications, are referred to together as baseline characteristics.

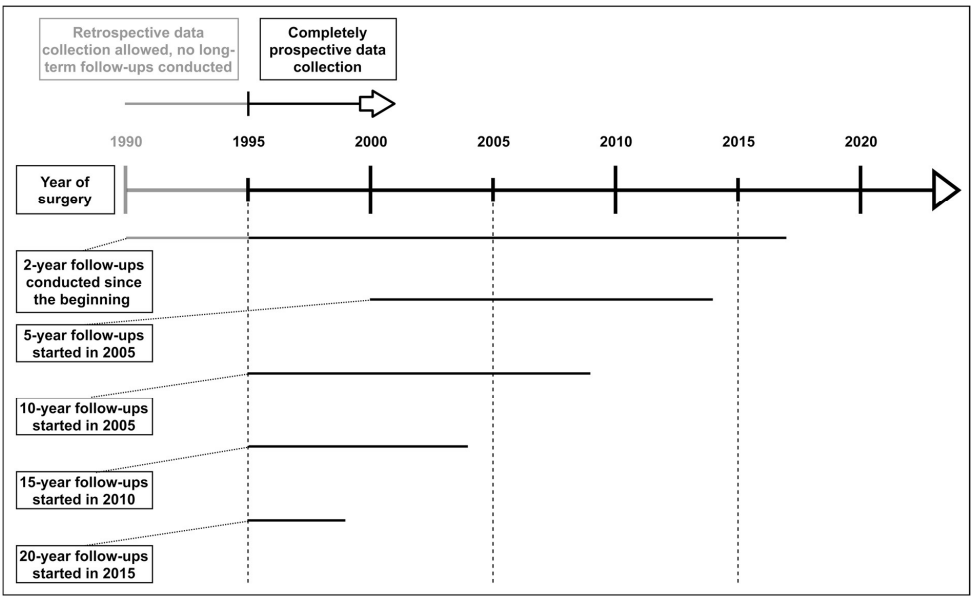

Figure 2: *Timeline of operations and follow-ups registered in the SNESUR as of 2020, i.e. when the last data extraction for this thesis took place. Horizontal lines under the main timeline represent the time spans during which patients that completed each follow-up were operated. For example: In 2020, 15-year follow-up data were available in patients operated between 1995 and 2004. Grey segments represent operations not included in any paper in this thesis, i.e. in patients operated 1990-1994.*

Since the start of the SNESUR, follow-ups two years after surgery have been conducted. These follow-ups are constituted by inpatient admissions or outpatient visits to the neurological or neuropaediatric clinic at the hospital where the patient was operated. At the 2-year follow-up, information about the current seizure situation and the use of ASMs is registered along with social data. Patients operated between 1990 and 1994 were only followed up two years after surgery and are not included in the papers in this thesis. Long-term follow-ups of patients operated in 1995 and onwards were initiated in 2005. These follow-ups are conducted in the form of structured telephone interviews by epilepsy nurses at the participating centres. Long-term follow-ups of each patient are conducted every fifth year since surgery meaning that patients operated between 1995 and 1999 had their first long-term follow-up ten years after surgery. The first 15-year and 20-year follow-ups were conducted in 2010 and 2015, respectively, as can be seen in Figure 2.

Paper I

In Paper I, data on patients operated before 19 years of age between 1995 and 2012 undergoing all types of epilepsy surgery procedures were analysed. Four partly overlapping follow-up cohorts containing patients with 5-year, 10-year, 15-year and 20-year follow-up data, respectively, were formed. Inclusion into each cohort was restricted to patients who were at least 19 years old at the time of follow-up. This restriction was added as to only include patients who had reached an age at which paid work or participation in postsecondary education is norm. In all, 72, 127, 105 and 42 patients were included in the 5-year, 10-year, 15-year and 20-year follow-up cohorts, respectively.

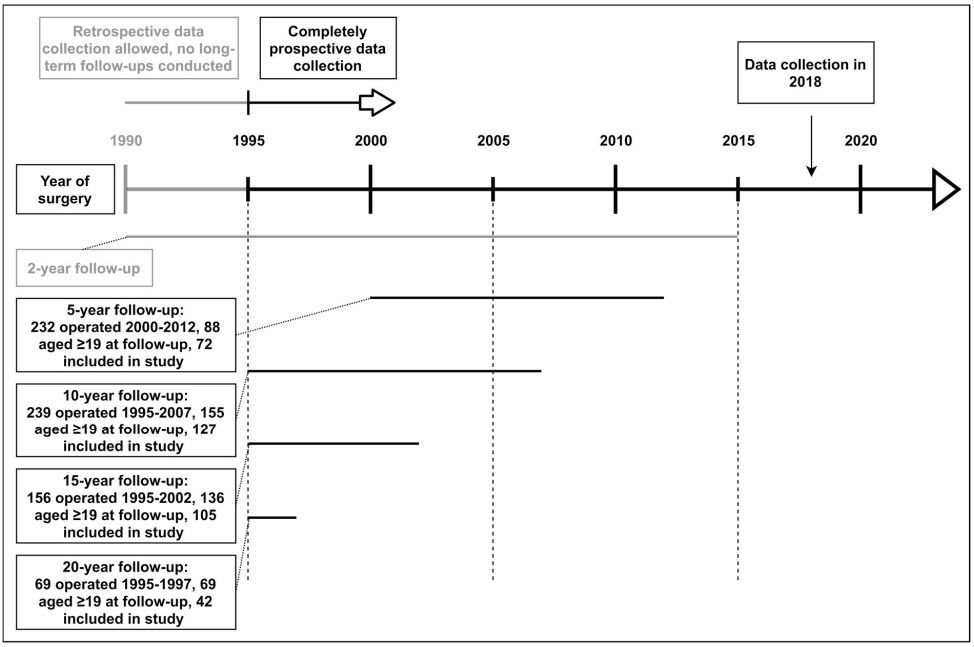

Figure 3: *Timeline of operations and subsequent follow-ups in patients included in the four follow-up cohorts of Paper I. 2-year follow-ups were not included. All patients were operated before 19 years of age. As the length of follow-up increased and more patients entered adulthood, the percentage of patients eligible for inclusion gradually increased from 88/232 (38%) at the 5-year follow-up to 69/69 (100%) at the 20-year follow-up. Reasons for non-participation among eligible patients are presented in Figure 4 below.*

The following baseline variables were analysed: gender, age at epilepsy onset, age at surgery, epilepsy duration (time between onset and surgery), neurological deficits, IQ, seizure frequency, ASM treatment and type of surgery. The IQ variable was dichotomised as ≥70 or <70. The outcome measures of Paper I were seizure outcome, educational attainment, and employment status. Seizure outcome was categorised as follows: sustained seizure freedom without auras since surgery (corresponding to

Engel class I A and ILAE class 1a), seizure freedom with or without auras during ≥1 year preceding follow-up (Engel classes I B-D and ILAE classes 1-2) or ongoing seizures during the year preceding follow-up. Educational attainment was defined as the highest level of ongoing or finished education at the time of follow-up. The following classification was used: special education (individually adapted education provided until the age of 20 years for young persons with ID), compulsory school (9 years), high school (3 further years following compulsory school) and postsecondary education (university, college or advanced vocational training). Employment status was classified into four categories: full-time employment, part-time employment, engagement in studies or reliance on social welfare benefits.

As ID is inherently linked to difficulties in obtaining a postsecondary education and finding work in the regular labour market [161,162], outcomes of patients with IQ ≥70 and IQ <70 were analysed separately. The presentation of educational and employment outcomes at each follow-up time point was stratified according to seizure outcome. In the IQ ≥70 group, Fisher's exact test was used to compare educational and employment outcomes between seizure-free and non-seizure-free patients. Two-tailed tests were used, and the significance level was set at 0.05. For the purpose of these comparisons, educational outcome was dichotomised according to attainment of postsecondary education whereas employment outcome was analysed using two different dichotomisations. In the first analysis, employment was dichotomised as full-time work vs. all other categories whereas in the second analysis, any employment was contrasted with ongoing studies and social benefits. These analyses were not performed in the IQ <70 group due to the low number of seizure-free patients.

Educational and employment outcomes of seizure-free patients with IQ ≥70 were compared to general population reference data obtained from the Swedish national statistics agency Statistics Sweden (Statistiska centralbyrån). For the purpose of these comparisons, patients were dichotomised according to age at follow-up as either 19-24 or ≥25 years old. This dichotomisation was chosen to reflect the age categories in the national reference data (i.e. 19-24 and 25-34). A few patients in the 20-year follow-up group were between 35 and 38 years old at follow-up. To avoid forming excessively small subgroups, these patients were included in the ≥25 age group and their social outcomes were hence compared to peers aged 25-34. The proportions of seizure-free patients with IQ ≥70 who attained postsecondary or high school education and who worked full-time were calculated along with 95% confidence intervals derived from the single proportion *z*-test. Educational attainment reference data were obtained from the register "Educational Attainment of the Population" which is individual based. Figures from the register thus represent absolute values for the whole population and confidence intervals are not provided by Statistics Sweden. Employment reference data including confidence intervals were taken from the register "Labour Force Surveys" which is based on samples.

Yearly general population education and employment figures for the period during which the clinical follow-ups took place (2005-2017) were analysed and mean values for the whole follow-up period were calculated. The reference figures were also weighted as to reflect the sex distribution in the patient groups of the study.

Potential predictors of employment were analysed using univariable binary logistic regression. The dependent variable was employment (full-time or part-time) and the independent variables were seizure outcome (dichotomised as seizure-free or not seizure-free during the year preceding follow-up), presence of neurological impairment at baseline, age at surgery, relative epilepsy duration (duration of epilepsy divided by age at surgery), presence of >30 seizures/month at baseline and gender. The independent variables were chosen based on findings from earlier studies. [122,163]

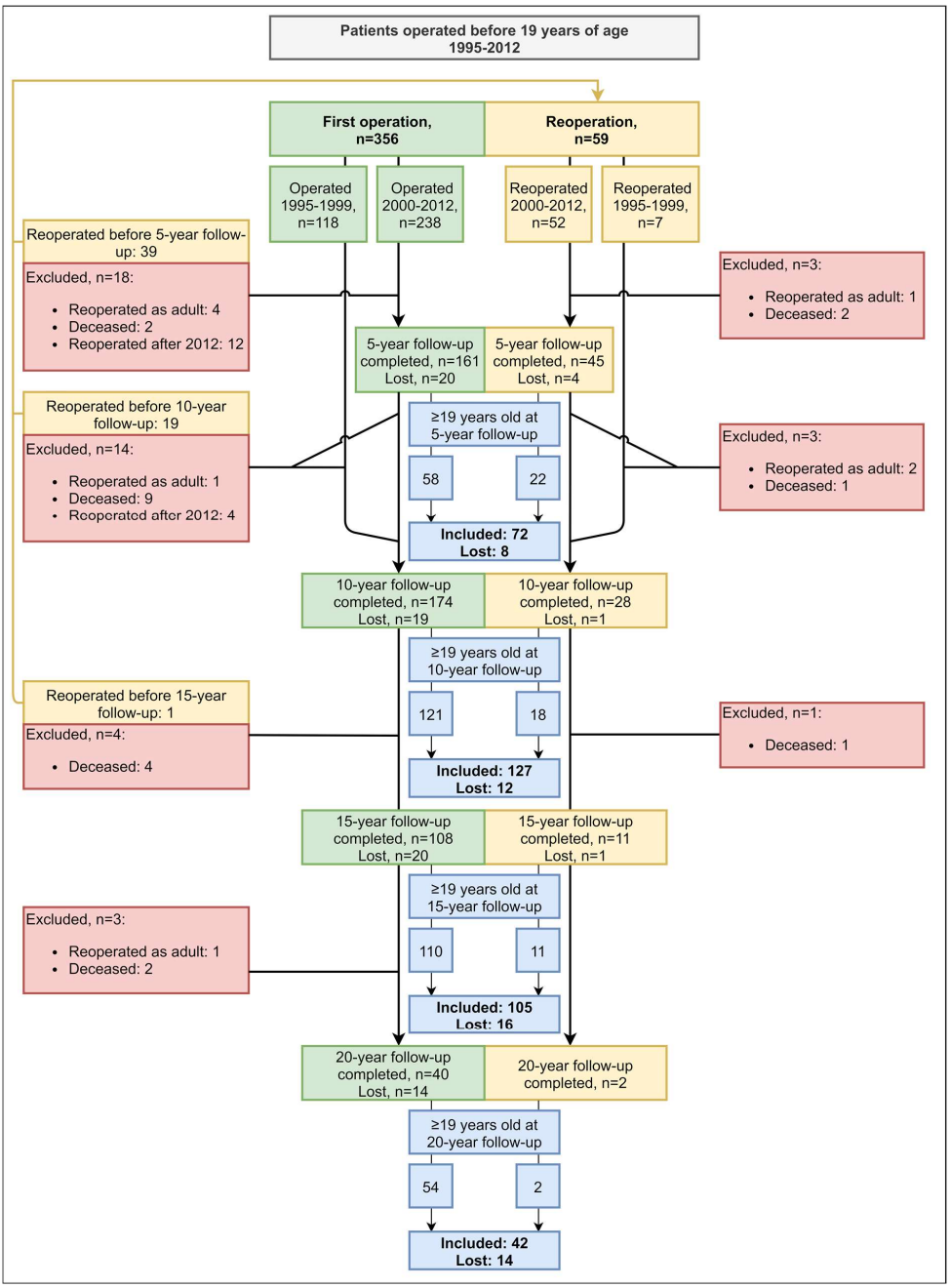

Figure 4: *Flowchart of patients included in Paper I. From: Reinholdson et al. Long-term employment outcomes after epilepsy surgery in childhood, Neurology 2020;94:e205-e216. Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.*

Paper II

Paper II included a population-based cohort of 884 patients aged ≥4 years at surgery who had focal resective procedures between 1995 and 2017. Of these, 79 had a baseline IQ <70. Analyses of the full cohort and of 74 propensity score matched pairs were performed, each pair consisting of one patient with IQ <70 and one with IQ ≥70. Outcomes at the 2-year and 5-year follow-ups and at long term were analysed. In Paper II, long term was defined as the last available follow-up out of the 10-year, 15-year and 20-year follow-ups. Patients having multilobar or hemispheric resections were not included.

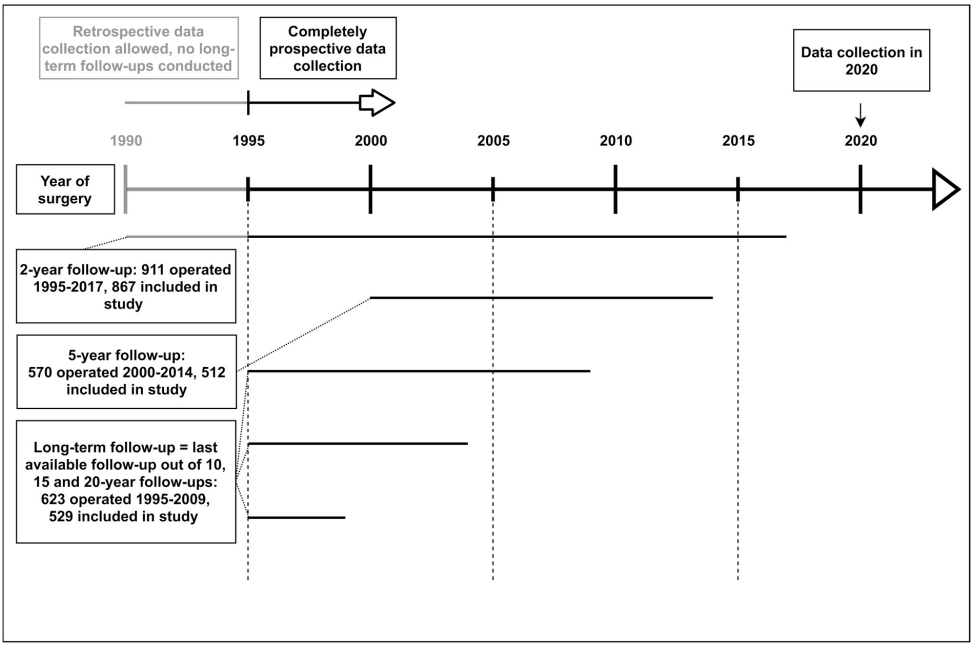

Figure 5: *Timeline of operations and subsequent follow-ups in patients included in Paper II. Reasons for non-participation are given in Figure 6 below.*

The following baseline variables were analysed: age at epilepsy onset and surgery, seizure frequency, history of FBTCs, ASM treatment, preoperative IQ, occurrence of a co-existing neurological impairment, MRI findings, type of resection and histopathological diagnosis. The outcome variable was seizure outcome at the 2-year, 5-year, and long-term follow-ups. Seizure outcome was classified into four categories with two each representing seizure-freedom and persisting seizures. Category 1 was defined as persisting freedom from all seizures, including auras, since surgery and corresponds to Engel class I A/ILAE class 1a. Category 2 corresponds to Engel classes I B-D and ILAE classes 1-2 and included patients who had only had auras since surgery or who had previously had postoperative seizures

followed by a minimum of one year of seizure freedom preceding follow-up. Patients with persisting seizures were categorised according to the change in mean monthly seizure frequency between surgery and follow-up. A reduction ≥75% was classified as category 3 while those <75% reduction, unchanged or increased seizure frequency were classified as category 4.

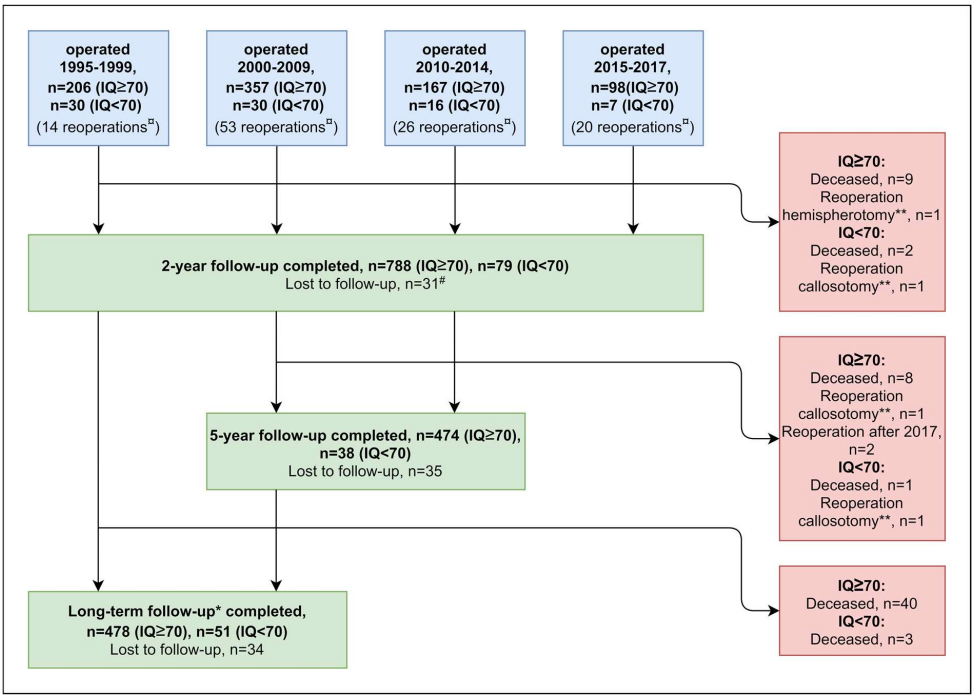

Figure 6: *Flowchart of patients included in Paper II dichotomised according to baseline IQ < or ≥70. From: Reinholdson et al. Low IQ predicts worse long-term seizure outcome after resective epilepsy surgery – A propensity score matched analysis. Epilepsy Research 2023;191:107110. Copyright © 2023 The Author(s). Published by Elsevier B.V.*

Seizure outcomes of patients with IQ <70 and IQ ≥70 were compared in the full population-based cohort and between propensity score matched groups. Matched controls for the patients with IQ <70 were selected from the larger group of patients who had IQ ≥70 by means of propensity score matching in order to adjust for confounding through differences in baseline characteristics. [164-166] Propensity scores for the full cohort were derived from a multivariable binary logistic regression analysis with IQ dichotomised as ≥70 or <70 as the dependent variable. The selection of variables was based on findings from earlier studies and included age at epilepsy onset, age at surgery, mean monthly seizure frequency at baseline dichotomised as ≤30 or >30, history of FBTCS, MRI focality, occurrence of neuroimpairment, type of surgery and histopathology. [53,54,79] Matched controls were selected using

caliper matching without replacement with a caliper width of 0.4 standard deviations of the logit of the propensity score. [165,167] Matches were found for 74/79 patients. Balance with regard to baseline variables between the matched groups was assessed by analysing standardised differences. Values <0.1 were considered insignificant. Predictors of seizure freedom in the IQ <70 group were explored using univariable binary logistic regression analysis. Seizure freedom (categories 1+2) was the dependent variable and all variables used to calculate the propensity score were tested as independent variables.

When comparing independent groups, i.e. when analysing data from the full cohort before matching, Fisher's exact test was used for dichotomous variables whereas Pearson's $\chi 2$ test was used for categorical variables with >2 categories. For continuous and ordered categorical variables the Mann-Whitney *U*-test and the Mantel-Haenszel $\chi 2$ test were used, respectively. When analysing matched data, McNemar's test, the Marginal Homogeneity test, the Wilcoxon signed-rank test and the Sign test were used as appropriate. The significance level was set at 0.05 and all tests were two-tailed.

Paper III

Paper III is an analysis of outcomes in 47 infants and young children operated before the age of four years between 1995 and 2010. Children having had all types of resective surgery, including multilobar and hemispheric resections, were included. Two-year follow-up data from all 47 children and long-term data from 32 children were analysed. In Paper III, long-term was defined as the last available follow-up out of the 5-year and 10-year follow-ups.

The baseline variables analysed include age at epilepsy onset and surgery, neurological impairments, previous and current ASM treatment, type of surgery and histopathology. The outcome variables were seizure outcome, ASM treatment and complications. The definition of seizure freedom used in Paper III allows auras as such phenomena may be hard to distinguish and thus to reliably rule out in very young children. As all children who were seizure-free at the 2-year follow-up had been so since surgery, the seizure-free outcome category at the 2-year follow-up is analogous to Engel classes I A-B and ILAE classes 1-2. When it comes to seizure freedom at the long-term follow-up, outcomes were further specified as either sustained seizure freedom since surgery or late remission of seizures, i.e. after the 2-year follow-up. Outcomes of children with persisting seizures were categorised according to the change in mean monthly seizure frequency at follow-up compared to baseline.

Seizure outcomes at the 2-year follow-up were stratified according to type of surgery and histopathology whereas long-term seizure outcomes were presented longitudinally for the whole

cohort. Results were described using means, medians, frequencies, and percentages. Due to the low number of patients in the study, no further statistical analyses were undertaken.

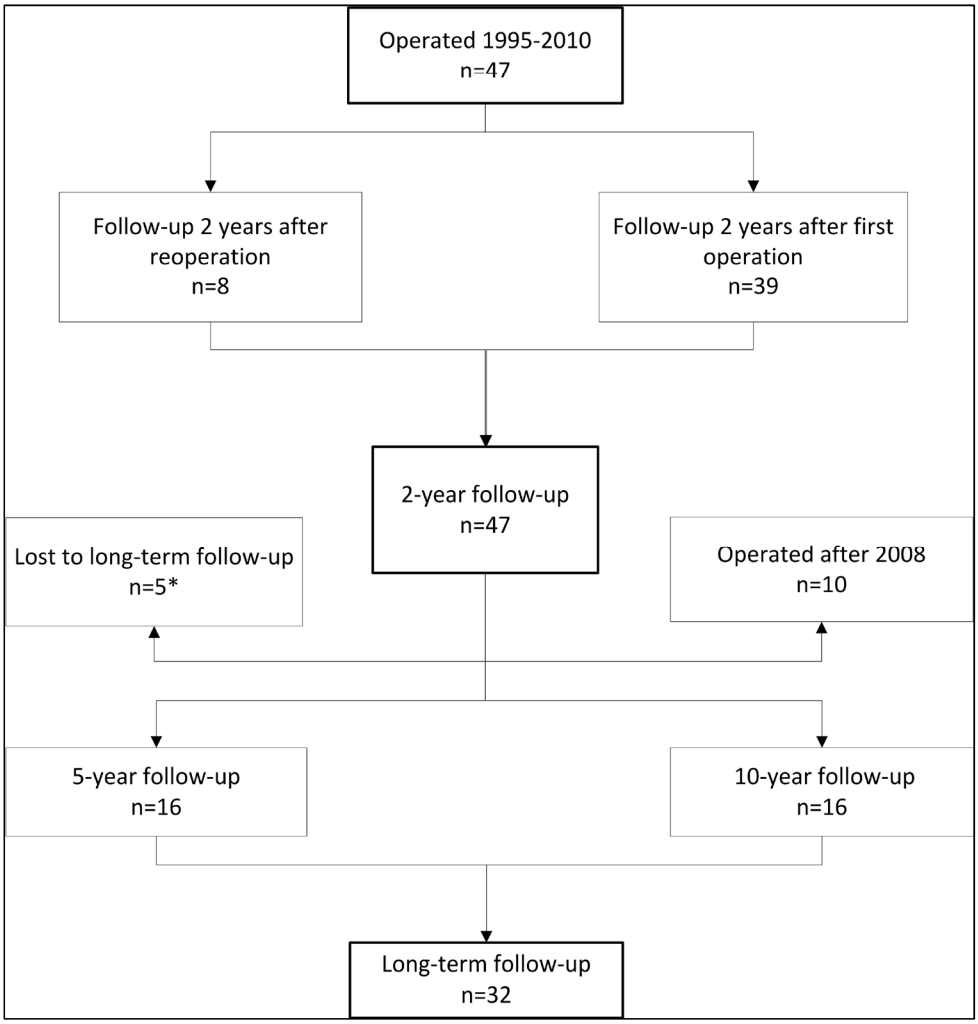

Figure 7: *Flowchart of patients included in Paper III. * One emigrated, two were reoperated >2 years after first operation, one could not be reached (all lost to 10-year follow-up), one died of reasons unrelated to epilepsy (lost to 5-year follow-up). From: Reinholdson et al., Long-term follow-up after epilepsy surgery in infancy and early childhood – A prospective population based observational study, Seizure 2015;30:83-89. Copyright © 2015 Elsevier Ltd. Published by Elsevier Ltd. on behalf of the British Epilepsy Association. Reproduced with permission from the publisher.*

Ethical approval

The research presented in this thesis is observational. All operations and other medical procedures described were undertaken based on established clinical norms within the context of the publicly funded Swedish health care system. Hence, the studies in the thesis did not alter the treatment of patients and were not associated with any risk of physical harm. Observational studies do however entail risks as regards the right to privacy due to use of sensitive personal information. To counteract these risks, register data were de-identified at an early stage in the data management and analysis process and results were only reported on group level.

Papers I-III and the extended follow-up programme presented in Paper IV were approved by the Regional Board of Medical Research Ethics at the University of Gothenburg. As Papers I-III all build upon register data, the requirement to obtain informed consent for each individual study was waived by the board. Informed consent from parents/legal guardians and, when applicable, from the children themselves, is required prior to inclusion in the extended follow-up programme presented in Paper IV. The data collection protocol in Paper IV was also approved by the relevant authorities in Denmark, Finland, and Norway.

RESULTS AND DISCUSSION

4: EDUCATIONAL AND EMPLOYMENT OUTCOMES AFTER EPILEPSY SURGERY IN CHILDHOOD OR ADOLESCENCE (PAPER I)

Long-term observational studies of people with childhood onset epilepsy have demonstrated lower educational attainment and employment rates in adult age as compared to healthy controls or general population reference figures. [25,168] Although this pattern is noticeable also in people who respond well to ASM treatment and in those without significant co-morbidities, the risk of a poor long-term social outcome is dramatically increased in people with DRE and/or neurodevelopmental co-morbidity. [25,169] Educational and employment outcomes after epilepsy surgery in childhood are of interest as such data may give an indication as to whether successful surgical treatment can mitigate the long-term adverse social effects of DRE. In this chapter, the results from Paper I will be presented and discussed in relation to earlier studies.

Description of the population included in Paper I

In all, 203 patients who had epilepsy surgery before the age of 19 years were included. Of these, 134 had an IQ ≥70 and the remaining 69 an IQ <70 at baseline. The mean age at epilepsy onset as well as at surgery was higher in the IQ ≥70 group at 7.1 and 13.6 years, respectively, compared to 1.8 and 10.6 years in the IQ <70 group. The preoperative seizure frequency and the prevalence of accompanying neurological impairments were both higher in the IQ <70 group. Temporal lobe resections predominated in both IQ groups although more so in those with IQ ≥70. Hemispherotomy, callosotomy and hypothalamic hamartoma procedures were proportionally more common in the IQ <70 group.

Educational attainment of patients with IQ ≥70

Among patients with IQ ≥70, about 80% had completed at least high school education at all follow-up time points. With increasing length of follow-up, and thus with higher age, the proportion of patients with post-secondary education increased. At the 20-year follow-up when the patients had a mean age of 31 years, 45% in the IQ ≥70 group had attained post-secondary education. We did not find any statistically significant differences in the attainment of post-secondary education between seizure-free and non-seizure-free patients except at the 5-year follow-up.

Prior to our study, educational outcome in adult age after paediatric epilepsy surgery has only been reported in a few publications, all of which have a cross-sectional design. In these studies, the proportion of patients who had attained post-secondary education ranged from 24% to 57%. [170-174] This heterogeneity may in part be explained by variations in duration of follow-up, cohort composition

with regard to clinical variables as well as age, and differences in educational systems between countries. Some studies did not clearly report on the cognitive level of the included patients, a circumstance that complicates the interpretations of educational attainment figures. [171,173,174]

One study on focal resections from Toronto, Canada, which only included patients aged >18 at follow-up, reported outcomes separately for those with normal IQ and found that 80% had attained post-secondary education at a mean age at follow-up of 22 years. In contrast to our study, IQ was assessed at follow-up and the cut-off used was 85, i.e. corresponding to -1 standard deviation. This may contribute to the considerably higher proportion with post-secondary education in that study as compared to ours. Furthermore, an earlier Canadian multi-centre study showed that 30% attained post-secondary education, a markedly lower proportion. [171] Although age at follow-up, duration of follow-up and inclusion criteria (only focal resections, age >18 at follow-up) were comparable across the two Canadian studies, no data on cognitive level were reported in the multi-centre study.

Two Dutch studies presented outcomes after all types of surgery (resective and palliative) combined [173] and resections including hemispherotomy (palliative procedures excluded). [174] In the first study, 10% had attained post-secondary education [174] whereas in the second, the corresponding figure was 24%. [173] The interpretation of these findings is complicated by the fact that both studies included a significant number of children who were still underage at the time of follow-up and that intellectual functioning was insufficiently reported. Moreover, duration of follow-up varied widely in both studies (1-17 years in the former, 4-13 years in the latter).

As for specific aetiologies, a single-centre Swedish study found that 50% of patients aged >18 had attained post-secondary education after resection of LEATs during childhood or adolescence. It should be noted that the surgical indication was tumour-related and not DRE-related in a minority. No patients had ID although two had learning difficulties. [170]

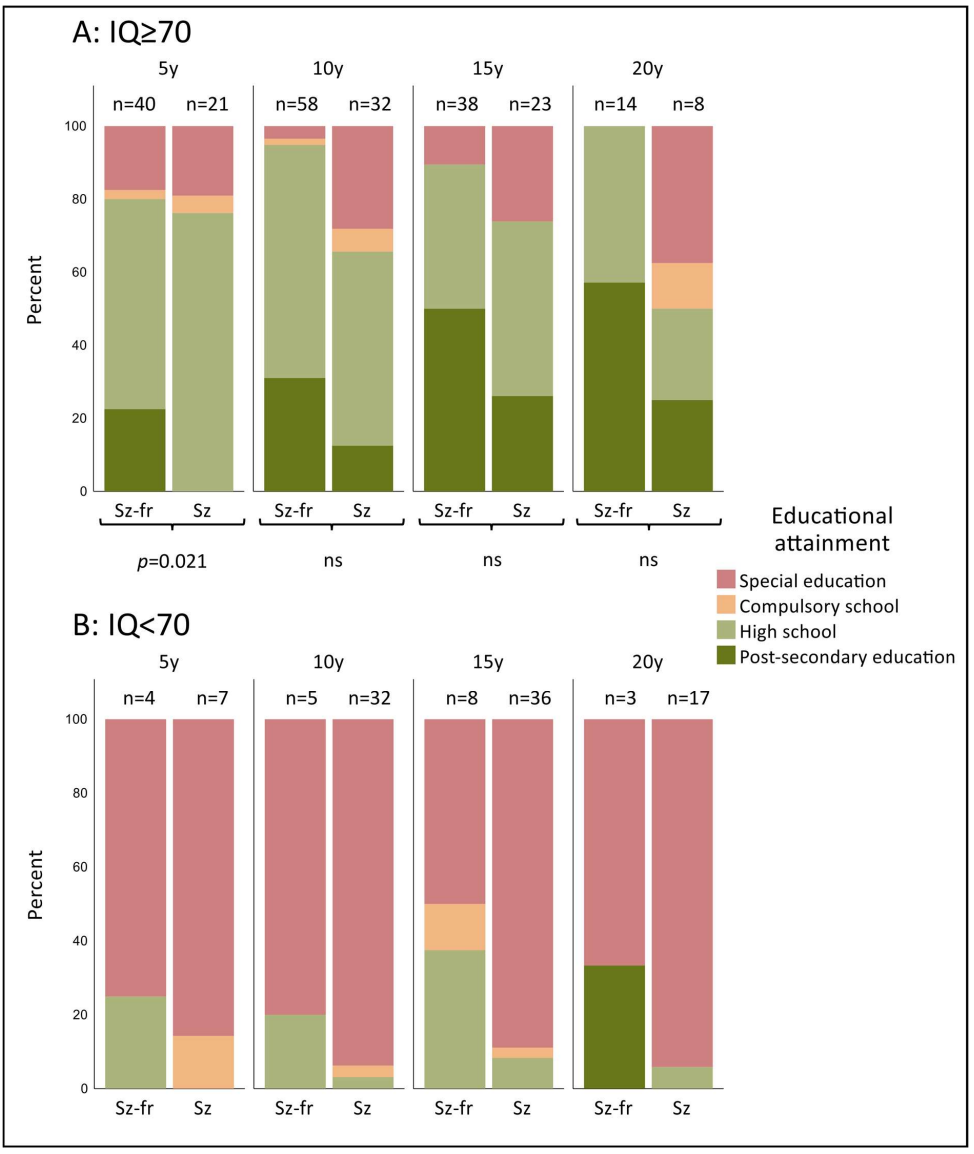

Figure 8: *Educational attainment of patients in Paper I at the 5-year, 10-year, 15-year and 20-year follow-ups stratified according to baseline IQ. P-values represent comparisons between patients in the IQ ≥70 group with and without seizure freedom at follow-up with respect to attainment of postsecondary education. Abbreviations: Sz-fr: seizure-free; Sz: seizures.*

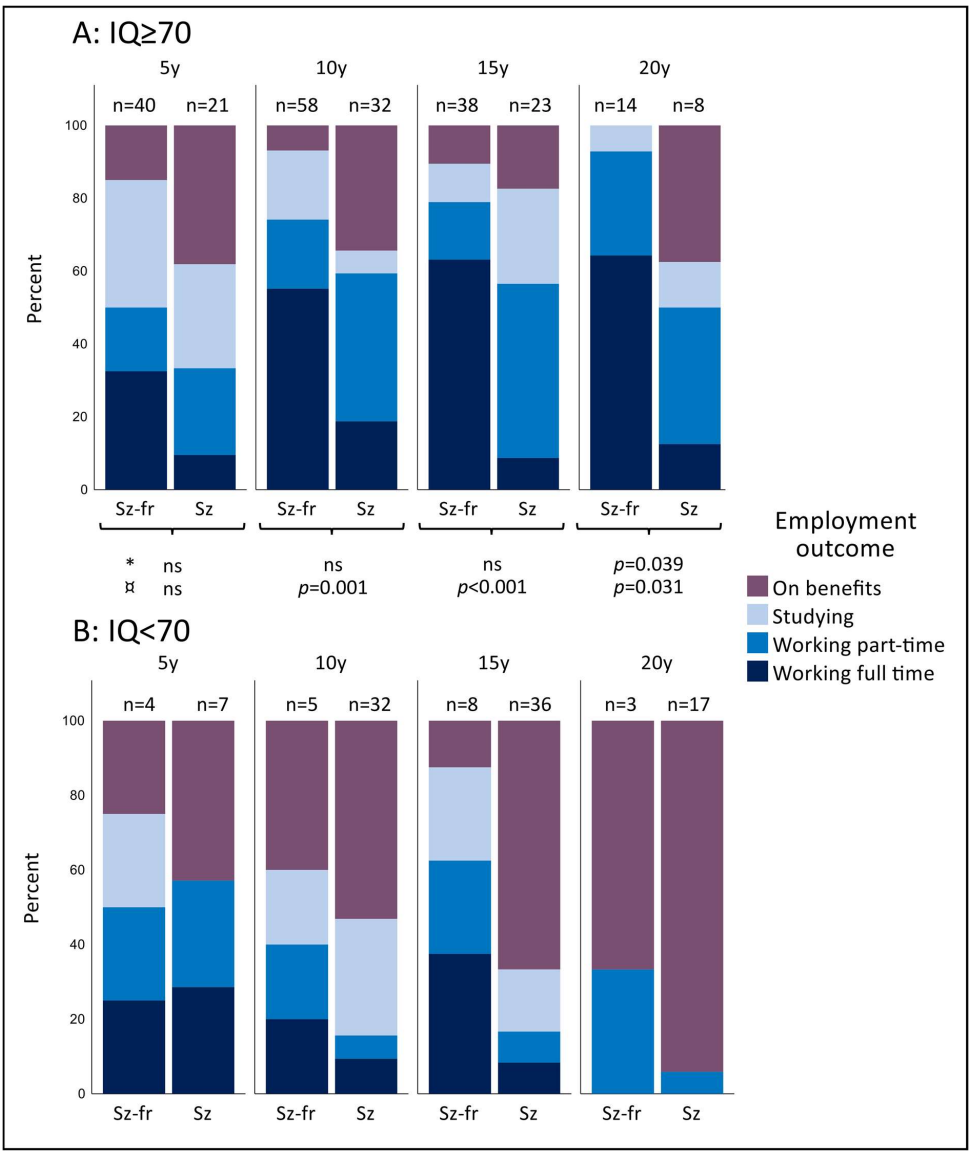

Figure 9: *Employment outcome of patients in Paper I at the 5-year, 10-year, 15-year and 20-year follow-ups stratified according to baseline IQ. P-values represent comparisons between patients in the IQ ≥70 group with and without seizure freedom at follow-up with respect to *: full-time and part-time employment combined and ¤: full-time employment. Abbreviations: Sz-fr: seizure-free; Sz: seizures.*

Employment outcome of patients with IQ ≥70

In Paper I, the proportions of patients with baseline IQ ≥70 who worked full-time were 25%, 42%, 43% and 45%, respectively, at the 5-year, 10-year, 15-year and 20-year follow-up. For part-time work, the corresponding figures were 20%, 27%, 28% and 32%. With increasing time passed since surgery, a greater proportion of patients were employed and fewer were studying. Thus, combined study and employment rates were relatively constant across the four follow-up time points at 77%, 83%, 87%, and 86%, respectively.

Like reports on educational attainment, studies of employment outcomes after epilepsy surgery in childhood are relatively scarce, arguably due to the long follow-up time required. Rates of employment (full-time or part-time) in the literature range from 33% to 81%. [123,124,170-176] In addition to geographical heterogeneity, this rather wide span reflects differences in follow-up time, age at surgery and follow-up, and cohort composition with regard to types of surgical procedures. Taking methodological differences into account, the employment outcomes in our study were generally in line with previous paediatric studies.

Most earlier studies have measured outcomes during early adulthood or late adolescence. These studies, which are best compared to the 5-year follow-up cohort in our study with respect to age at follow-up, have yielded employment rates of 33-48% whereas combined study/employment rates were 72-84%. [124,171,172,175] All four studies were from Canada; one of the studies included only patients having had TLR [175], two included focal resections in different localisations [171,172] and one study included all types of resections including hemispherotomy. [124] One of the studies reported outcomes separately for patients with IQ >85 and found an employment rate of 55% (20% full-time) and a combined study/employment rate of 95%. [172]

Few studies have followed patients beyond the first years of early adulthood. In the two previous studies with the longest duration of follow-up (mean duration 15 years [123] and 19 years [176]), 44% and 81%, respectively, were employed at last follow-up. The age at follow-up in these studies was more similar to the later follow-up cohorts in our study. The first study, which is from Japan, included patients having had all types of resections including hemispherotomy whereas the second, a series from Mayo Clinic, Minnesota, USA, only included TLR. The favourable employment outcome in the latter study is not surprising as TLR patients, on group level, tend to have less neurodevelopmental co-morbidity compared to mixed surgical cohorts.

Employment figures from studies on epilepsy surgery in adults vary, in analogy with the paediatric literature. Among larger studies, the best employment outcome has been reported after TLR (70%

employed). [115] Studies of cohorts consisting of different types of resections have yielded figures ranging from 34% to 55%. [120,122,177] Hence, long-term employment rates in our study, especially at the 15-year and 20-year follow-ups, were higher than in many studies on adults. As many adults who undergo epilepsy surgery have had epilepsy at least since adolescence, this finding indicates a potential benefit of early epilepsy surgery.

Educational attainment and full-time employment in patients with IQ ≥70 compared to the general population

An important methodological issue when comparing data on educational and vocational outcomes from different studies pertains to variations in educational systems, labour market policies and macroeconomic conditions between countries. In part, these factors can be adjusted for by comparing patient outcomes to healthy controls or a general population reference. In our study, seizure-free patients in the IQ ≥70 group had attained high school and post-secondary education to the same degree as the general population. Also, full-time employment rates in seizure-free patients with IQ ≥70 were similar to reference figures. These results are in agreement with the only other study published to date that also included general population reference data, namely the single-centre study from Toronto referred to above. [172] The authors found that 57% of the operated patients, regardless of seizure outcome, had attained postsecondary education as compared to 57% in the provincial census. It should be noted that the Canadian census data represented the 20-29 years age span. On the other hand, the Swedish reference data used in Paper I were divided into two categories: 19-24 years and 25-34 years. In the younger age span, 20% had attained post-secondary education whereas in the older, the corresponding figure was 45%. This discrepancy suggests a difference between Sweden and Canada in terms of how post-secondary education is provided and/or defined. As for employment, a composite measure of work and ongoing education was used in the Toronto study. In all, 84% of the patients were either studying or employed as compared to 87% in the provincial census. Part-time and full-time employment rates of the patients in the Toronto study were not compared to census figures. However, the study showed that wages earned by patients were significantly lower than the general population reference indicating employment in lower complexity positions and/or fewer hours worked. The aspect of occupational complexity and wages could not be addressed in our study as such detailed data are not included in the SNESUR.

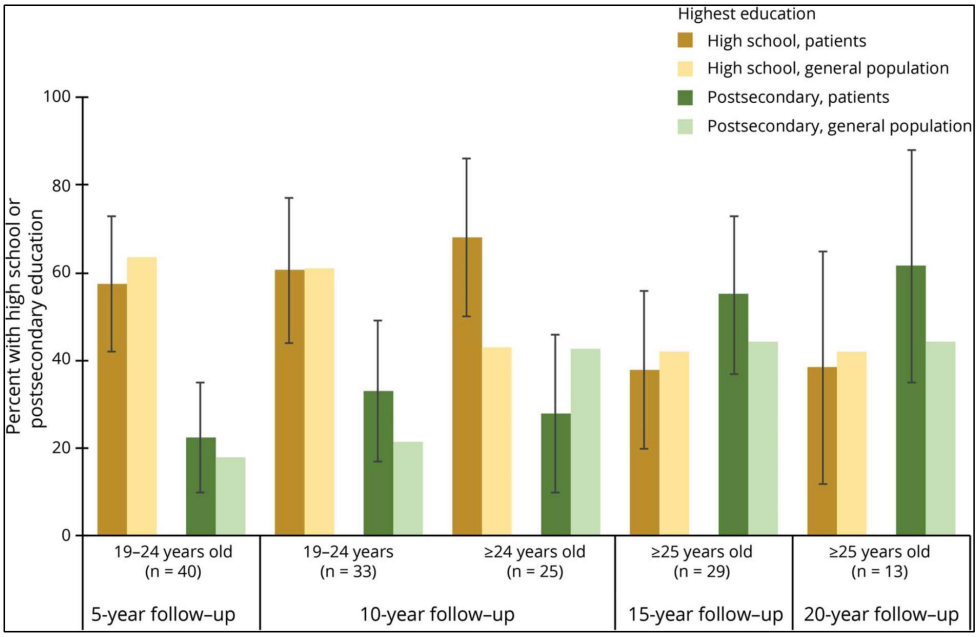

Figure 10: *Educational attainment of seizure-free patients with preoperative IQ ≥70 compared to general population reference data. Error bars represent 95% confidence intervals. From: Reinholdson et al. Long-term employment outcomes after epilepsy surgery in childhood, Neurology 2020;94:e205-e216. Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.*

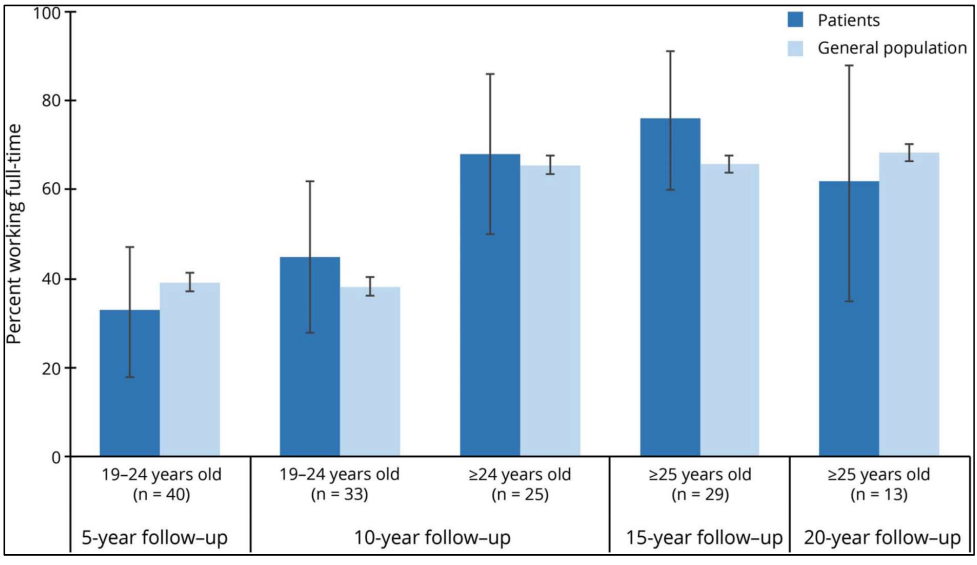

Figure 11 *(previous page)**:** Full-time employment in seizure-free patients with IQ ≥70 compared to general population reference data. Error bars represent 95% confidence intervals. From: Reinholdson et al. Long-term employment outcomes after epilepsy surgery in childhood, Neurology 2020;94:e205-e216. Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.*

Educational attainment and employment outcome of patients with IQ <70

As expected, baseline intellectual functioning proved to be strongly associated with educational attainment as a clear majority in the IQ <70 group had attended special education at all four time points. This finding is mirrored in a number of non-surgical studies which have shown the presence or absence of ID at the time of epilepsy diagnosis to be the strongest predictor of long-term educational achievement. [169,178-180] It should be noted that the number of patients with IQ <70 in Paper I was low, especially when looking at those with postoperative seizure freedom. Although the results should be interpreted with caution, a few patients with low IQ in our study, most of whom were seizure-free, had attended regular high school education and in one case even post-secondary education.

Analogous to the results with respect to educational outcomes, employment outcomes were considerably worse in patients with IQ <70 at baseline compared to those with an IQ in the normal range. The differences between the IQ groups were statistically significant at all time points apart from the 5-year follow-up ($p=1.00$, $p=0.001$, $p=0.002$, and $p<0.001$ at 5-, 10-, 15-, and 20-year follow-ups for full-time employment and $p=0.744$, $p<0.001$, $p<0.001$, and $p<0.001$ for any employment). Except at the 5-year follow-up, when the number of included patients was low (n=11), a majority were reliant on benefits. There appeared to be a trend towards more frequent engagement in work or studies among seizure-free patients, although tests for significance were not undertaken due to the low absolute number of patients. Nonetheless, our findings indicate that surgical treatment, even when successful in terms of seizure outcome, cannot be expected to substantially improve prospects of educational attainment or self-sustaining employment in the ID population.

Predictors of employment

Among patients with IQ ≥70 in Paper I, full-time employment was significantly associated with seizure freedom at the 10-year, the 15-year and the 20-year follow-ups. The point estimates of combined rates of full-time and part-time employment were also higher in seizure-free patients but the differences did not reach statistical significance except for at the 20-year follow-up. The finding that seizure freedom is associated with superior employment outcomes is not surprising and corroborates the results of a few earlier studies of people operated in childhood. [123,124,170,171] In other studies, the association between employment and seizure outcome has not been tested, presumably due to small

sample sizes and the inclusion of a significant number of underage patients. [173,174,176] Finally, two studies used a composite outcome measure consisting of work and ongoing studies. One study showed no difference depending on seizure outcome [172] whereas the other found a trend towards better outcome in the seizure-free group. [175]

As described above, baseline IQ and seizure outcome were the two major determinants of employment outcome in our study. In addition, predictors of employment (full-time or part-time) were analysed by means of binary logistic regression in the IQ ≥70 group. Few associations were found; apart from seizure freedom, only higher age at surgery (positive predictor at 10 and 15-year follow-ups) and a history of >30 seizures/month at baseline (negative predictor at 15-year follow-up) were significant in univariable analysis. Similar analyses have only been reported in one earlier study which found a positive correlation between age at epilepsy onset and the number of months employed during the study period. [171] This is in agreement with our findings and is likely to primarily reflect the fact that employment rates tend to rise with higher age in the young adult age span, a relationship not specific to people with epilepsy. Furthermore, age at surgery is strongly associated with age at epilepsy onset and with aetiology. Thus, the fact that higher age at surgery predicted better employment outcome may also, in part, be due to confounding caused by a higher prevalence of neurodevelopmental co-morbidity in children with early epilepsy onset. Finally, studies on patients operated on as adults have shown an association between lower age at surgery and higher employment rates. [115,122] The patients included in these studies had often had DRE at least since adolescence. Thus, the most appropriate interpretation of the findings in Paper I is not that surgery should be delayed; in light of previous evidence, efforts should on the contrary be made to refer children and adolescents with DRE for presurgical evaluation as early as possible to minimise the psychosocial impact of uncontrolled epilepsy during the formative period that is adolescence and early adulthood.

Strengths and limitations

Our study is the largest to date on social outcomes in a cohort of adults who underwent epilepsy surgery in childhood or adolescence. The longitudinal design and the long follow-up time make it unique among paediatric studies. Moreover, we have been able to present educational and employment outcomes stratified according to age at follow-up along with comparisons to general population reference data. These design features simplify the interpretation of the results in comparison to many earlier studies which have included both young adults and patients who were still underage at follow-up.

The study also has some limitations. These include the lack of a non-surgical reference group and small sample sizes of some subgroups, notably the 20-year follow-up cohort and seizure-free patients with

IQ <70 at all time points. Furthermore, the register-based design restricted the level of detail of the variables analysed. For example, this precluded analyses of occupational complexity.

Conclusions

Children and adolescents without ID who undergo epilepsy surgery may well have long-term educational and employment outcomes similar to the general population, if they become seizure-free. A clear majority of patients with baseline IQ in the normal range were either studying or working at follow-up, and employment rates were in line with, or more favourable than, those reported in previous smaller studies. The importance of baseline intellectual functioning and seizure outcome for predicting social outcomes found in previous surgical and non-surgical studies of childhood epilepsy was confirmed. Further studies are needed to determine if the favourable outcomes persist with increasing age and to analyse occupational complexity and wages earned.

5: SEIZURE OUTCOME AFTER RESECTIVE EPILEPSY SURGERY IN PATIENTS WITH LOW IQ (PAPER II)

Epilepsy in general, and DRE in particular, is overrepresented in people with ID. [181-184] Despite this, people with ID constitute a minority in most resective epilepsy surgery cohorts in the literature. In part, this apparent underrepresentation may be explained by the fact that multi-focal or generalised onset epilepsy of structural origin is comparatively more common in people with ID than in those without. [185] Historically, ID in itself has been considered a relative contraindication for resective surgery, at least in adult patients. The rationale for this has been that ID is a marker of widespread brain dysfunction that comes with a heightened risk for unsatisfactory seizure outcome. [186] Although the evidence behind this reasoning stems predominantly from the era before the introduction of high-resolution MRI, several studies since have found ID/low IQ to be associated with lower chances of post-operative seizure freedom. On the other hand, the relationship between low IQ and seizure outcome has rarely been analysed using multivariable or matching models to account for differences in baseline characteristics. In this chapter, Paper II will be presented and the impact of preoperative intellectual functioning on seizure outcome will be discussed.

Description of the population included in Paper II

A total of 884 patients who underwent focal resective surgery (hemispherotomy and multilobe resection excluded) at age ≥4 years were included. Of these, 79 had a preoperative IQ <70. The patients with IQ <70 differed significantly from those with IQ ≥70 on most baseline variables. Age at epilepsy onset and at surgery were both lower in the IQ <70 group. Furthermore, a greater proportion had a history of >30 seizures/month and of FBTCSs prior to surgery in the low IQ group. Accompanying neurological impairments and non-focal brain MRI-findings were also more common among patients with IQ <70. As for histopathological diagnosis, LEATs and cavernomas as well as HS were more common in the IQ ≥70 group whereas MCD and findings of non-specific gliosis predominated in the IQ <70 group. As described in Chapter 2, propensity score matching was used to select a comparison group from the full IQ ≥70 cohort that had a similar distribution of baseline variables as the IQ <70 patients. Matches were found for 74 of the 79 patients with IQ <70.

Long-term seizure outcome of the full cohort of patients with IQ <70

Seizure outcome in Paper II was reported at 2 and 5 years after surgery and at long term, the latter time point consisting of the last completed follow-up out of the 10, 15 and 20-year follow-ups. Of the patients with IQ <70, 27%, 34% and 29%, respectively, were seizure free (Engel Class I) at the 2-year, 5-year and long-term follow-ups. The proportion of patients who remained free from all seizures

including auras (i.e. Engel class I A/ILAE class 1a) declined with prolonged follow-up and was only 6% at long term. A reduction of seizure frequency ≥75% compared to baseline was observed in 35.5%, 29% and 45% of patients in the IQ <70 group at 2-year, 5-year and long-term follow-ups.

Data on long-term seizure outcomes after resective surgery in the ID population have not been published prior to our study. Most previous studies of patients with low IQ have only measured short-term outcomes, typically in the form of 1 or 2-year follow-ups. [93,185,187-192] A few cross-sectional studies have followed some patients during a longer period of up to a maximum of 7 years although mean duration of follow-up was less 5 years in most cases. [193-197] Studies including only children have yielded rates of seizure freedom, usually defined as Engel class I, that range from 33-67%. [189,191,193,195,198] Furthermore, studies on adults have shown similar figures ranging from 44-66% [185,188,190,192,197] whereas a few series including both children and adults have shown 33-47% of patients to be seizure-free after surgery. [93,187,194] Data on reduction in seizure frequency in those with persisting seizures are missing in many earlier studies. When reported, a combined category of Engel classes II-III (i.e. "rare disabling seizures" or "worthwhile improvement") has usually been used. Between 7% and 31% have, by this definition, been reported to have a favourable outcome despite persisting seizures. [187,193,197]

Upon simple comparison with the existing literature, it is clear that the proportion of seizure-free patients with low IQ in our study was markedly lower than in most previous reports. However, such comparisons are complicated by differences in study design and composition of patient cohorts. Firstly, definitions of low IQ differ across studies; even if <70 is the most common cut-off, higher limits at IQ 75 or 85 have been used by some authors. [188,190,197] Further, many previous studies have exclusively focused on TLR. [185,188,192,194,195,197,198] As TLR is well known to be associated with higher chances of seizure freedom as compared to extratemporal surgery, this may explain some of the difference in seizure outcome. Moreover, in some of the studies that also included extratemporal resections the prevalence of well-circumscribed lesions (i.e. HS, LEATs and cavernomas) was markedly higher than in the present cohort. [189,190] While the reasons for these observed differences in aetiology are unknown, one might speculate about variations in referral patterns and surgical candidate selection criteria as underlying factors. Finally, it should also be emphasised that the cohort in Paper II was population-based whereas most previous evidence comes from single-centre studies. Thus, the possibility of selection bias in some previous studies cannot be excluded.

Predictors of seizure outcome in patients with IQ <70

Few predictors of seizure outcome among patients with low IQ were found in our study, presumably due to the relatively small sample size. In univariable logistic regression analysis, only LEAT/cavernoma pathology (positive predictor) and >30 seizures/month at baseline and FLR (negative predictors) were

significantly associated with seizure outcome. These predictors have been identified also in larger studies which included patients functioning in the normal IQ range. [53,54] Previous studies focusing specifically on the ID population have not included analyses of predictors of seizure outcome.

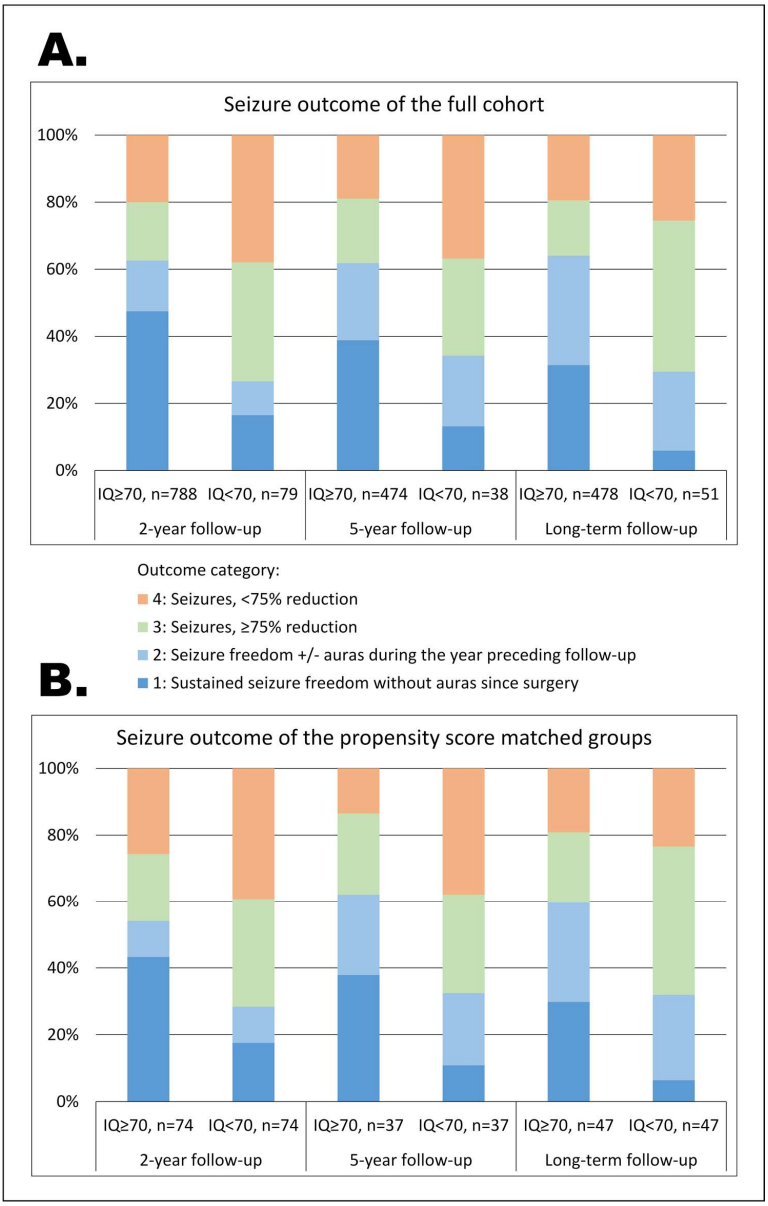

Figure 12: *Longitudinal seizure outcome stratified by baseline IQ in A) the full cohort and B) in the propensity score matched groups. From: Reinholdson et al. Low IQ predicts worse long-term seizure outcome after resective epilepsy surgery – A propensity score matched analysis. Epilepsy Research 2023;191:107110. Copyright © 2023 The Author(s). Published by Elsevier B.V.*

Low IQ as a predictor of seizure outcome

In Paper II, patients with IQ <70 had significantly worse seizure outcome at all three time points compared to patients with IQ ≥70 when results from the full cohort were analysed. At the 2-year, 5-year and long-term follow-ups, the relative risk of persisting seizures for patients with low IQ were 1.96 (95% CI: 1.67-2.30), 1.72 (95% CI 1.33-2.26) and 1.96 (95% CI 1.58-2.43), respectively. When comparing the propensity score matched groups, the corresponding figures were 1.59 (95% CI: 1.17-2.07), 1.79 (95% CI 1.12-2.86) and 1.68 (95% CI 1.13-2.51). As the propensity score matching procedure allowed for a selection of IQ ≥70 patients with baseline characteristics that did not differ significantly from the IQ <70 group, the findings indicate that low baseline IQ is an independent negative predictor of seizure freedom both at short and at long term.

A number of previous studies have shown baseline cognitive impairment to be predictive of lower chances of postoperative seizure freedom after resective surgery [53,58,93,188,192,194,195,198,199] whereas others have not found such an association. [185,189,196,197,200] As was made evident in Paper II, low IQ in surgical cohorts tends be associated with a number of other baseline characteristics that have been shown to correlate with poor seizure outcomes. Such characteristics include poorly localised brain MRI pathology, a high burden of disease both in terms of overall seizure frequency and occurrence of FBTCSs, and histopathology findings of gliosis and MCD. [53,54,88-92] In order to assess the predictive value of ID/low IQ alone, a multivariable approach is needed. This has been done in a few earlier studies which will be discussed below.

One short-term study on adults undergoing TLR showed that low IQ predicted lower chances of seizure freedom also after adjustment using multivariable logistic regression. Length of follow-up was two years and baseline IQ had an odds ratio for seizure freedom at 1.04 (95% CI 1.01-1.06) per one-step increment after adjustment for age at epilepsy onset and surgery, histopathology, and MRI and EEG findings. [192] Furthermore, an earlier study from our research group showed IQ <70 to be a negative predictor of 2-year seizure freedom in a logistic regression model adjusted for localisation of resection, histopathology, age at onset and surgery, baseline seizure frequency and accompanying neurological impairment. [93] Both children and adults were included, a subset of whom were also followed up at long-term in Paper II. Finally, Gleissner et al. used direct matching on baseline variables to compare 1-year outcomes in three groups of children with IQ <70, IQ 70-85 and IQ ≥85. Each group consisted of about 20 children matched with respect to age at epilepsy onset and surgery as well as localisation and type of resection. As mentioned previously, the proportion of children with HS or LEAT pathology was higher than in most other low IQ series. In the IQ <70 group, 67% became seizure free as compared to

77% and 78% in the other two IQ groups. The difference was not statistically significant even though it should be noted that the sample size was small. [189]

As for studies with longer follow up, Bell et al. explored longitudinal seizure outcomes in a large single centre cohort from UCL, UK. A total of 693 adults who had undergone focal resections were included and the mean follow-up time was 10 years. Temporal lobe resections constituted 82% of all procedures and 6% had a diagnosis of learning disability (as the term is understood in the UK, i.e. equivalent to ID). A multivariable cox regression model that also included age at epilepsy onset, MRI pathology, site of resection, history of FBTCS and history of psychiatric illness yielded a hazard ratio for seizure recurrence of 1.75 (95% CI 1.17-2.63) associated with learning disability. [53] Although differences in statistical models have to be accounted for, the estimated hazard ratio is strikingly similar to the relative risk ratio estimates in our study. Finally, Ka et al. found moderate to severe developmental disability defined as DQ <75 to be a negative predictor of seizure freedom at last follow-up in a paediatric cohort of 132 patients having had varying types of resections. The regression model was however insufficiently described and all covariates included could therefore not be identified. [58]

Strengths and limitations

The major strength of our study is the propensity score matching design which enabled adjustment for differences between IQ groups in a number of important baseline variables. Thus, the demonstrated association between baseline IQ and seizure outcome is unlikely to be due to confounding. Furthermore, the study is the largest to date considering the number of included patients with low IQ. It is also the first study to report long-term seizure outcomes specifically for a resective surgery low IQ cohort.

Limitations of the study include the lack of yearly seizure outcome assessments which precluded the use of survival methods, and the absence of HRQoL data in the SNESUR. The latter should be included in future studies in order to analyse how reductions in seizure frequency translate into changes in HRQoL. Moreover, the use of register data restricted the resolution of detail with regard to some variables in the study. For example, it is possible that a more detailed aetiological categorisation would have revealed additional predictors of seizure outcome in the low IQ group.

Conclusions

Despite the methodological drawbacks of some previous studies including small sample sizes, lack of data regarding important baseline variables and selectively recruited cohorts, a majority of reports in the existing literature clearly indicate that ID / low IQ at baseline is indeed associated with lower chances of seizure freedom after resective surgery. Our study strengthens the evidence base for this

claim through the inclusion of a large population based cohort, rigorous adjustment for differences in baseline variables, and a long follow-up time. The findings of our study have several clinical implications. Firstly, patients with ID and their relatives should be counselled about the relatively low chances of seizure freedom after resective surgery and especially so for sustained long-term seizure freedom. On the other hand, for a significant proportion a reduced seizure frequency by ≥75% compared to baseline was achieved meaning that about two thirds were either seizure-free or had a substantially decreased seizure burden. Given the high baseline seizure frequency in the ID population, also a substantial reduction may be of great value to patients and lead to increased HRQoL. [145] Thus, resective surgery has an important palliative potential for people with ID and DRE and this group of patients should not be excluded from access to presurgical evaluation.

6: SEIZURE OUTCOME AFTER RESECTIVE EPILEPSY SURGERY IN INFANCY AND EARLY CHILDHOOD (PAPER III)

Drug-resistant epilepsy with onset during the first years of life has a substantial negative impact on the neurodevelopment of the child. This circumstance was mirrored by the findings of Paper II which showed that the median age of seizure onset was only 1.2 years in the group of patients who were diagnosed with ID before surgery. Moreover, a large multinational survey showed that more than 50% of all children who underwent surgery had epilepsy onset before two years of age. [201] Despite this, epilepsy surgery in very young children constitute a minority of all paediatric operations undertaken. Most cohorts in the existing literature are small and especially longitudinal data are lacking. In this chapter, Paper III will be presented and discussed in relation to the existing literature on resective surgery in the very young.

Description of the population included in Paper III

During the study period, 47 children aged <4 years underwent resective epilepsy surgery in Sweden. All were followed up two years after surgery and 32 also had a long-term follow-up which was defined as the last available out of the 5- and 10-year follow-ups. A majority had onset of epilepsy during the first year of life (median 3 months, mean 7 months) whereas the median and mean age at surgery were both 25 months. Baseline seizure frequency was high with a median of 150 seizures/month during the year preceding surgery. More than two thirds had neurodevelopmental impairments, most commonly motor impairments (36%) and IQ/DQ <70 (30%) or not-otherwise-specified developmental delay (9%).

Eight patients had a reoperation during the study period whereas the other 39 were only operated once. Final surgical procedures comprised TLR in 12 (25.5%) cases, extratemporal focal/unilobar resection in 15 (32%), multilobar resection in 8 (17%) and hemispherotomy in 12 (25.5%) cases. Pathological examination of surgical specimens revealed MCD in 62% of cases. The most prevalent subtypes were unspecified FCD and hemimegalencephaly. After MCD, the most common finding was non-specific gliosis (15%).

Seizure outcome two years after surgery

At the 2-year follow-up, 21 children (45%) were seizure-free (Engel Class I). Another 12 children (26%) had a ≥75% reduction in seizure frequency, eight (17%) had a 50-74% reduction and two (4%) had a 0-50% reduction whereas four children (9%) had an increased seizure frequency. In accordance with earlier studies, seizure freedom without auras was not distinguished as a separate outcome category as auras are likely to go unnoticed in young children. Previous studies on resective surgery in infants

and young children have typically been restricted to operations undertaken before three years of age. Rates of seizure freedom in studies published prior to [107-109,202-206] or after [111,112] [110,207] our study range from 48% to 90%. Thus, the 2-year figures from our study lie at the low end of the spectrum. When comparing our study to the existing literature, it should be noted that all other studies have been cross sectional and that durations of follow-up vary considerably. A few studies have included children with less than one year of follow up [107,205,207] while others have required a minimum of one year. [109,202-204,206] [110] In the three earlier reports with a minimum of two years of follow-up, 48%, 71% and 70% were seizure-free. [108,111,112] Other factors that may influence outcomes are differences in cohort composition with regard to types of surgery and pathology, something that will be discussed below. Finally, the small size of most studies, including ours, makes point estimates uncertain.

Two-year seizure outcome in relation to type of surgery

Children who had TLR had the best seizure outcome with 8/12 (67%) being seizure-free and another 2 (16%) having ≥75% reduction in seizure frequency. In the group operated with hemispherotomy, the corresponding figures were 7/12 (58%) and 2/12 (16%). These high success rates are consistent with findings from studies of older children. [57] Although hemispherotomy counted as the most common type of surgery (25.5%, tied with TLR and FLR), all other studies on infants and young children have included a higher proportion of hemispherotomy cases. In most cases, the difference has been considerable with hemispherotomy constituting between 40% and 60% of all operations. [107-109,111,202-204] [110] While the reasons for this discrepancy are unknown, it may in part explain the higher rates of seizure freedom in many other studies as hemispherotomy is known to be associated with high chances of seizure relief.

Children having FLR and MLR had poorer outcomes in our study with only 4/12 (33%) and 1/8 (13%), respectively, being seizure-free. Surgery in the frontal lobe is known to be associated with lower chances of seizure freedom compared to temporal or hemispheric surgery. [208,209] In part, this is because proximity to eloquent cortex in the frontal lobe may preclude complete resection of the epileptogenic zone. Multilobar resections have also previously been shown to yield comparatively low rates of seizure freedom, especially when resections were done in the frontotemporal or parietal-temporal regions. [210]

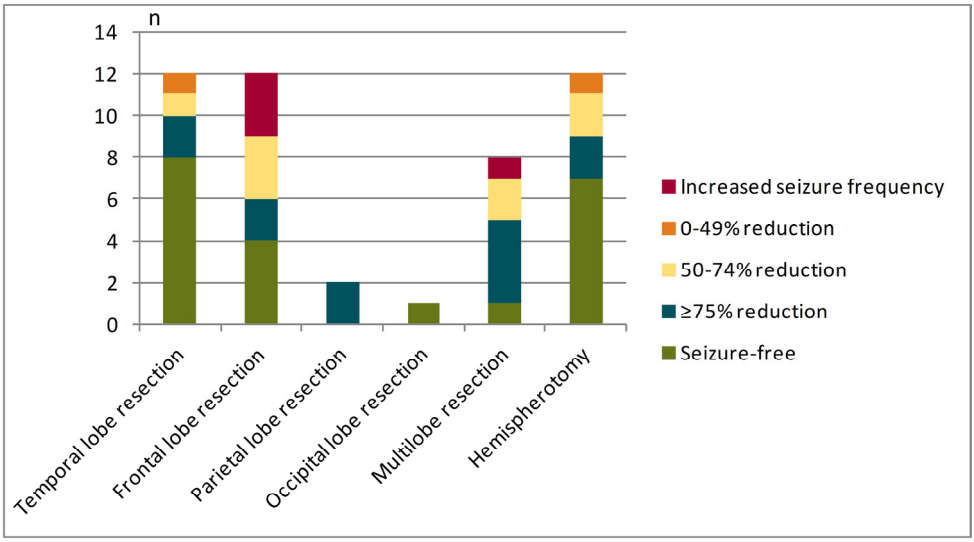

Figure 13: *Seizure outcome at the 2-year follow-up stratified according to type of surgery. From: Reinholdson et al., Long-term follow-up after epilepsy surgery in infancy and early childhood – A prospective population based observational study, Seizure 2015;30:83-89. Copyright © 2015 Elsevier Ltd. Published by Elsevier Ltd. on behalf of the British Epilepsy Association. Reproduced with permission from the publisher.*

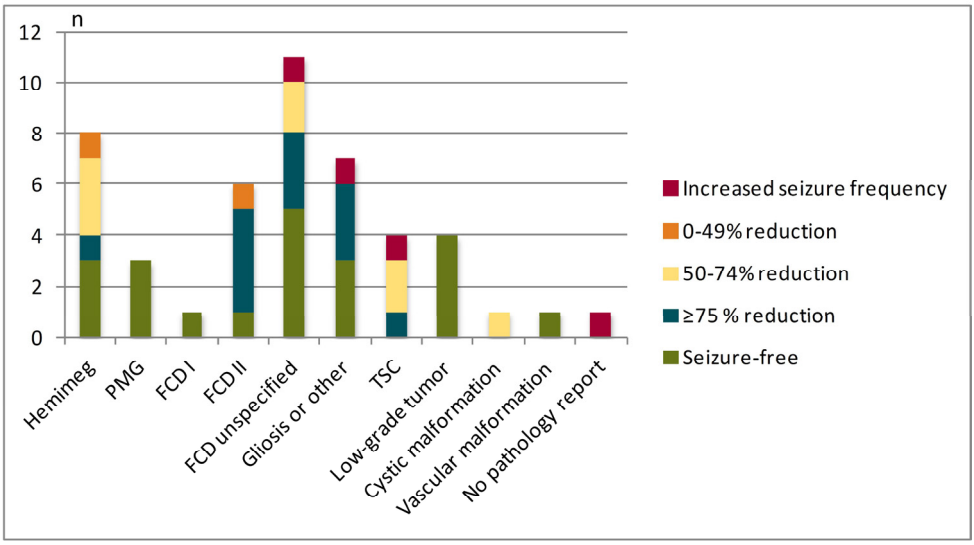

Figure 14: *Seizure outcome at the 2-year follow-up stratified according to histopathological diagnosis. Abbreviations: Hemimeg: hemimegalencephaly; PMG: polymicrogyria; FCD: focal cortical dysplasia; TSC: tuberous sclerosis complex. From: Reinholdson et al., Long-term follow-up after epilepsy surgery in infancy and early childhood – A prospective population based observational study, Seizure 2015;30:83-89. Copyright © 2015 Elsevier Ltd. Published by Elsevier Ltd. on behalf of the British Epilepsy Association. Reproduced with permission from the publisher.*

Two-year seizure outcome in relation to histopathology

In line with all other reports on infants and young children, MCD predominated in terms of histopathology. In all, 13/29 (45%) children with MCD pathology were seizure-free two years after surgery. This figure can be compared to a Japanese study of surgical treatment for MCD in children <6 years of age in which 66% were seizure-free after a mean follow-up of four years. Malformations of cortical development comprise a heterogeneous category that consists of several specific malformations which in larger studies have been shown to differ in terms of prospects for seizure freedom. [78] In the Japanese study, 52% of the children had FCD type II which indeed was associated with postoperative seizure freedom. In our study, each MCD subcategory was small and no clear pattern in terms of seizure outcome was found. It should also be noted that the largest subgroup consisted of unspecified FCD, i.e. cases that could not be further classified due to insufficient data in the register.

Five children (11%) had tumour or vascular lesion pathology, all of whom were seizure-free two years after surgery. This finding is not surprising as such well-circumscribed lesions are typically amenable to complete resection. [211-213] The prevalence of tumour aetiology in our study was markedly lower than in population-based cohorts which included also older children; in the full paediatric age span, tumour or vascular pathology is found in about 30% of cases. [174,214] The comparatively low prevalence of tumours was however in accordance with most previous studies of infants and young children. [107-112,206]

Four children (9%) had epilepsy caused by TSC. The presurgical investigation in these children is often challenging as multiple brain lesions with varying epileptogenic potential are often present. In our study, none of the four patients were seizure-free and only one had a ≥75% reduction in seizure frequency. Even though the sample size was small, the results stand in contrast to a systematic review in which about 50% of children having resective surgery for TSC were seizure-free after a median follow-up of 2.3 years. [215]

Long-term seizure outcome

Long-term outcome data were available in 32 children: 16 were followed up after five years and 16 were followed up ten years after surgery. Hence, the mean follow-up time at long term was 7.5 years. The results from our study indicate that improvements seen at two years after surgery are consistent over a prolonged follow-up period in most children. In all, 16 (50%) were seizure-free at long-term follow-up and 14 (44%) had sustained seizure freedom since surgery. There were four cases of late seizure recurrence and two cases of late seizure remission. Thus, the decrease in sustained seizure

freedom between the 2-year and long-term follow-ups was 12 percentage units. Of the children with persisting seizures at long term, 10 (31%) had a ≥75% reduction in seizure frequency.

Data regarding longitudinal seizure outcome are scarce in the literature on epilepsy surgery in the very young. In two earlier studies, early seizure outcomes after 6 months and 1 year, respectively, were compared to cross-sectional follow-up data collected 4.1 and 5.2 years after surgery. In the first study, the proportion of seizure-free children decreased from 73% to 70% [109] whereas in the other, the decrease was from 83% to 71%. [112] A considerably larger study on resective surgery in adults showed that the proportion of seizure-free patients declined from 63% after two years to 52% and 47% after five and ten years, respectively. [79] A similar decline in sustained seizure freedom between 2-year and 5/10-year follow-ups was also observed in older children as well as adults in a previous study based on data from SNESUR. [54] Thus, the results from our study suggest that the risk for late seizure recurrence is not higher for children operated early in life compared to other patient groups.

Medication outcome

Reduction or discontinuation of ASMs after surgery is desirable in order to minimise adverse effects on cognitive development. [216,217] In our study, eight children (17%) were seizure-free without pharmacological treatment two years after surgery. At long-term follow-up, the proportion had doubled to 11/32 (34%). Among the children who were seizure-free at long term, ASM treatment had been discontinued in 11/16 (69%). Rates of ASM cessation in other studies of children undergoing early resective surgery vary between 24% and 50% of all operated children and between 38% and 75% of seizure-free children. [107-112,202-206] Differences between studies can in part be explained by varying local practices with regard to timing of ASM tapering attempts. Moreover, variations in follow-up time also contribute as clinicians and parents can be assumed to be more likely to try ASM tapering after a longer period of seizure freedom. Thus, the comparatively large proportion of children who were completely off medication at long-term follow up in our study may be attributable to the long duration of follow-up.

Complications

Out of the 47 children in our study, two (4%) had a perioperative complication. One complication was considered major (epidural abscess causing motor deficits persisting for more than three months) and the other was considered minor (pneumonia). In addition to these unexpected events, two children required implantation of a ventriculoperitoneal shunt within two years of epilepsy surgery. The children had undergone a complete functional hemispherotomy in one case and an extensive MLR in the form of a partial hemispherotomy in the other. No deaths associated with epilepsy surgery were

registered in our study. In other studies of infants and young children, complication rates vary considerably (3-19%). [107-109,111,112,202-206] [110] The most common kinds of complications in a majority of studies were infections and bleedings/haematomas. Postoperative death attributable to the surgical procedure has been reported in a few cases in two small studies from the 1990s [204,205] whereas one child in the Canadian multi-centre study from 2009 died during surgery. [206]

Due to varying definitions, the complication rates vary also in larger studies of older children and adults. In a systematic review, surgical adverse events have been reported after 6-7% of focal resective procedures whereas a study based on SNESUR data on all types of epilepsy surgery showed a surgical complication rate of 5%. [67,68] When it comes to neurological complications, i.e. unexpected postoperative neurological deficits, only one case (2%) was registered in our study. This can be compared to 6% (3% persisting beyond three months) in the above referenced SNESUR complications study. [68] In light of these findings, our study indicates that the surgical risk is not higher for infants and young children compared to older patients if managed by teams with appropriate experience.

Strengths and limitations

The strengths of Paper III include the population-based recruitment of patients and the prospective data collection which minimise the risk of selection bias. Furthermore, the longitudinal design allows for a more detailed description of seizure relapses as well as late remissions during the study period compared to earlier studies which have predominantly been cross-sectional. Despite the multi-centre, register-based approach, the study is limited by its sample size although it counts among the larger cohorts in the literature on epilepsy surgery in infants and young children. Specifically, the small sample size precluded the use of inferential statistics for the purpose of analysing predictors of seizure and medication outcomes. The lack of yearly audits of seizure outcome is another limitation which made it unfeasible to use survival analysis methods. Finally, the lack of cognitive/neurodevelopmental outcome data and HRQoL assessments in the SNESUR meant that our study could not answer important research questions related to non-seizure outcomes.

Conclusions

Paper III shows that resective epilepsy surgery is safe and effective in achieving seizure freedom or a substantial reduction in seizure frequency when used in carefully selected infants and young children. The findings of several smaller, single-centre series were thus confirmed in a prospectively recruited population-based cohort. The improvements seen at two years postoperatively were generally consistent over a prolonged follow-up period ranging up to 10 years and most seizure-free children could eventually stop taking ASMs altogether. Larger multi-centre studies are needed to allow for

statistically sound subgroup analyses in order to improve prediction of outcomes as well as the selection of surgical candidates.

7: METHODOLOGICAL ISSUES IN THE STUDY OF RARE PAEDIATRIC EPILEPSY SURGERY PROCEDURES (PAPER IV)

Although the overall efficacy and safety of epilepsy surgery is undisputed given careful selection of eligible patients, adequately sized and methodologically robust studies are lacking when it comes to a number of surgical subgroups. Detailed outcome data for specific age groups or types of surgical procedures are important in the presurgical counselling situation. In this chapter, methodological issues in the study of rare epilepsy surgery interventions in children will be discussed with an emphasis on non-seizure outcomes. Specifically, an extended prospective follow-up programme for children operated before four years of age and children of all ages undergoing hemispherotomy, callosotomy and interventions for hypothalamic hamartoma will be described (Paper IV).

Study design and cohort size – general considerations

The RCT is considered to be the gold standard for assessments of effects of medical interventions. To date, three RCTs comparing epilepsy surgery to standard pharmacological treatment have been published, one of which included children. The main effect measure in all three studies was seizure outcome and the results turned out strongly in favour of surgery. [74-76] As regards long-term outcomes, the RCT design is however unsuitable due to practical as well as ethical issues. These issues pertain to the difficulty of separating the treatment arms of randomised study over a prolonged period of time. For example, in the only paediatric RCT to date, children randomised to medical treatment were put on a one-year waiting list for surgery, an approach that would be unfeasible for a study spanning over five years of follow-up. [74] Moreover, the use of RCTs to study non-seizure outcomes is ethically problematic due to the questionable clinical equipoise with regard to surgery versus continued ASM treatment only. More specifically, the surgical indication is based on the presence of DRE and the aim of all epilepsy surgery procedures is to stop or reduce seizures. Although improvements in non-seizure outcome domains are desirable, expectations of such secondary treatment effects are not sufficient to motivate surgery alone. Hence, it would be unethical to withhold surgery for the purpose of studying non-seizure outcomes as the available evidence from previous RCTs and large observational studies unequivocally shows that surgery reduces seizures. Knowledge of long-term non-seizure outcomes will therefore have to be sought through observational studies.

Control groups in observational epilepsy surgery studies typically consist of patients who underwent presurgical investigation but, for various reasons, did not proceed to surgery. [54,172,218] These reasons are at times not clearly described and as a consequence, the confounding inherent to non-random treatment assignment may be hard to characterise and quantify. Two recent studies on adults have systematically evaluated motivations for not recommending or accepting surgery after completed

preoperative evaluation. Both found that multifocal or poorly localised seizure onset or seizure onset within eloquent cortex were the most common reasons. In only about 10% of cases, patients declined for personal reasons. [219,220] Assuming that the figures are somewhat similar for children, it would probably be unfeasible to recruit sufficiently large control groups consisting of suitable surgical candidates whose parents declined surgery for non-medical reasons. This holds true especially for studies of rare surgical procedures.

A clear majority of all epilepsy surgery studies have a retrospective cross-sectional design, regardless of the age group or specific surgical intervention studied. Furthermore, patient recruitment is in many cases restricted to a single referral centre. These features incur risks of bias related to non-representative patient populations and incomplete accounting for patients lost to follow-up during the course of the study. Moreover, widely varying follow-up times in cross-sectional studies along with considerable heterogeneity in definitions of prognostic markers and outcome measures complicate comparisons across studies. [77] Many of these limitations can be overcome through prospective multi-centre studies using a common data collection protocol.

The clinical spectrum of paediatric epilepsy surgery with regard to age, type of surgery and aetiology is heterogeneous. Although the total surgical volume across the whole paediatric age span and including all types of surgery may be considerable in tertiary referral centres, the number of procedures undertaken each year in specific surgical subgroups or within a certain age stratum may still be very limited. For instance, only 47 children were included in Paper III despite the use of a national population-based register methodology and an inclusion period of 16 years. Likewise, earlier studies of hemispherotomy and callosotomy based on SNESUR data included 29 and 31 patients, respectively, over inclusion periods of 13 years. [96,151] With a few notable exceptions [85,206,221], these figures are representative of the cohort size in most available studies of children operated in infancy or early childhood and in those undergoing hemispherotomy, callosotomy or interventions for hypothalamic hamartoma. Thus, recruitment from a single large referral centre, or national multi-centre recruitment in a small country such as Sweden, is insufficient for the purpose of analysis of outcomes after rare procedures.

Methodological issues in the assessment of health-related quality of life outcome

Health-related quality of life is a broadly defined construct that can be measured using a large number of different instruments. These instruments, in turn, can be thought of as to capture different aspects of HRQoL and the choice of instrument in a clinical study depends both on the research aim and on the characteristics of the individuals that are to be assessed. Specifically, an appropriate instrument should

be validated by means of psychometric testing in a population which resembles the study subjects. With regard to their content, HRQoL instruments can be classified as either generic or condition specific. The former type of instrument gauges HRQoL in a general sense that is thought to be applicable for all people regardless of specific diagnoses and health conditions. In contrast, condition-specific instruments also measure aspects which are unique to a certain diagnosis or group of related health conditions. [126] In the case of epilepsy, such specific aspects may include cognitive ASM side effects and seizure-related injury.

In the existing literature on paediatric epilepsy surgery, HRQoL has mostly been analysed in children with normal or lower-normal range intellectual functioning who have had focal resective surgery. [124,137-142,144,146,147] Measurement of HRQoL has either been done using proxy assessments by parents/caregivers or by means of self-report instruments administered during adolescence or, after long-term follow-up, when patients had reached adult age. As can be seen in Table 2, different versions of the Quality of Life in Childhood Epilepsy (QOLCE) scale are the most commonly used instruments in previous studies. It is a proxy instrument aimed at parents of children aged 4-18 years that was developed for use in general paediatric epilepsy populations. [222,223] While the instrument has been shown to be responsive to change in general paediatric surgical cohorts, it is not clear whether it is suitable for use in children with severe cognitive and neurological co-morbidity as floor effects may prevent identification of clinically relevant HRQoL changes. In the few studies of HRQoL after hemispherotomy, QOLCE has not been used. Instead, one study used the Epilepsy and Learning Disability Quality of Life (ELDQOL) scale which is a condition-specific proxy instrument validated for use in children with epilepsy and concurrent ID. [151] In contrast to the detailed ELDQOL instrument, another study used the brief, generic EQ-5D scale. [150] While both studies generally showed high HRQoL scores at long-term follow-up after hemispherotomy, it should be noted that the instruments used are quite different in their content and therefore, in part, answer different questions.

There are also examples of studies in which instruments that are obviously unsuitable for the study population have been used. For example, the Quality of Life in Epilepsy - 31 items (QOLIE-31) has been used for HRQoL assessments in children undergoing callosotomy in two studies. Almost all children in both studies had ID and the authors concluded that HRQoL increased after surgery on group level. As QOLIE-31 is a self-report instrument validated for use in adults with normal intellectual functioning, there is good reason to question the validity of these findings.

Table 2: HRQoL instruments used in previous studies paediatric epilepsy surgery studies.

Name of instrument	Purpose of instrument	Target population	Respondent	Type of surgery*		
				Hemisphe-rotomy	Callosotomy	Focal resections
EQ-VAS+EQ-5D	Measurement of generic HRQoL	From age 8 years (self-report), from age 4 years (proxy)	Self-report or proxy	Van Schoone-veld 2016[150]	-	-
QOLIE-31	Measurement of epilepsy-specific HRQoL	Adults with epilepsy age 18+	Self-report	-	Liang 2014[224], Cukiert 2013[152]	Elliot 2012[138], Keene 1997[143]
QOLIE-AD-48	Measurement of epilepsy-specific HRQoL	Adolescents with epilepsy age 11-18	Self-report	-	-	Puka 2015[137], Zupanc 2010[139]
QOLCE-74/76	Measurement of epilepsy-specific HRQoL	Children with epilepsy age 4-18	Proxy	-	-	Jain 2020[144], Conway 2018[146], Puka 2015[137], Titus 2013[147], Zupanc 2010[139], Mikati 2010[140] and 2008[141]
ELDQOL	Measurement of epilepsy-specific HRQoL	Children age 2-18 years with epilepsy and intellectual disability	Proxy	Verdinelli 2015[151]	-	-
HARCES	Measurement of restrictions in daily life due to epilepsy	Children with epilepsy age 4-16	Proxy	Griffiths 2007[130]	-	Van Empelen 2005[142]
ICI	Measurement of impact of chronic illness on child and family HRQoL	Children with chronic health conditions age 6-17	Proxy	Griffiths 2007[130]	-	-
CHQ	Measurement of generic HRQoL	Children age 5-18	Self-report or proxy	-	-	Gilliam 1997[225]

Abbreviations: HRQoL: Health-related quality of life; EQ-VAS: EuroQoL Visual Analogue Scale; EQ-5D: EuroQoL 5 Dimensions; QOLIE-31: Quality of Life in Epilepsy 31 items; QOLIE-AD-48: Quality of Life in

Epilepsy Inventory for Adolescents 48 items; QOLCE-74/76: Quality of Life in Childhood Epilepsy 74/76 items; ELDQOL: Epilepsy and Learning Disability Quality of Life scale; HARCES: Hague Restrictions in Childhood Epilepsy Scale; ICI: Impact of Childhood Illness scale; CHQ: Child Health Questionnaire.

** HRQoL after hypothalamic hamartoma surgery has not been investigated using validated instruments.*

A substantial number of previous studies lack data on baseline HRQoL. [124,130,137-141,150,151,225] This complicates the interpretation of postsurgical scores, both because pre- and postoperative HRQoL have been shown to be strongly associated [144] and because preoperative scores serve as an important reference in the absence of a control group. Prospectively planned studies can mitigate this limitation through the implementation of a standardised study protocol. However, in the case of surgery in very young children, the collection of preoperative HRQoL data is unfeasible due to the lack of suitable instruments. In a wider sense, the individual HRQoL of infants is an ill-defined concept and its demarcation in relation to parental HRQoL is conceptually difficult, especially in the case of infants with severe chronic diseases. In addition, the developmental level of the child has significant impact on how HRQoL is defined. [226] Therefore, developmental/cognitive level and parental HRQoL are important variables that should be assessed at baseline in studies of children operated during infancy or early childhood.

Methodological issues in the assessment of cognitive and developmental outcome

Cognitive assessments in the form of IQ tests are not feasible in children during the first years of life. Instead, assessments of DQ are used. Like IQ, DQ is determined by means of standardised tests and the child's results are related to age-adjusted norms. Analogous to the IQ measure, the mean DQ in the reference population is 100 and cut-offs representing varying degrees of developmental delay exist. The DQ measure is however not nearly as stable over time as IQ [227,228] and DQ obtained before two years of age has been shown to have only moderate predictive value for full-scale IQ at age five. [229] This reflects the rapid pace of neurological development early in life, a circumstance that has to be accounted for when cognitive development is examined in very young children undergoing epilepsy surgery.

Cognitive level is not static in children and an unchanged IQ/DQ over time implies ongoing development at a rate similar to age peers. In children with abnormal cognitive development, the developmental trajectory may display different patterns. These include stagnation and regression but also ongoing positive development, albeit at a slower pace than age peers. [29] Epilepsy surgery, when successful, has the potential to alter the developmental trajectory through the elimination of the

detrimental effects of seizures. In order to fully appreciate the effects of surgery, the presurgical developmental trajectory needs be known. [103] Therefore, careful assessments of presurgical cognitive level are especially warranted in epilepsy surgery studies of young children.

A Nordic multi-centre study of rare paediatric epilepsy surgery procedures

The rarity of several paediatric epilepsy surgery procedures and the absence of data regarding important non-seizure outcome domains in the SNESUR have prompted the establishment of an extended follow-up programme encompassing also the other Nordic countries Denmark, Finland and Norway in addition to Sweden. In Paper IV, the follow-up protocol of this extended study is described in detail. The programme encompasses children having resective surgery before four years of age and children ≤18 years of age undergoing hemispherotomy, callosotomy or interventions for hypothalamic hamartoma. The rationale behind the study is twofold. Firstly, structured assessment of important non-seizure outcome domains including cognitive functioning and HRQoL will contribute to furthering the knowledge about long-term outcomes in a number of rare surgical subgroups. Secondly, the enlarged population base is expected to enable the recruitment of sufficiently large cohorts to allow for sound statistical analysis of the results, within a reasonable time frame.

Although the extended programme includes different surgical procedures, children eligible for inclusion share a number of characteristics which motivate a common follow-up methodology. The most important of these include a young age at seizure onset and surgery and a high prevalence of neurodevelopmental co-morbidity including ID. Many children also have a high burden of disease, both in terms of seizure frequency and severity.

Recruitment to the study is population-based. In line with the original SNESUR collaboration, all centres performing epilepsy surgery in Sweden are participating. The other Nordic countries all have publicly funded universal coverage health care systems similar to that of Sweden and paediatric epilepsy surgery is centralised to a few centres. Thereby, population-based recruitment is ensured also in Denmark, Finland and Norway.

Usual clinical data are collected according to the established SNESUR protocol. In addition, cognitive level, child and parental HRQoL and behaviour are assessed at baseline and at follow-up two and five years after surgery. Follow-ups are conducted in the form of physical hospital visits. A summary of the variables and time points in the protocol is shown in Figure 15.

Table 3: Overview of variables and data collection time points in the study.

Time of data collection	Variables in the SNESUR	New variables
Before surgery	Sex, age at surgery, age at seizure onset, seizure frequency, classification of seizure type(s) and/or epilepsy syndrome, ASM use, neuroradiological findings, gross neurological findings, educational attainment, vocational status, social insurance status	Formal neuropsychological assessment including IQ/DQ, patient HRQoL*, parent HRQoL**, parent report of behaviour¤, neuropsychiatric assessment¤¤
3 months after surgery	Type of surgery, complications, acute postoperative seizures, histopathological diagnosis	
2 and 5 years after surgery	Demographic data, seizure outcome, classification of seizure type(s) and/or epilepsy syndrome, ASM use, educational attainment, vocational status, social insurance status	Formal neuropsychological assessment including IQ/DQ, patient HRQoL*, parent HRQoL**, parent report of behaviour¤, neuropsychiatric assessment¤¤

Abbreviations: SNESUR: Swedish National Epilepsy Surgery Register; HRQoL: health-related quality of life; ASM: anti-seizure medication; ELDQOL: Epilepsy and Learning Disability Quality of Life scale; HADS: Hospital Anxiety and Depression scale; SF-36: Short Form Health Survey 36; SDQ: Strengths and Difficulties Questionnaire.

** Instruments for assessment of patient HRQoL: Children ≥4 years with intellectual disability – ELDQOL (parent-report). Children with normal range intellectual functioning 8–18 years – DISABKIDS with epilepsy-specific module (self-report). Children with normal range intellectual functioning 8–18 years without seizures and medication at follow-up – KIDSCREEN (self-report). Patients with intellectual disability >18 years at follow-up: ELDQOL (parent or caregiver report). Patients >18 years of age with normal range intellectual functioning – SF-36 and HAD (self-report). ** Instruments for assessment of parental HRQoL: SF-36 and HADS. ¤ SDQ. ¤¤ Neuropsychiatric assessment of all patients with SDQ scores or medical history indicating behavioural/psychiatric symptoms.*

Adapted from: Reinholdson et al. Method considerations and study protocol for a Nordic multi-centre prospective study on outcomes in rare paediatric epilepsy surgery subgroups, Acta Paediatrica 2023;94:e205-e216. Copyright © 2023 The Author(s). Published by John Wiley & Sons Ltd on behalf of Foundation Acta Paediatrica.

Choice of health-related quality of life instruments for the Nordic study

As the majority of children to be included are expected to have ID, the ELDQOL scale was chosen as the main HRQoL instrument in the Nordic study. The ELDQOL is a proxy instrument aimed at parents, relatives and formal carers of children and young people with epilepsy and concurrent ID. [230] It consists of 70 items covering 12 domains including, among others, behaviour, seizure severity and parental concerns. The instrument has previously been used in a retrospective study on hemispherotomy. [151]

Few children with normal-range intellectual functioning are expected to be included in the Nordic study. For this group, the self-report DISABKIDS instrument was chosen. The DISABKIDS instrument is comprised of two parts; the first is a generic module that includes questions about the impact of having a chronic illness in general whereas the second part is epilepsy specific. This feature makes comparisons to other paediatric patient groups with chronic diseases possible. [231] Although the DISABKIDS instrument has not yet been used in epilepsy surgery research, it has for instance been used successfully in a trial of a psychoeducational programme for children with epilepsy. [232] The decision to use DISABKIDS instead of one of the more frequently used parent-report instruments was motivated by an ambition to use self-report assessments when possible. This was considered important as child and parent assessments of child HRQoL have been shown to differ. [233] For the purpose of assessing parental HRQoL, the generic Short-Form Health Survey-36 (SF-36) along with Hospital Anxiety and Depression Scale (HADS) were chosen. The instruments have been widely used in diverse fields of research and valid population norms are available. [234,235]

Conclusions

Methodologically robust observational studies are essential for furthering the knowledge about long-term epilepsy surgery outcomes. The study of HRQoL in young children with accompanying impairments requires careful consideration regarding the choice of instruments to ensure the validity of the findings. Specifically, HRQoL instruments need to be appropriate for the age and cognitive abilities of the child and different instruments may have to be used along the course of a long-term follow-up study. When it comes to rare surgical subgroups, a multi-centre design is necessary in order to recruit sufficiently large cohorts. By using a prospectively designed study protocol, many of the limitations in the current literature can be overcome.

8: CONCLUSIONS IN SUMMARY

Long-term educational and employment outcomes of patients undergoing epilepsy surgery in childhood or adolescence depend on presurgical cognitive ability and on whether surgery leads to seizure freedom or not. Among children and young people with IQ in the normal range, a majority are engaged in either studies or work when followed up in adult age and employment rates appear to be higher than in most studies on patients operated as adults. For those who are seizure-free at follow-up, the chances of having attained post-secondary education and to hold a full-time job are similar to age peers in the general population. As for children and young people with a preoperative diagnosis of ID, most can be expected to require special education and to rely on social benefits as adults.

Among patients who undergo focal resective epilepsy surgery, ID is associated with a number of known negative predictors of seizure freedom. Even after adjustment for these factors, patients with a preoperative diagnosis of ID are at a considerably higher risk of seizure recurrence after surgery when compared to patients with IQ in the normal range. Despite this, a majority of patients with ID can still be expected to gain from surgery, either by prolonged seizure-free intervals in spite of some recurrent seizures or by a significantly reduced seizure frequency. Hence, access to presurgical evaluation should not be withheld on the basis of low IQ although patients and their relatives need to be informed about the low chances of sustained long-term seizure freedom for them to have realistic expectations.

Resective epilepsy surgery, when undertaken in infants and children under four years of age, is a rare intervention with only 47 children operated in Sweden over a 16-year inclusion period. Around 50% are seizure-free two years after surgery and most of these remain so at long-term follow-up five or ten years postoperatively. In another 25-30% of children, a significantly reduced seizure frequency is achievable. A clear majority of the seizure-free children can eventually stop taking ASMs. Complications are rare and seizure outcomes in the very young are in line with results in older children and adults operated in Sweden and also with single-centre series of infants and young children from larger countries. These findings support the referral also of the youngest children with DRE for presurgical evaluation.

Limitations related to small cohort size and retrospective study design are common in the paediatric epilepsy surgery literature, especially when it comes to studies of rare surgical subgroups. Multi-centre recruitment of patients is often necessary in order to achieve sufficient statistical power. The use of a prospectively designed protocol can increase the scientific quality of future studies by ensuring uniform definitions of baseline variables and outcomes. Finally, methods for assessment of HRQoL need to be appropriate for the age and the cognitive level of the included children.

9: FUTURE PERSPECTIVES

The technological evolution in epilepsy surgery is progressing at a rapid pace. It can therefore be argued that future long-term studies of patients operated today might yield more favourable results than those presented in this thesis in which outcomes after operations performed since the mid-1990s were analysed. When it comes to diagnostic techniques, high-resolution MRI, functional neuroimaging and invasive EEG (i.e. SEEG) allow for delineation of an epileptogenic zone in increasing numbers of patients who would previously have been considered "MRI-negative" and therefore would not have proceeded to surgery. While more advanced diagnostics can thereby enable surgical treatment for new groups of patients, others with widespread epileptogenic networks can be spared unnecessary surgery. [55,56,236]

The precision as well as the availability of genetic diagnostics have increased during the last decades. This has contributed substantially to the knowledge about aetiologies of early onset DRE. [17] When it comes to epilepsy surgery studies, genetic investigational findings have seldom been reported and its role in the presurgical evaluation remains to be clearly defined. Available evidence, although scarce, indicates that chances of seizure freedom are significantly higher in patients with mutations in genes involved in the mTOR signalling pathway compared to those with alterations of ion channel or synaptic function. [237-239] This being said, there are also reports of resective surgery leading to seizure freedom in patients with ion channel gene mutations given concordance of EEG and imaging findings. [240] Although more research is needed, it is safe to assume that genetic diagnostics will play a significant role in epilepsy surgery patient selection in the future, especially when it comes to young children and patients with neurodevelopmental co-morbidity such as ID. How these ongoing, fast-paced changes will influence treatment outcomes with respect to seizures and non-seizure domains in the long term will have to be evaluated in future prospective studies.

ACKNOWLEDGEMENTS

First and foremost, I would like to thank all patients and their families who have contributed clinical and personal information to the SNESUR. It is my sincere hope that this thesis will play a part in improving epilepsy surgery care, if not for you then for future patients.

I would also like to thank the following persons:

My main supervisor **Kristina Malmgren**. Without your generosity, in terms of knowledge as well as time, this thesis would not have been written. Thank you for sharing your vast experience in clinical research and for reminding me to keep sight of the big picture.

My co-supervisor **Ingrid 'Bobo' Olsson**, who introduced me scientifically to the field of epilepsy surgery and encouraged me to pursue a clinical career in paediatrics. I am grateful for your unwavering optimism and patience.

My co-supervisor **Anna Edelvik Tranberg**, who taught me how to understand and work with SNESUR data. Thank you for instructive discussions about research methodology and statistics, and for encouragement and support along the course of my PhD studies.

Co-authors **Tove Hallböök, John Chaplin, Bertil Rydenhag** and **Johan Lundgren** for valuable contributions to Papers III and IV.

Colin Reilly, psychologist at the Queen Silvia Children's Hospital in Gothenburg, for helpful discussion about psychological aspects of childhood epilepsy.

Mattias Molin and **Nils-Gunnar Pehrsson** at Statistiska konsultgruppen for statistical advice and assistance.

The steering committee of the SNESUR and all members, current and past, of the regional epilepsy surgery teams in Gothenburg, Linköping, Lund, Stockholm, Umeå and Uppsala for the many years of work upon which this thesis ultimately builds.

Judith Klecki, administrator of the SNESUR, for help with data extraction and for proof-reading the thesis frame.

My clinical mentor at the Department of Paediatrics at Skåne University Hospital, **Lotta Webb**, for invaluable encouragement and advice when clinical work and PhD studies in combination have threatened to overwhelm me.

All colleagues at the Department of Paediatrics at Skåne University Hospital for sharing both the joys and burdens of day-to-day clinical practice.

My dear friends in Malmö and elsewhere.

My parents **Anna-Clara** and **Klas**, my brother **Carl-Johan**, my sister **Maja** and her family, and my grandmother **Anita**.

Siri, my beloved companion in life. Thank you for believing in me and for your patience during my many hours in front of the computer. Every day spent together with you is a joy.

My work with this thesis has been made possible by grants from the Swedish state through an agreement between the government and the county councils - the ALF agreement. I would also like to

thank the Gothenburg Foundation for Neurological Research and Föreningen Margarethahemmet for supporting the work by means of personal research grants.

BIBLIOGRAPHY

1. Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia*. 2005;46(4):470-2.
2. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475-82.
3. Cross JH, Jayakar P, Nordli D, et al. Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the Subcommission for Pediatric Epilepsy Surgery. *Epilepsia*. 2006;47(6):952-9.
4. Jehi L, Jette N, Kwon C-S, et al. Timing of referral to evaluate for epilepsy surgery: Expert Consensus Recommendations from the Surgical Therapies Commission of the International League Against Epilepsy. *Epilepsia*. 2022;63(10):2491-2506.
5. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):522-530.
6. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):512-521.
7. Lemke JR, Lal D, Reinthaler EM, et al. Mutations in GRIN2A cause idiopathic focal epilepsy with rolandic spikes. *Nature genetics*. 2013;45(9):1067-72.
8. Specchio N, Wirrell EC, Scheffer IE, et al. International League Against Epilepsy classification and definition of epilepsy syndromes with onset in childhood: Position paper by the ILAE Task Force on Nosology and Definitions. *Epilepsia*. 2022;63(6):1398-1442.
9. McTague A, Howell KB, Cross JH, Kurian MA, Scheffer IE. The genetic landscape of the epileptic encephalopathies of infancy and childhood. *The Lancet Neurology*. 2016;15(3):304-316.
10. Baulac S, Ishida S, Marsan E, et al. Familial focal epilepsy with focal cortical dysplasia due to DEPDC5 mutations. *Annals of neurology*. 2015;77(4):675-83.
11. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. *The Lancet*. 2008;372(9639):657-668.
12. WHO Fact Sheet no. 999 - Epilepsy. World Health Organization. Updated 02 - 2022. Accessed 10 - 25, 2022 -. http://www.who.int/mediacentre/factsheets/fs999/en/
13. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. *Neurology*. 2017;88(3):296-303.
14. Forsgren L, Beghi E, Oun A, Sillanpää M. The epidemiology of epilepsy in Europe - a systematic review. *European journal of neurology : the official journal of the European Federation of Neurological Societies*. 2005;12(4):245-53.
15. Olafsson E, Ludvigsson P, Gudmundsson G, Hesdorffer D, Kjartansson O, Hauser WA. Incidence of unprovoked seizures and epilepsy in Iceland and assessment of the epilepsy syndrome classification: a prospective study. *Lancet neurology*. 2005;4(10):627-34.
16. Adelöw C, Andell E, Amark P, et al. Newly diagnosed single unprovoked seizures and epilepsy in Stockholm, Sweden: First report from the Stockholm Incidence Registry of Epilepsy (SIRE). *Epilepsia*. 2009;50(5):1094-101.
17. Symonds JD, Elliott KS, Shetty J, et al. Early childhood epilepsies: epidemiology, classification, aetiology, and socio-economic determinants. *Brain : a journal of neurology*. 2021;144(9):2879-2891.
18. Berg AT, Langfitt JT, Testa FM, et al. Global cognitive function in children with epilepsy: a community-based study. *Epilepsia*. 2008;49(4):608-14.
19. Jennum P, Pickering L, Christensen J, Ibsen R, Kjellberg J. Morbidity and mortality of childhood- and adolescent-onset epilepsy: A controlled national study. *Epilepsy & behavior : E&B*. 2017;66:80-85.

20. Reilly C, Atkinson P, Das KB, et al. Neurobehavioral comorbidities in children with active epilepsy: a population-based study. *Pediatrics*. 2014;133(6):e1586-93.
21. Ko T-S, Holmes GL. EEG and clinical predictors of medically intractable childhood epilepsy. *Clinical Neurophysiology*. 1999;110(7):1245-1251.
22. Ramos-Lizana J, Aguilera-López P, Aguirre-Rodríguez J, Cassinello-García E. Early prediction of refractory epilepsy in childhood. *Seizure : the journal of the British Epilepsy Association*. 2009;18(6):412-416.
23. Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rapaport S, Beckerman B. Early development of intractable epilepsy in children: a prospective study. *Neurology*. 2001;56(11):1445-52.
24. Wirrell E, Wong-Kisiel L, Mandrekar J, Nickels K. Predictors and course of medically intractable epilepsy in young children presenting before 36 months of age: a retrospective, population-based study. *Epilepsia*. 2012;53(9):1563-9.
25. Geerts A, Brouwer O, van Donselaar C, et al. Health perception and socioeconomic status following childhood-onset epilepsy: the Dutch study of epilepsy in childhood. *Epilepsia*. 2011;52(12):2192-202.
26. Reilly C, Atkinson P, Das KB, et al. Neurobehavioral Comorbidities in Children With Active Epilepsy: A Population-Based Study. *Pediatrics*. 2014;133(6):e1586-e1593.
27. Hunter MB, Yoong M, Sumpter RE, et al. Neurobehavioral problems in children with early-onset epilepsy: A population-based study. *Epilepsy & Behavior*. 2019;93:87-93.
28. Berg AT, Plioplys S, Tuchman R. Risk and correlates of autism spectrum disorder in children with epilepsy: a community-based study. *Journal of child neurology*. 2011;26(5):540-7.
29. Nickels KC, Zaccariello MJ, Hamiwka LD, Wirrell EC. Cognitive and neurodevelopmental comorbidities in paediatric epilepsy. *Nature reviews Neurology*. 2016;12(8):465-76.
30. Howell KB, Harvey AS, Archer JS. Epileptic encephalopathy: Use and misuse of a clinically and conceptually important concept. *Epilepsia*. 2016;57(3):343-347.
31. O'Callaghan FJ, Lux AL, Darke K, et al. The effect of lead time to treatment and of age of onset on developmental outcome at 4 years in infantile spasms: evidence from the United Kingdom Infantile Spasms Study. *Epilepsia*. 2011;52(7):1359-64.
32. O'Callaghan FJK, Edwards SW, Alber FD, et al. Vigabatrin with hormonal treatment versus hormonal treatment alone (ICISS) for infantile spasms: 18-month outcomes of an open-label, randomised controlled trial. *The Lancet Child & adolescent health*. 2018;2(10):715-725.
33. Macdonald RL, Kelly KM. Antiepileptic drug mechanisms of action. *Epilepsia*. 1995;36 Suppl 2:S2-12.
34. Rogawski MA, Löscher W. The neurobiology of antiepileptic drugs. *Nature Reviews Neuroscience*. 2004;5(7):553-564.
35. Loring DW, Marino S, Meador KJ. Neuropsychological and Behavioral Effects of Antiepilepsy Drugs. *Neuropsychology Review*. 2007;17(4):413-425.
36. Loring DW, Meador KJ. Cognitive side effects of antiepileptic drugs in children. *Neurology*. 2004;62(6):872-7.
37. Carpay JA, Aldenkamp AP, van Donselaar CA. Complaints associated with the use of antiepileptic drugs: results from a community-based study. *Seizure : the journal of the British Epilepsy Association*. 2005;14(3):198-206.
38. Quon RJ, Mazanec MT, Schmidt SS, et al. Antiepileptic drug effects on subjective and objective cognition. *Epilepsy & behavior : E&B*. 2020;104(Pt A):106906.
39. Witt J-A, Elger CE, Helmstaedter C. Adverse cognitive effects of antiepileptic pharmacotherapy: Each additional drug matters. *European Neuropsychopharmacology*. 2015;25(11):1954-1959.
40. Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs. *Lancet neurology*. 2012;11(9):792-802.
41. Kellogg M, Meador KJ. Neurodevelopmental Effects of Antiepileptic Drugs. *Neurochemical research*. 2017;42(7):2065-2070.

42. Meador KJ, Loring DW. Developmental effects of antiepileptic drugs and the need for improved regulations. *Neurology*. 2016;86(3):297-306.
43. Wilmshurst JM, Gaillard WD, Vinayan KP, et al. Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics. *Epilepsia*. 2015;56(8):1185-97.
44. Berg AT, Levy SR, Testa FM, D'Souza R. Remission of epilepsy after two drug failures in children: A prospective study. *Annals of neurology*. 2009;65(5):510-519.
45. Arts WF, Brouwer OF, Peters AC, et al. Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood. *Brain : a journal of neurology*. 2004;127(Pt 8):1774-84.
46. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *The New England journal of medicine*. 2000;342(5):314-9.
47. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs: A 30-Year Longitudinal Cohort Study. *JAMA neurology*. 2018;75(3):279-286.
48. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2010;51(6):1069-1077.
49. Young CC, Williams JR, Feroze AH, et al. Pediatric functional hemispherectomy: operative techniques and complication avoidance. *Neurosurgical focus*. 2020;48(4):E9.
50. Hoppe C, Witt JA, Helmstaedter C, Gasser T, Vatter H, Elger CE. Laser interstitial thermotherapy (LiTT) in epilepsy surgery. *Seizure : the journal of the British Epilepsy Association*. 2017;48:45-52.
51. Hoppe C, Helmstaedter C. Laser interstitial thermotherapy (LiTT) in pediatric epilepsy surgery. *Seizure : the journal of the British Epilepsy Association*. 2020;77:69-75.
52. Bourdillon P, Rheims S, Catenoix H, et al. Surgical techniques: Stereoelectroencephalography-guided radiofrequency-thermocoagulation (SEEG-guided RF-TC). *Seizure : the journal of the British Epilepsy Association*. 2020;77:64-68.
53. Bell GS, de Tisi J, Gonzalez-Fraile JC, et al. Factors affecting seizure outcome after epilepsy surgery: an observational series. *Journal of neurology, neurosurgery, and psychiatry*. 2017;88(11):933-940.
54. Edelvik A, Rydenhag B, Olsson I, et al. Long-term outcomes of epilepsy surgery in Sweden: a national prospective and longitudinal study. *Neurology*. 2013;81(14):1244-51.
55. Jehi L, Friedman D, Carlson C, et al. The evolution of epilepsy surgery between 1991 and 2011 in nine major epilepsy centers across the United States, Germany, and Australia. *Epilepsia*. 2015;56(10):1526-33.
56. Cloppenborg T, May TW, Blümcke I, et al. Trends in epilepsy surgery: stable surgical numbers despite increasing presurgical volumes. *Journal of neurology, neurosurgery, and psychiatry*. 2016;87(12):1322-1329.
57. Widjaja E, Jain P, Demoe L, Guttmann A, Tomlinson G, Sander B. Seizure outcome of pediatric epilepsy surgery: Systematic review and meta-analyses. *Neurology*. 2020;94(7):311-321.
58. Ka A, Taher A, D'Souza S, et al. Predictors of longitudinal seizure outcomes after epilepsy surgery in childhood. *Epilepsy & Behavior Reports*. 2022;19100561.
59. Blumcke I, Thom M, Aronica E, et al. The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. *Epilepsia*. 2011;52(1):158-74.
60. Najm I, Lal D, Alonso Vanegas M, et al. The ILAE consensus classification of focal cortical dysplasia: An update proposed by an ad hoc task force of the ILAE diagnostic methods commission. *Epilepsia*. 2022;63(8):1899-1919.
61. Striano S, Striano P. Clinical features and evolution of the gelastic seizures-hypothalamic hamartoma syndrome. *Epilepsia*. 2017;58 Suppl 2:12-15.

62. Bourdillon P, Ferrand-Sorbet S, Apra C, et al. Surgical treatment of hypothalamic hamartomas. *Neurosurgical review*. 2021;44(2):753-762.
63. Malmgren K, Rydenhag B, Hallböök T. Reappraisal of corpus callosotomy. *Current opinion in neurology*. 2015;28(2):175-81.
64. Rolston JD, Englot DJ, Wang DD, Garcia PA, Chang EF. Corpus callosotomy versus vagus nerve stimulation for atonic seizures and drop attacks: A systematic review. *Epilepsy & behavior : E&B*. 2015;51:13-7.
65. Englot DJ. A modern epilepsy surgery treatment algorithm: Incorporating traditional and emerging technologies. *Epilepsy & behavior : E&B*. 2018;80:68-74.
66. Nair DR, Laxer KD, Weber PB, et al. Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy. *Neurology*. 2020;95(9):e1244-e1256.
67. Hader WJ, Tellez-Zenteno J, Metcalfe A, et al. Complications of epilepsy surgery: a systematic review of focal surgical resections and invasive EEG monitoring. *Epilepsia*. 2013;54(5):840-7.
68. Bjellvi J, Flink R, Rydenhag B, Malmgren K. Complications of epilepsy surgery in Sweden 1996-2010: a prospective, population-based study. *Journal of neurosurgery*. 2015;122(3):519-25.
69. Tanriverdi T, Ajlan A, Poulin N, Olivier A. Morbidity in epilepsy surgery: an experience based on 2449 epilepsy surgery procedures from a single institution. *Journal of neurosurgery*. 2009;110(6):1111-23.
70. Behrens E, Schramm J, Zentner J, König R. Surgical and neurological complications in a series of 708 epilepsy surgery procedures. *Neurosurgery*. 1997;41(1):1-9; discussion 9-10.
71. Rydenhag B, Silander HC. Complications of epilepsy surgery after 654 procedures in Sweden, September 1990-1995: a multicenter study based on the Swedish National Epilepsy Surgery Register. *Neurosurgery*. 2001;49(1):51-6; discussion 56-7.
72. Engel J, Van Ness PC, Rasmussen TB, Ojemann LM. Outcome with Respect to Epileptic Seizures. In: Engel J, ed. *Surgical Treatment of the Epilepsies*. 2nd ed. Raven Press; 1993:609-621.
73. Wieser HG, Blume WT, Fish D, et al. ILAE Commission Report. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. *Epilepsia*. 2001;42(2):282-6.
74. Dwivedi R, Ramanujam B, Chandra PS, et al. Surgery for Drug-Resistant Epilepsy in Children. *The New England journal of medicine*. 2017;377(17):1639-1647.
75. Wiebe S, Blume WT, Girvin JP, Eliasziw M, Effectiveness, Efficiency of Surgery for Temporal Lobe Epilepsy Study G. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *The New England journal of medicine*. 2001;345(5):311-8.
76. Engel J, Jr., McDermott MP, Wiebe S, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. *JAMA : the journal of the American Medical Association*. 2012;307(9):922-30.
77. West S, Nevitt SJ, Cotton J, et al. Surgery for epilepsy. *The Cochrane database of systematic reviews*. 2019;6(6):Cd010541.
78. Lamberink HJ, Otte WM, Blümcke I, Braun KPJ. Seizure outcome and use of antiepileptic drugs after epilepsy surgery according to histopathological diagnosis: a retrospective multicentre cohort study. *Lancet neurology*. 2020;19(9):748-757.
79. de Tisi J, Bell GS, Peacock JL, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. *Lancet*. 2011;378(9800):1388-95.
80. Tellez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. *Brain : a journal of neurology*. 2005;128(Pt 5):1188-98.
81. D'Argenzio L, Colonnelli MC, Harrison S, et al. Seizure outcome after extratemporal epilepsy surgery in childhood. *Developmental medicine and child neurology*. 2012;54(11):995-1000.

82. Englot DJ, Breshears JD, Sun PP, Chang EF, Auguste KI. Seizure outcomes after resective surgery for extra-temporal lobe epilepsy in pediatric patients. *Journal of neurosurgery Pediatrics*. 2013;12(2):126-33.
83. Englot DJ, Rolston JD, Wang DD, Sun PP, Chang EF, Auguste KI. Seizure outcomes after temporal lobectomy in pediatric patients. *Journal of neurosurgery Pediatrics*. 2013;12(2):134-41.
84. Griessenauer CJ, Salam S, Hendrix P, et al. Hemispherectomy for treatment of refractory epilepsy in the pediatric age group: a systematic review. *Journal of neurosurgery Pediatrics*. 2015;15(1):34-44.
85. Moosa AN, Gupta A, Jehi L, et al. Longitudinal seizure outcome and prognostic predictors after hemispherectomy in 170 children. *Neurology*. 2013;80(3):253-60.
86. Lopez-Gonzalez MA, Gonzalez-Martinez JA, Jehi L, Kotagal P, Warbel A, Bingaman W. Epilepsy surgery of the temporal lobe in pediatric population: a retrospective analysis. *Neurosurgery*. 2012;70(3):684-92.
87. Hsieh JK, Pucci FG, Sundar SJ, et al. Beyond seizure freedom: Dissecting long-term seizure control after surgical resection for drug-resistant epilepsy. *Epilepsia*. 2023;64(1):103-113.
88. Foldvary N, Nashold B, Mascha E, et al. Seizure outcome after temporal lobectomy for temporal lobe epilepsy: a Kaplan-Meier survival analysis. *Neurology*. 2000;54(3):630-4.
89. McIntosh AM, Kalnins RM, Mitchell LA, Fabinyi GCA, Briellmann RS, Berkovic SF. Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence. *Brain : a journal of neurology*. 2004;127(9):2018-2030.
90. Spencer SS, Berg AT, Vickrey BG, et al. Predicting long-term seizure outcome after resective epilepsy surgery: the multicenter study. *Neurology*. 2005;65(6):912-8.
91. Simasathien T, Vadera S, Najm I, Gupta A, Bingaman W, Jehi L. Improved outcomes with earlier surgery for intractable frontal lobe epilepsy. *Annals of neurology*. 2013;73(5):646-54.
92. Ramantani G, Stathi A, Brandt A, et al. Posterior cortex epilepsy surgery in childhood and adolescence: Predictors of long-term seizure outcome. https://doi.org/10.1111/epi.13654. *Epilepsia*. 2017;58(3):412-419.
93. Malmgren K, Olsson I, Engman E, Flink R, Rydenhag B. Seizure outcome after resective epilepsy surgery in patients with low IQ. *Brain : a journal of neurology*. 2008;131(Pt 2):535-42.
94. Ferrand-Sorbets S, Fohlen M, Bourdillon P, et al. Complete callosotomy in children with drop attacks; A retrospective monocentric study of 50 patients. *Seizure : the journal of the British Epilepsy Association*. 2022;96:34-42.
95. Graham D, Gill D, Dale RC, Tisdall MM. Seizure outcome after corpus callosotomy in a large paediatric series. *Developmental medicine and child neurology*. 2018;60(2):199-206.
96. Stigsdotter-Broman L, Olsson I, Flink R, Rydenhag B, Malmgren K. Long-term follow-up after callosotomy--a prospective, population based, observational study. *Epilepsia*. 2014;55(2):316-21.
97. Taylor DC, McMacKin D, Staunton H, Delanty N, Phillips J. Patients' aims for epilepsy surgery: desires beyond seizure freedom. *Epilepsia*. 2001;42(5):629-33.
98. Sylvén I, Olsson I, Hallböök T, Rydenhag B, Reilly C. 'In the best case seizure-free' - Parental hopes and worries before and satisfaction after their child's epilepsy surgery. *Epilepsy & behavior : E&B*. 2020;110:107153.
99. Malmgren K, Baxendale S, Cross JH, Ryvlin P. Long-Term Outcomes of Epilepsy Surgery: Knowledge Gaps and Future Directions. In: Malmgren K, Baxendale S, Cross JH, eds. *Long-Term Outcomes of Epilepsy Surgery in Adults and Children*. Springer International Publishing; 2015:269-275.
100. Sherman EM, Wiebe S, Fay-McClymont TB, et al. Neuropsychological outcomes after epilepsy surgery: systematic review and pooled estimates. *Epilepsia*. 2011;52(5):857-69.
101. Helmstaedter C, Kurthen M, Lux S, Reuber M, Elger CE. Chronic epilepsy and cognition: a longitudinal study in temporal lobe epilepsy. *Annals of neurology*. 2003;54(4):425-32.
102. Baxendale S, Thompson PJ, Duncan JS. Neuropsychological function in patients who have had epilepsy surgery: a long-term follow-up. *Epilepsy & behavior : E&B*. 2012;23(1):24-9.

103. Van Schooneveld MM, Braun KP. Cognitive outcome after epilepsy surgery in children. *Brain & development*. 2013;35(8):721-9.
104. 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;76(15):1330-7.
105. Gleissner U, Sassen R, Schramm J, Elger CE, Helmstaedter C. Greater functional recovery after temporal lobe epilepsy surgery in children. *Brain : a journal of neurology*. 2005;128(Pt 12):2822-9.
106. Baldeweg T, Skirrow C. Long-Term Cognitive Outcomes After Epilepsy Surgery in Children. In: Malmgren K, Baxendale S, Cross JH, eds. *Long-Term Outcomes of Epilepsy Surgery in Adults and Children*. Springer International Publishing; 2015:85-101.
107. Loddenkemper T, Holland KD, Stanford LD, Kotagal P, Bingaman W, Wyllie E. Developmental outcome after epilepsy surgery in infancy. *Pediatrics*. 2007;119(5):930-5.
108. Dunkley C, Kung J, Scott RC, et al. Epilepsy surgery in children under 3 years. *Epilepsy research*. 2011;93(2-3):96-106.
109. Ramantani G, Kadish NE, Strobl K, et al. Seizure and cognitive outcomes of epilepsy surgery in infancy and early childhood. *European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society*. 2013;17(5):498-506.
110. Kadish NE, Bast T, Reuner G, et al. Epilepsy Surgery in the First 3 Years of Life: Predictors of Seizure Freedom and Cognitive Development. *Neurosurgery*. 2019;84(6):E368-e377.
111. Groppel G, Dorfer C, Dressler A, et al. Epilepsy surgery in infants : Safety issues and developmental outcome. *Wiener klinische Wochenschrift*. 2017;
112. Iwasaki M, Iijima K, Kawashima T, et al. Epilepsy surgery in children under 3 years of age: surgical and developmental outcomes. *Journal of neurosurgery Pediatrics*. 2021:1-9.
113. Wilson SJ, Saling MM, Kincade P, Bladin PF. Patient expectations of temporal lobe surgery. *Epilepsia*. 1998;39(2):167-74.
114. Sperling MR, Saykin AJ, Roberts FD, French JA, O'Connor MJ. Occupational outcome after temporal lobectomy for refractory epilepsy. *Neurology*. 1995;45(5):970-7.
115. Zarroli K, Tracy JI, Nei M, Sharan A, Sperling MR. Employment after anterior temporal lobectomy. *Epilepsia*. 2011;52(5):925-31.
116. Dupont S, Tanguy ML, Clemenceau S, Adam C, Hazemann P, Baulac M. Long-term prognosis and psychosocial outcomes after surgery for MTLE. *Epilepsia*. 2006;47(12):2115-24.
117. Jones JE, Berven NL, Ramirez L, Woodard A, Hermann BP. Long-term psychosocial outcomes of anterior temporal lobectomy. *Epilepsia*. 2002;43(8):896-903.
118. Andersson-Roswall L, Engman E, Samuelsson H, Malmgren K. Psychosocial status 10 years after temporal lobe resection for epilepsy, a longitudinal controlled study. *Epilepsy & behavior : E&B*. 2013;28(1):127-31.
119. Asztely F, Ekstedt G, Rydenhag B, Malmgren K. Long term follow-up of the first 70 operated adults in the Goteborg Epilepsy Surgery Series with respect to seizures, psychosocial outcome and use of antiepileptic drugs. *Journal of neurology, neurosurgery, and psychiatry*. 2007;78(6):605-9.
120. Wasade VS, Elisevich K, Tahir R, et al. Long-term seizure and psychosocial outcomes after resective surgery for intractable epilepsy. *Epilepsy & behavior : E&B*. 2015;43:122-7.
121. Jones JE, Blocher JB, Jackson DC. Life outcomes of anterior temporal lobectomy: serial long-term follow-up evaluations. *Neurosurgery*. 2013;73(6):1018-25.
122. Edelvik A, Flink R, Malmgren K. Prospective and longitudinal long-term employment outcomes after resective epilepsy surgery. *Neurology*. 2015;85(17):1482-90.
123. Hosoyama H, Matsuda K, Mihara T, et al. Long-term outcomes of epilepsy surgery in 85 pediatric patients followed up for over 10 years: a retrospective survey. *Journal of neurosurgery Pediatrics*. 2017;19(5):606-615.
124. Keene DL, Loy-English I, Ventureyra EC. Long-term socioeconomic outcome following surgical intervention in the treatment of refractory epilepsy in childhood and adolescence. *Child's*

nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery. 1998;14(8):362-5.
125. Thurman DJ, Beghi E, Begley CE, et al. Standards for epidemiologic studies and surveillance of epilepsy. *Epilepsia*. 2011;52 Suppl 7:2-26.
126. Fayers PM, Machin D. Chapter 1: Introduction. *Quality of Life : The Assessment, Analysis and Reporting of Patient-Reported Outcomes*. 3rd ed. John Wiley & Sons, Incorporated; 2016:4-33.
127. Taft C, Sager Magnusson E, Ekstedt G, Malmgren K. Health-related quality of life, mood, and patient satisfaction after epilepsy surgery in Sweden--a prospective controlled observational study. *Epilepsia*. 2014;55(6):878-85.
128. Seiam AH, Dhaliwal H, Wiebe S. Determinants of quality of life after epilepsy surgery: systematic review and evidence summary. *Epilepsy & behavior : E&B*. 2011;21(4):441-5.
129. Spencer SS, Berg AT, Vickrey BG, et al. Health-related quality of life over time since resective epilepsy surgery. *Annals of neurology*. 2007;62(4):327-34.
130. Griffiths SY, Sherman EM, Slick DJ, Eyrl K, Connolly MB, Steinbok P. Postsurgical health-related quality of life (HRQOL) in children following hemispherectomy for intractable epilepsy. *Epilepsia*. 2007;48(3):564-70.
131. von Lehe M, Lutz M, Kral T, Schramm J, Elger CE, Clusmann H. Correlation of health-related quality of life after surgery for mesial temporal lobe epilepsy with two seizure outcome scales. *Epilepsy & behavior : E&B*. 2006;9(1):73-82.
132. Mikati MA, Comair Y, Ismail R, Faour R, Rahi AC. Effects of epilepsy surgery on quality of life: a controlled study in a Middle Eastern population. *Epilepsy & behavior : E&B*. 2004;5(1):72-80.
133. Markand ON, Salanova V, Whelihan E, Emsley CL. Health-related quality of life outcome in medically refractory epilepsy treated with anterior temporal lobectomy. *Epilepsia*. 2000;41(6):749-59.
134. McLachlan RS, Rose KJ, Derry PA, Bonnar C, Blume WT, Girvin JP. Health-related quality of life and seizure control in temporal lobe epilepsy. *Annals of neurology*. 1997;41(4):482-9.
135. Malmgren K, Sullivan M, Ekstedt G, Kullberg G, Kumlien E. Health-related quality of life after epilepsy surgery: a Swedish multicenter study. *Epilepsia*. 1997;38(7):830-8.
136. Kellett MW, Smith DF, Baker GA, Chadwick DW. Quality of life after epilepsy surgery. *Journal of neurology, neurosurgery, and psychiatry*. 1997;63(1):52-8.
137. Puka K, Smith ML. Predictors of long-term quality of life after pediatric epilepsy surgery. *Epilepsia*. 2015;56(6):873-81.
138. Elliott I, Kadis DS, Lach L, et al. Quality of life in young adults who underwent resective surgery for epilepsy in childhood. *Epilepsia*. 2012;53(9):1577-86.
139. Zupanc ML, Rubio EJ, Werner RR, et al. Epilepsy surgery outcomes: quality of life and seizure control. *Pediatric neurology*. 2010;42(1):12-20.
140. Mikati MA, Ataya N, Ferzli J, et al. Quality of life after surgery for intractable partial epilepsy in children: a cohort study with controls. *Epilepsy research*. 2010;90(3):207-13.
141. Mikati MA, Rahi AC, Shamseddine A, Mroueh S, Shoeib H, Comair Y. Marked benefits in physical activity and well-being, but not in functioning domains, 2 years after successful epilepsy surgery in children. *Epilepsy & behavior : E&B*. 2008;12(1):145-9.
142. van Empelen R, Jennekens-Schinkel A, van Rijen PC, Helders PJ, van Nieuwenhuizen O. Health-related quality of life and self-perceived competence of children assessed before and up to two years after epilepsy surgery. *Epilepsia*. 2005;46(2):258-71.
143. Keene DL, Higgins MJ, Ventureyra EC. Outcome and life prospects after surgical management of medically intractable epilepsy in patients under 18 years of age. *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery*. 1997;13(10):530-5.
144. Jain P, Smith ML, Speechley K, et al. Seizure freedom improves health-related quality of life after epilepsy surgery in children. *Developmental medicine and child neurology*. 2020;62(5):600-608.

145. Sheikh S, Thompson N, Bingaman W, Gonzalez-Martinez J, Najm I, Jehi L. (Re)Defining success in epilepsy surgery: The importance of relative seizure reduction in patient-reported quality of life. *Epilepsia*. 2019;60(10):2078-2085.
146. Conway L, Widjaja E, Smith ML. Impact of resective epilepsy surgery on health-related quality of life in children with and without low intellectual ability. *Epilepsy & behavior : E&B*. 2018;83:131-136.
147. Titus JB, Lee A, Kasasbeh A, et al. Health-related quality of life before and after pediatric epilepsy surgery: the influence of seizure outcome on changes in physical functioning and social functioning. *Epilepsy & behavior : E&B*. 2013;27(3):477-83.
148. Liang S, Zhang G, Li Y, et al. Hemispherectomy in adults patients with severe unilateral epilepsy and hemiplegia. *Epilepsy research*. 2013;106(1-2):257-63.
149. Schramm J, Delev D, Wagner J, Elger CE, von Lehe M. Seizure outcome, functional outcome, and quality of life after hemispherectomy in adults. *Acta neurochirurgica*. 2012;154(9):1603-12.
150. van Schooneveld MM, Braun KP, van Rijen PC, van Nieuwenhuizen O, Jennekens-Schinkel A. The spectrum of long-term cognitive and functional outcome after hemispherectomy in childhood. *European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society*. 2016;20(3):376-84.
151. Verdinelli C, Olsson I, Edelvik A, Hallbook T, Rydenhag B, Malmgren K. A long-term patient perspective after hemispherotomy - A population based study. *Seizure : the journal of the British Epilepsy Association*. 2015;30:76-82.
152. Cukiert A, Cukiert CM, Burattini JA, et al. Long-term outcome after callosotomy or vagus nerve stimulation in consecutive prospective cohorts of children with Lennox-Gastaut or Lennox-like syndrome and non-specific MRI findings. *Seizure : the journal of the British Epilepsy Association*. 2013;22(5):396-400.
153. Liang S, Li A, Jiang H, et al. Anterior corpus callosotomy in patients with intractable generalized epilepsy and mental retardation. *Stereotactic and functional neurosurgery*. 2010;88(4):246-52.
154. Andersen B, Rogvi-Hansen B, Kruse-Larsen C, Dam M. Corpus callosotomy: seizure and psychosocial outcome. A 39-month follow-up of 20 patients. *Epilepsy research*. 1996;23(1):77-85.
155. Park MS, Nakagawa E, Schoenberg MR, Benbadis SR, Vale FL. Outcome of corpus callosotomy in adults. *Epilepsy & behavior : E&B*. 2013;28(2):181-4.
156. Yang TF, Wong TT, Kwan SY, Chang KP, Lee YC, Hsu TC. Quality of life and life satisfaction in families after a child has undergone corpus callostomy. *Epilepsia*. 1996;37(1):76-80.
157. Cukiert A, Burattini JA, Mariani PP, et al. Extended, one-stage callosal section for treatment of refractory secondarily generalized epilepsy in patients with Lennox-Gastaut and Lennox-like syndromes. *Epilepsia*. 2006;47(2):371-4.
158. Gilliam F, Wyllie E, Kotagal P, Geckler C, Rusyniak G. Parental assessment of functional outcome after corpus callosotomy. *Epilepsia*. 1996;37(8):753-7.
159. Iwasaki M, Uematsu M, Nakayama T, et al. Parental satisfaction and seizure outcome after corpus callosotomy in patients with infantile or early childhood onset epilepsy. *Seizure : the journal of the British Epilepsy Association*. 2013;22(4):303-5.
160. ICD-10 : International Statistical Classification of Diseases and Related Health Problems : Tenth Revision, 2019 Version. Chapter V: Mental and Behavioural Disorders. World Health Organization (WHO), 2019. https://icd.who.int/browse10/2019/en
161. Arvidsson J, Widén S, Tideman M. Post-school options for young adults with intellectual disabilities in Sweden. *Research and Practice in Intellectual and Developmental Disabilities*. 2015;2(2):180-193.
162. Bush KL, Tasse MJ. Employment and choice-making for adults with intellectual disability, autism, and down syndrome. *Research in developmental disabilities*. 2017;65:23-34.
163. Reeves AL, So EL, Evans RW, et al. Factors associated with work outcome after anterior temporal lobectomy for intractable epilepsy. *Epilepsia*. 1997;38(6):689-95.

164. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70(1):41-55.
165. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate behavioral research*. 2011;46(3):399-424.
166. Austin PC, Xin Yu AY, Vyas MV, Kapral MK. Applying Propensity Score Methods in Clinical Research in Neurology. *Neurology*. 2021;97(18):856-863.
167. Rosenbaum PR, Rubin DB. Constructing a Control Group Using Multivariate Matched Sampling Methods That Incorporate the Propensity Score. *The American statistician*. 1985;39(1):33-38.
168. Sillanpaa M, Jalava M, Kaleva O, Shinnar S. Long-term prognosis of seizures with onset in childhood. *The New England journal of medicine*. 1998;338(24):1715-22.
169. Baca CB, Barry F, Vickrey BG, Caplan R, Berg AT. Social outcomes of young adults with childhood-onset epilepsy: A case-sibling-control study. *Epilepsia*. 2017;58(5):781-791.
170. Ehrstedt C, Moreira NC, Casar-Borota O, Strömberg B, Ahlsten G. Glioneuronal tumors in childhood - Before and after surgery. A long-term follow-up study. *Epilepsy & behavior : E&B*. 2017;72:82-88.
171. Lach LM, Elliott I, Giecko T, et al. Patient-reported outcome of pediatric epilepsy surgery: social inclusion or exclusion as young adults? *Epilepsia*. 2010;51(10):2089-97.
172. Puka K, Smith ML. Where are they now? Psychosocial, educational, and vocational outcomes after epilepsy surgery in childhood. *Epilepsia*. 2016;57(4):574-81.
173. Engelhart MC, van Schooneveld MM, Jennekens-Schinkel A, van Nieuwenhuizen O. 'With the benefit of hindsight': would you opt again for epilepsy surgery performed in childhood? *European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society*. 2013;17(5):462-70.
174. Van Oijen M, De Waal H, Van Rijen PC, Jennekens-Schinkel A, van Huffelen AC, Van Nieuwenhuizen O. Resective epilepsy surgery in childhood: the Dutch experience 1992-2002. *European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society*. 2006;10(3):114-23.
175. Benifla M, Rutka JT, Otsubo H, et al. Long-term seizure and social outcomes following temporal lobe surgery for intractable epilepsy during childhood. *Epilepsy research*. 2008;82(2-3):133-8.
176. Jarrar RG, Buchhalter JR, Meyer FB, Sharbrough FW, Laws E. Long-term follow-up of temporal lobectomy in children. *Neurology*. 2002;59(10):1635-7.
177. Chin PS, Berg AT, Spencer SS, et al. Employment outcomes following resective epilepsy surgery. *Epilepsia*. 2007;48(12):2253-7.
178. Berg AT, Baca CB, Rychlik K, et al. Determinants of Social Outcomes in Adults With Childhood-onset Epilepsy. *Pediatrics*. 2016;137(4)
179. Puka K, Tavares TP, Speechley KN. Social outcomes for adults with a history of childhood-onset epilepsy: A systematic review and meta-analysis. *Epilepsy & Behavior*. 2019;92:297-305.
180. Chin RF, Cumberland PM, Pujar SS, Peckham C, Ross EM, Scott RC. Outcomes of childhood epilepsy at age 33 years: a population-based birth-cohort study. *Epilepsia*. 2011;52(8):1513-21.
181. Forsgren L, Edvinsson SO, Blomquist HK, Heijbel J, Sidenvall R. Epilepsy in a population of mentally retarded children and adults. *Epilepsy research*. 1990;6(3):234-48.
182. McGrother CW, Bhaumik S, Thorp CF, Hauck A, Branford D, Watson JM. Epilepsy in adults with intellectual disabilities: prevalence, associations and service implications. *Seizure : the journal of the British Epilepsy Association*. 2006;15(6):376-86.
183. Robertson J, Hatton C, Emerson E, Baines S. Prevalence of epilepsy among people with intellectual disabilities: A systematic review. *Seizure : the journal of the British Epilepsy Association*. 2015;29:46-62.

184. Steffenburg U, Hedstrom A, Lindroth A, Wiklund LM, Hagberg G, Kyllerman M. Intractable epilepsy in a population-based series of mentally retarded children. *Epilepsia*. 1998;39(7):767-75.
185. Davies R, Baxendale S, Thompson P, Duncan JS. Epilepsy surgery for people with a low IQ. *Seizure : the journal of the British Epilepsy Association*. 2009;18(2):150-2.
186. Engel J, Shewmon A. Who Should Be Considered a Surgical Candidate? In: Engel J, ed. *Surgical Treatment of the Epilepsies*. 2nd ed. Raven Press; 1993:23-32.
187. Bjornaes H, Stabell KE, Heminghyt E, Roste GK, Bakke SJ. Resective surgery for intractable focal epilepsy in patients with low IQ: predictors for seizure control and outcome with respect to seizures and neuropsychological and psychosocial functioning. *Epilepsia*. 2004;45(2):131-9.
188. Chelune GJ, Naugle RI, Hermann BP, et al. Does presurgical IQ predict seizure outcome after temporal lobectomy? Evidence from the Bozeman Epilepsy Consortium. *Epilepsia*. 1998;39(3):314-8.
189. Gleissner U, Clusmann H, Sassen R, Elger CE, Helmstaedter C. Postsurgical outcome in pediatric patients with epilepsy: a comparison of patients with intellectual disabilities, subaverage intelligence, and average-range intelligence. *Epilepsia*. 2006;47(2):406-14.
190. Gleissner U, Johanson K, Helmstaedter C, Elger CE. Surgical outcome in a group of low-IQ patients with focal epilepsy. *Epilepsia*. 1999;40(5):553-9.
191. Olsson I, Danielsson S, Hedstrom A, et al. Epilepsy surgery in children with accompanying impairments. *European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society*. 2013;17(6):645-50.
192. Yu HY, Shih YH, Su TP, et al. Preoperative IQ predicts seizure outcomes after anterior temporal lobectomy. *Seizure : the journal of the British Epilepsy Association*. 2009;18(9):639-43.
193. Freitag H, Tuxhorn I. Cognitive function in preschool children after epilepsy surgery: rationale for early intervention. *Epilepsia*. 2005;46(4):561-7.
194. Hennessy MJ, Elwes RD, Honavar M, Rabe-Hesketh S, Binnie CD, Polkey CE. Predictors of outcome and pathological considerations in the surgical treatment of intractable epilepsy associated with temporal lobe lesions. *Journal of neurology, neurosurgery, and psychiatry*. 2001;70(4):450-8.
195. Smyth MD, Limbrick DD, Jr., Ojemann JG, et al. Outcome following surgery for temporal lobe epilepsy with hippocampal involvement in preadolescent children: emphasis on mesial temporal sclerosis. *Journal of neurosurgery*. 2007;106(3 Suppl):205-10.
196. Wyllie E, Comair YG, Kotagal P, Bulacio J, Bingaman W, Ruggieri P. Seizure outcome after epilepsy surgery in children and adolescents. *Annals of neurology*. 1998;44(5):740-8.
197. Gaça LB, Garcia M, Sandim GB, et al. Morphometric MRI features and surgical outcome in patients with epilepsy related to hippocampal sclerosis and low intellectual quotient. *Epilepsy & behavior : E&B*. 2018;82:144-149.
198. Miserocchi A, Cascardo B, Piroddi C, et al. Surgery for temporal lobe epilepsy in children: relevance of presurgical evaluation and analysis of outcome. *Journal of neurosurgery Pediatrics*. 2013;11(3):256-67.
199. Novais F, Andrea M, Andrade G, Loureiro S, Pimentel J, Câmara Pestana L. Intelligence quotient (IQ) as a predictor of epilepsy surgery outcome. *Epilepsy & behavior : E&B*. 2022;132:108708.
200. Paolicchi JM, Jayakar P, Dean P, et al. Predictors of outcome in pediatric epilepsy surgery. *Neurology*. 2000;54(3):642-7.
201. Harvey AS, Cross JH, Shinnar S, Mathern GW. Defining the spectrum of international practice in pediatric epilepsy surgery patients. *Epilepsia*. 2008;49(1):146-55.
202. Bittar RG, Rosenfeld JV, Klug GL, Hopkins IJ, Harvey AS. Resective surgery in infants and young children with intractable epilepsy. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia*. 2002;9(2):142-6.
203. Sugimoto T, Otsubo H, Hwang PA, Hoffman HJ, Jay V, Snead OC, 3rd. Outcome of epilepsy surgery in the first three years of life. *Epilepsia*. 1999;40(5):560-5.

204. Duchowny M, Jayakar P, Resnick T, et al. Epilepsy surgery in the first three years of life. *Epilepsia*. 1998;39(7):737-43.
205. Wyllie E, Comair YG, Kotagal P, Raja S, Ruggieri P. Epilepsy surgery in infants. *Epilepsia*. 1996;37(7):625-37.
206. Steinbok P, Gan PY, Connolly MB, et al. Epilepsy surgery in the first 3 years of life: a Canadian survey. *Epilepsia*. 2009;50(6):1442-9.
207. Jenny B, Smoll N, El Hassani Y, et al. Pediatric epilepsy surgery: could age be a predictor of outcomes? *Journal of neurosurgery Pediatrics*. 2016;18(2):235-41.
208. Castagno S, D'Arco F, Tahir MZ, et al. Seizure outcomes of large volume temporo-parieto-occipital and frontal surgery in children with drug-resistant epilepsy. *Epilepsy research*. 2021;177:106769.
209. Ansari SF, Maher CO, Tubbs RS, Terry CL, Cohen-Gadol AA. Surgery for extratemporal nonlesional epilepsy in children: a meta-analysis. *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery*. 2010;26(7):945-51.
210. Sarkis RA, Jehi L, Najm IM, Kotagal P, Bingaman WE. Seizure outcomes following multilobar epilepsy surgery. *Epilepsia*. 2012;53(1):44-50.
211. Faramand AM, Barnes N, Harrison S, et al. Seizure and cognitive outcomes after resection of glioneuronal tumors in children. *Epilepsia*. 2018;59(1):170-178.
212. Englot DJ, Berger MS, Barbaro NM, Chang EF. Factors associated with seizure freedom in the surgical resection of glioneuronal tumors. *Epilepsia*. 2012;53(1):51-7.
213. Baumann CR, Acciarri N, Bertalanffy H, et al. Seizure outcome after resection of supratentorial cavernous malformations: a study of 168 patients. *Epilepsia*. 2007;48(3):559-63.
214. Barba C, Specchio N, Guerrini R, et al. Increasing volume and complexity of pediatric epilepsy surgery with stable seizure outcome between 2008 and 2014: A nationwide multicenter study. *Epilepsy & behavior : E&B*. 2017;75:151-157.
215. Fallah A, Guyatt GH, Snead OC, 3rd, et al. Predictors of seizure outcomes in children with tuberous sclerosis complex and intractable epilepsy undergoing resective epilepsy surgery: an individual participant data meta-analysis. *PloS one*. 2013;8(2):e53565.
216. Cross JH. Neurodevelopmental effects of anti-epileptic drugs. *Epilepsy research*. 2010;88(1):1-10.
217. Marsh ED, Brooks-Kayal AR, Porter BE. Seizures and antiepileptic drugs: does exposure alter normal brain development? *Epilepsia*. 2006;47(12):1999-2010.
218. Skirrow C, Cross JH, Harrison S, et al. Temporal lobe surgery in childhood and neuroanatomical predictors of long-term declarative memory outcome. *Brain : a journal of neurology*. 2015;138(Pt 1):80-93.
219. Khoo A, de Tisi J, Mannan S, O'Keeffe AG, Sander JW, Duncan JS. Reasons for not having epilepsy surgery. *Epilepsia*. 2021;62(12):2909-2919.
220. Weber J, Gustafsson C, Malmgren K, et al. Evaluation for epilepsy surgery - Why do patients not proceed to operation? *Seizure : the journal of the British Epilepsy Association*. 2019;69:241-244.
221. Moosa AN, Jehi L, Marashly A, et al. Long-term functional outcomes and their predictors after hemispherectomy in 115 children. *Epilepsia*. 2013;54(10):1771-9.
222. Sabaz M, Cairns DR, Lawson JA, Nheu N, Bleasel AF, Bye AM. Validation of a new quality of life measure for children with epilepsy. *Epilepsia*. 2000;41(6):765-74.
223. Sabaz M, Lawson JA, Cairns DR, et al. Validation of the quality of life in childhood epilepsy questionnaire in American epilepsy patients. *Epilepsy & behavior : E&B*. 2003;4(6):680-91.
224. Liang S, Zhang S, Hu X, et al. Anterior corpus callosotomy in school-aged children with Lennox-Gastaut syndrome: a prospective study. *European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society*. 2014;18(6):670-6.
225. Gilliam F, Wyllie E, Kashden J, et al. Epilepsy surgery outcome: comprehensive assessment in children. *Neurology*. 1997;48(5):1368-74.

226. Oliveira C, de Silva NT, Ungar WJ, et al. Health-related quality of life in neonates and infants: a conceptual framework. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation*. 2020;29(5):1159-1168.
227. Harris SR, Megens AM, Backman CL, Hayes VE. Stability of the Bayley II Scales of Infant Development in a sample of low-risk and high-risk infants. *Developmental medicine and child neurology*. 2005;47(12):820-3.
228. Kvestad I, Hysing M, Ranjitkar S, et al. The stability of the Bayley scales in early childhood and its relationship with future intellectual abilities in a low to middle income country. *Early human development*. 2022;170:105610.
229. Sutcliffe AG, Soo A, Barnes J. Predictive value of developmental testing in the second year for cognitive development at five years of age. *Pediatric reports*. 2010;2(2):e15.
230. Buck D, Smith M, Appleton R, Baker GA, Jacoby A. The development and validation of the Epilepsy and Learning Disabilities Quality of Life (ELDQOL) scale. *Epilepsy & behavior : E&B*. 2007;10(1):38-43.
231. Ravens-Sieberer U, Schmidt S, Gosch A, Erhart M, Petersen C, Bullinger M. Measuring subjective health in children and adolescents: results of the European KIDSCREEN/DISABKIDS Project. *Psycho-social medicine*. 2007;4:Doc08.
232. Svanström K, Hallböök T, Rezanova J, Olsson I, Carlén C, Reilly C. Supporting Attention in Children with Epilepsy (SPACE): Pilot of a psychoeducational intervention. *Epilepsy & behavior : E&B*. 2023;138:108996.
233. Khadka J, Kwon J, Petrou S, Lancsar E, Ratcliffe J. Mind the (inter-rater) gap. An investigation of self-reported versus proxy-reported assessments in the derivation of childhood utility values for economic evaluation: A systematic review. *Social science & medicine*. 2019;240:112543.
234. Sullivan M, Karlsson J, Ware JE, Jr. The Swedish SF-36 Health Survey--I. Evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden. *Social science & medicine*. 1995;41(10):1349-58.
235. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta psychiatrica Scandinavica*. 1983;67(6):361-70.
236. Baud MO, Perneger T, Racz A, et al. European trends in epilepsy surgery. *Neurology*. 2018;91(2):E96-E106.
237. Bosselmann CM, San Antonio-Arce V, Schulze-Bonhage A, et al. Genetic testing before epilepsy surgery-An exploratory survey and case collection from German epilepsy centers. *Seizure-European Journal of Epilepsy*. 2022;95:4-10.
238. Sanders M, Lemmens CMC, Jansen FE, Brilstra EH, Koeleman BPC, Braun KPJ. Implications of genetic diagnostics in epilepsy surgery candidates: A single-center cohort study. *Epilepsia Open*. 2019;4(4):609-617.
239. Stevelink R, Sanders MW, Tuinman MP, et al. Epilepsy surgery for patients with genetic refractory epilepsy: a systematic review. *Epileptic disorders : international epilepsy journal with videotape*. 2018;20(2):99-115.
240. Scheffer IE, Harkin LA, Grinton BE, et al. Temporal lobe epilepsy and GEFS+ phenotypes associated with SCN1B mutations. *Brain : a journal of neurology*. 2007;130(Pt 1):100-9.