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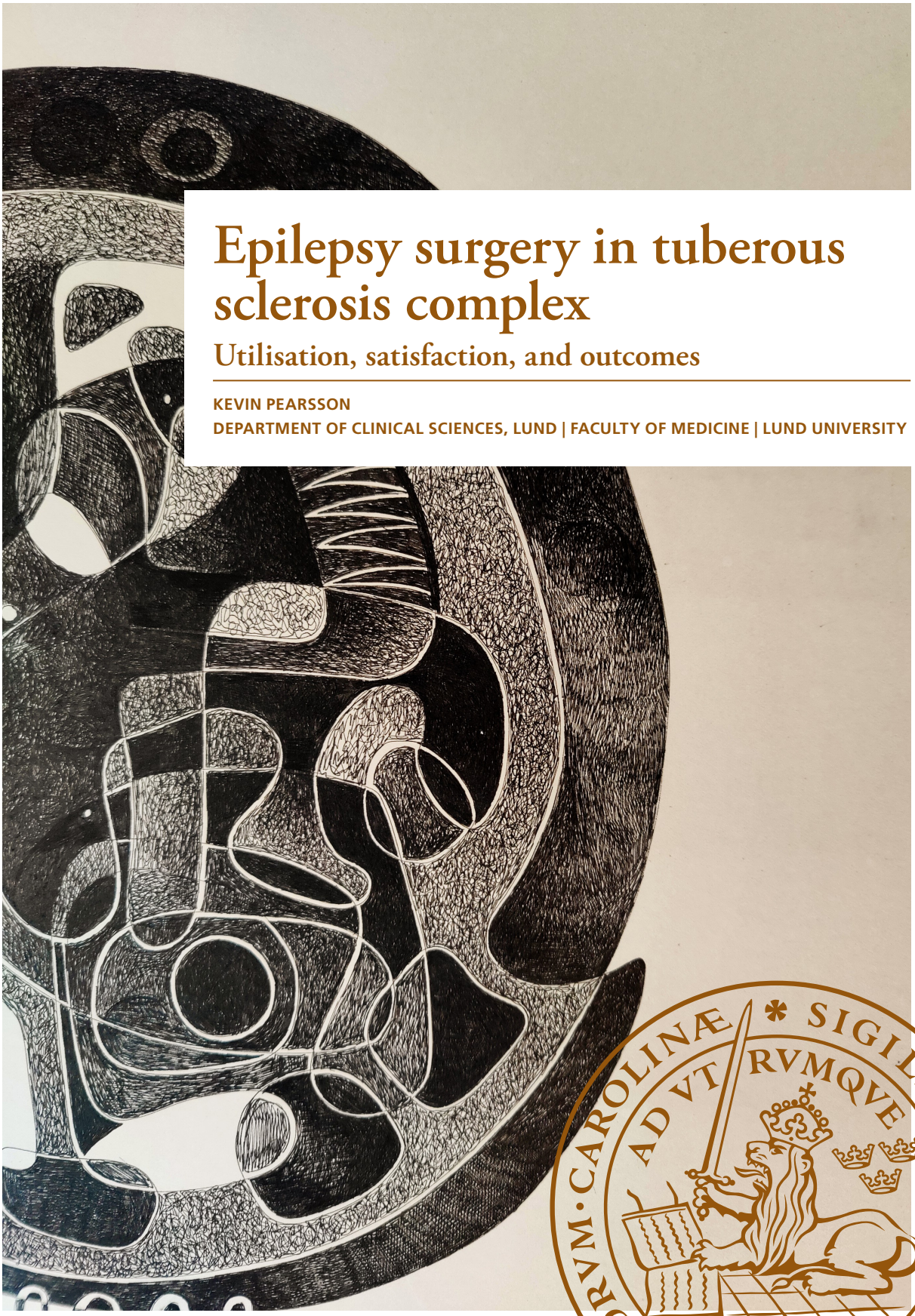
## Utilisation, satisfaction, and outcomes

Pearson, Kevin

2024

*Document Version:*
Publisher's PDF, also known as Version of record



# Epilepsy surgery in tuberous sclerosis complex

## Utilisation, satisfaction, and outcomes

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## Utilisation, satisfaction, and outcomes

Kevin Pearsson


DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on the 12th of December at 13.00 in the Medicinhistoriska Museet, Bergaliden 20, Helsingborg

*Faculty opponent*
Professor Johan Zelano, MD, PhD
University of Gothenburg, Sahlgrenska University Hospital

**Organization:** LUND UNIVERSITY

**Document name:** Doctoral Dissertation **Date of issue**: December 12, 2024

**Author(s):** Kevin Pearsson **Sponsoring organization:**

**Title and subtitle:** Epilepsy Surgery in tuberous sclerosis complex - Utilisation, satisfaction, and outcomes

**Abstract:**

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**Methods:** Individuals with TSC but no history of previous epilepsy surgery were identified through a search of medical records at a Lund university hospital. The prospective Swedish national epilepsy-surgery register (SNESUR) was utilised to identify the surgical cohort. Questionnaires were used to obtain data regarding neuropsychiatric disorders and surgical satisfaction. Trends in symptoms and outcomes were compared before and after the year 2010.

**Results:** A search of medical records identified 52 patients: 43 (83%) had epilepsy, 27 (63%) had DRE at some point, and 20 (74%) were considered for surgery, 14 (52%) at a multidisciplinary epilepsy surgery round. At the 2-year follow-up after resection, seizure freedom increased from 1/9 (11%) in 1997-2010 to 5/9 (56%) in 2011-2018. Eight out of 15 patients were seizure-free at LTFU (3–15 years). In 9/15 cases (6/8 seizure-free), satisfaction was very high, and surgery was perceived as beneficial; 13/15 recommended surgery to others. Although the seizure-free group exhibited fewer neuropsychiatric problems, no significant differences were observed between the surgery and reference groups with a similar phenotype, but without surgery.

At the LTFU after callosotomy, 4/7 patients were free from drop attacks. None was highly satisfied, 2/5 patients perceived callosotomy as beneficial, and 1/5 as harmful.

**Conclusion:** DRE is highly prevalent in TSC, and two-fourths are considered for the only known cure of epilepsy; surgery. The rate of seizure freedom in Sweden has increased over time and is now comparable to some specialized TSC centres. Future studies are needed to identify predictors of outcomes and the most suitable patients for surgery.

**Key words:** Tuberous sclerosis complex, epilepsy surgery, drug-resistant epilepsy, tuberectomy, corpus callosotomy, TSC-associated neuropsychiatric disorders

Classification system and/or index terms (if any) Supplementary bibliographical information

**Language:** English **ISSN and key title**: 1652-8220

**ISBN:** 978-91-8021-638-8

Recipient's notes **Number of pages**: 102

Price Security classification



Signature Date 2024-10-24

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Coverphoto by the paternal grandmother of Kevin Pearsson, Maj-Britt Larson, circa 1960.



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ISBN 978-91-8021-638-8
ISSN 1652-8220
Doctoral Dissertation Series 2024:140

Printed in Sweden by Media-Tryck, Lund University
Lund 2024

*To Rebecka, my love*

*"Look at everything.*
*Don't close your eyes to the world around you. Look and become curious and interested in what there is to see."*
Johan Cage

# Table of Contents

# Abstract

**Background**: Tuberous sclerosis (TSC) is a rare genetic disorder associated with a high prevalence of drug-resistant epilepsy (DRE), for which epilepsy surgery may be a viable therapeutic option. National prospective studies with long-term follow-up (LTFU) and the identification of outcome predictors are needed.

**Methods**: Individuals with TSC but no history of previous epilepsy surgery were identified through a search of medical records at a Lund university hospital. The prospective Swedish national epilepsy-surgery register (SNESUR) was utilised to identify the surgical cohort. Questionnaires were used to obtain data regarding neuropsychiatric disorders and surgical satisfaction. Trends in symptoms and outcomes were compared before and after the year 2010.

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# Populärvetenskaplig sammanfattning

Tuberös skleros är en ovanlig genetisk sjukdom som drabbar ungefär 1/10 000. En tredjedel ärver sjukdomen från en förälder. Vid tuberös skleros är det antingen genen TSC1 eller TSC2 som förlorat sin funktion. Detta leder till att de drabbade cellerna tillväxer och gör fler kopior av sig själv än den borde. Tumörer bildas därför i flera olika organ, bland annat hjärnan. Den vanligaste manifestationen i hjärnan kallas tuber och ger upphov till epilepsi.

Generellt sett blir ungefär en tredjedel av alla personer med epilepsi inte anfallsfria på enbart läkemedel, jämfört med två tredjedelar vid tuberös skleros. Individen har då en ”farmakoresistent epilepsi” och andra behandlingsalternativ ska övervägas, som exempelvis epilepsikirurgi. Epilepsikirurgi är i nuläget den enda potentiellt botande behandling vi har för epilepsi och möjliggör i många fall en minskning av läkemedelsbördan. Vissa kan till och med helt sluta med epilepsiläkemedel efteråt.

Personer med tuberös skleros drabbas också ofta av tumörer på njurarna, huden och i ögonen samt hjärtat. En växande tumör som kallas SEGA (*subependymal giant cell astrocytoma*, subependymalt jättecellsastrocytom) kan förekomma och ge högt tryck i hjärnan, så kallad vattenskalle eller hydrocefalus. Det som i de flesta fall ger mest symtom är dock de neuropsykiatriska besvär som i olika grad drabbar nästan alla personer med tuberös skleros men ofta är underdiagnostiserat. Begreppet TAND (*Tuberous sclerosis Associated Neuropsychiatric Disorder*, tuberös skleros associerade neuropsykiatriska symtom) myntandes 2012 och inkluderar de flesta neuropsykiatriska besvär dessa individer kan ha. Allt från lättare skolsvårigheter, till autism, ADHD, intellektuell funktionsnedsättning (tidigare kallat utvecklingsstörning) av olika grad, samt ångest, depression och beteendeproblematik. Det är sedan tidigare känt att epilepsi i sig kan ge en påverkan på kognition och att anfallsfrihet vid ung ålder förbättrar prognosen. Även förändringarna i hjärnan som finns vid tuberös skleros kan ge upphov till besvär inom TAND.

Triaden av intellektuell funktionsnedsättning, epilepsi och hudförändringarna som ofta ses vid tuberös skleros beskrevs 1908. Den första rapporten om epilepsikirurgi vid tuberös skleros kom 50 år senare, inkluderande 2 patienter, varav 1 blev anfallsfri. Mellan 1967 och 1987 publicerades inga nya artiklar inom ämnet, men därefter har antalet publikationer ökat för nästan varje år. När detta avhandlingsprojekt påbörjades 2018 hade i princip bara små studier gjorts på enstaka patienter från en enskild klinik, ofta i USA. Därefter har det kommit ett antal studier där den största är från Kina och inkluderar drygt 350 patienter, varav 71% var anfallsfria vid 1 årsuppföljning, men andelen minskade i takt med uppföljningstiden. I tidigare publikationer blir i genomsnitt 50–60% anfallsfria. Resultatet efter epilepsikirurgi i Skandinavien hos denna grupp av patienter har tidigare inte studerats.

Denna avhandling kunde med hjälp av journaldata från 52 individer som följts på Skånes universitetssjukhus visa att omhändertagandet av individer med tuberös skleros har förbättrats över tid. Diagnosen ställs nu ofta före det första anfallet, vilket möjliggör tidiga insatser. Behandling med epilepsiläkemedel före första anfallet har i vissa fall visat sig minska risken för framtida epilepsi och neuropsykiatriska besvär.

Denna avhandling använde det svenska nationella epilepsikirurgiregistret (SNESUR), ett världsunikt register som inkluderar alla epilepsioperationer i Sverige sedan 1990. Registret samlar löpande in data, både om genomförda undersökningar före operation och, med jämna mellanrum, utfallet efter operationen. Från denna registerdata såg vi att antalet individer som opereras har blivit fler för varje årtionde, att operationen nu görs i yngre ålder och att resultaten markant förbättrats: 1997–2010 var en av nio anfallsfria vid 2-årsuppföljningen efter operation jämfört med fem av nio 2011–2018. Vid långtidsuppföljning efter 3–15 år var 8 av 15 individer anfallsfria. Andelen individer med tuberös skleros som blir anfallsfria efter epilepsikirurgi i Sverige är nu likvärdig med stora specialiserade center i Kina och USA. Ingen av de opererade individerna fick någon allvarlig komplikation efter ingreppet. Glädjande nog togs epilepsikirurgi upp som ett behandlingsalternativ hos tre fjärdedelar av alla som skulle kunna vara aktuella och en fjärdedel opererades. Det verkar därför som att svenska läkare tagit till sig de senaste internationella riktlinjerna som betonar vikten av tidig diagnos och remittering för epilepsikirurgiutredning.

Överlag var individerna som opererats, eller deras anhöriga, väldigt nöjda med operationen. Nio av femton var genomgående helt nöjda och skulle rekommendera kirurgi till andra i en liknande situation, detta trots att tre av dessa inte blev anfallsfria. Vi rekommenderar därför att framtida studier mer ingående inkluderar nöjdhet i utvärderingen av epilepsikirurgi samt tar reda på vad som upplevs viktigt och påverkar nöjdheten efter operation, för det verkar som att anfallsfrihet inte är det enda som påverkar.

Vid jämförelse av neuropsykiatriska besvär mellan individer som genomgått epilepsioperation och individer med en svår epilepsi som inte genomgått operation fann vi inga skillnader. Dock såg vi att individer som var anfallsfria, oavsett om det var med eller utan operation, hade lägre grad av neuropsykiatriska besvär och inte lika många hade en intellektuell funktionsnedsättning. Tidigare studier har visat att familjer ibland kan ställa sig tvekande till epilepsikirurgi på basen av de svåra neuropsykiatriska problemen som ofta finns. Förhoppningsvis kan våra resultat, att familjer i en liknande situation tidigare lyckats och att ingen fick komplikationer, bidra till att fler vågar genomgå den process som krävs för att kunna få tillgång till den idag enda botande behandlingen vi har för epilepsi – epilepsikirurgi. Vi rekommenderar att alla individer med tuberös skleros regelbundet screenas för förekomsten av neuropsykiatriska besvär och, vid behov, remitteras för tidig behandling. På så sätt hoppas vi minska lidandet, göra besvären mindre påtagliga

och förhoppningsvis öka chansen att dessa familjer vågar genomgå epilepsikirurgiutredning och därefter operation.

Sammanfattningsvis har avhandlingen visat att epilepsikirurgi vid tuberös skleros utnyttjas i allt större utsträckning, patienterna och anhöriga är efteråt nöjda med operationen och under det senaste årtiondet har mycket goda resultat uppnåtts. Trots att vi i Sverige bara opererar en fjärdedel så många patienter som på ett enda högspecialiserat sjukhus i Kina under samma tid kan samma långtidsresultat uppnås.

# List of Papers

*Paper I*

**Pearson, K**., Björk Werner, J., Lundgren, J., Gränse, L., Karlsson, E., Källen, K., Eklund, E. A., & Bekassy, Z. (2023). Childhood tuberous sclerosis complex in southern Sweden: A paradigm shift in diagnosis and treatment. *BMC Pediatrics*, *23*(1), Article 329. https://doi.org/10.1186/s12887-023-04137-4

*Paper II*

**Pearsson, K**., Compagno-Strandberg, M., Eklund, E. A., Rask, O., & Källén, K. (2022). Satisfaction and seizure outcomes of epilepsy surgery in tuberous sclerosis: A Swedish population-based long-term follow-up study. *Seizure, 103*, 39-45. https://doi.org/10.1016/j.seizure.2022.10.011

*Paper III*

**Pearsson, K**., Eklund, E. A., Rask, O., & Compagno-Strandberg, M. (2024). Seizure freedom but not epilepsy surgery is associated with fewer neuropsychiatric difficulties in patients with tuberous sclerosis. Epilepsy and Behavior, 157, Article 109875. https://doi.org/10.1016/j.yebeh.2024.109875

*Paper IV*

**Pearson, K**., Eklund, E., Rask, O., Rosén, I., Sjunnesson, H., & Compagno-Strandberg, M. (2023). The evolution of epilepsy surgery in tuberous sclerosis in Sweden: A national registry study. *Seizure*, *112*, 54-61. https://doi.org/10.1016/j.seizure.2023.09.016

# Author's contribution to the papers

*Paper I*

The PhD student performed data collection regarding drug-resistant epilepsy and epilepsy surgery, requisitioned all external medical records, assisted with data collection for other neurological manifestations, wrote the draft manuscript on neurological manifestations, and helped with the response to the reviewers.

*Paper II*

The PhD student drafted the initial ethical application, managed all data collection, wrote the first draft of the manuscript, submitted the paper, and wrote responses to the reviewers.

*Paper III*

The PhD student drafted the initial ethical application, managed all data collection, wrote the first draft of the manuscript, performed statistical analysis, created all figures, and wrote responses to the reviewers.

*Paper IV*

The PhD student drafted the initial ethical application, managed all data collection, wrote the first draft of the manuscript, submitted the paper, and wrote responses to the reviewers.

# Abbreviations

| | |
|---|---|
| [number]FU | follow-up (the preceding number indicate years of follow-up) |
| ADHD | attention-deficit hyperactivity disorder |
| AML | angiomyolipomas |
| AMT | α-[11C]-Methyl-l-tryptophan |
| ASM | anti-seizure medication |
| Cohort (1) | non-surgical cohort |
| Cohort (2) | surgical cohort |
| CVI | cerebral visual impairment |
| DRE | drug-resistant epilepsy |
| EEG | electroencephalogram |
| IS | infantile spasms |
| IQ | intelligence quotient |
| LTFU | long-term follow-up |
| MRI | magnetic resonance imaging |
| mTORC1 | mechanistic target of rapamycin complex 1 |
| PET | positron emission tomography |
| SEGA | subependymal giant cell astrocytomas |
| SISCOM | subtraction ictal SPECT coregistered to MRI |
| SNESUR | Swedish National Epilepsy-Surgery Register |
| SPECT | single-photon emission computed tomography |
| TACERN | TSC Autism Center of Excellence Network |
| TAND | TSC-associated neuropsychiatric disorders |
| TOSCA | TuberOus SClerosis registry to increase disease Awareness |
| TSC | tuberous sclerosis complex |
| TSCNHD | Tuberous Sclerosis Alliance Natural History Database |

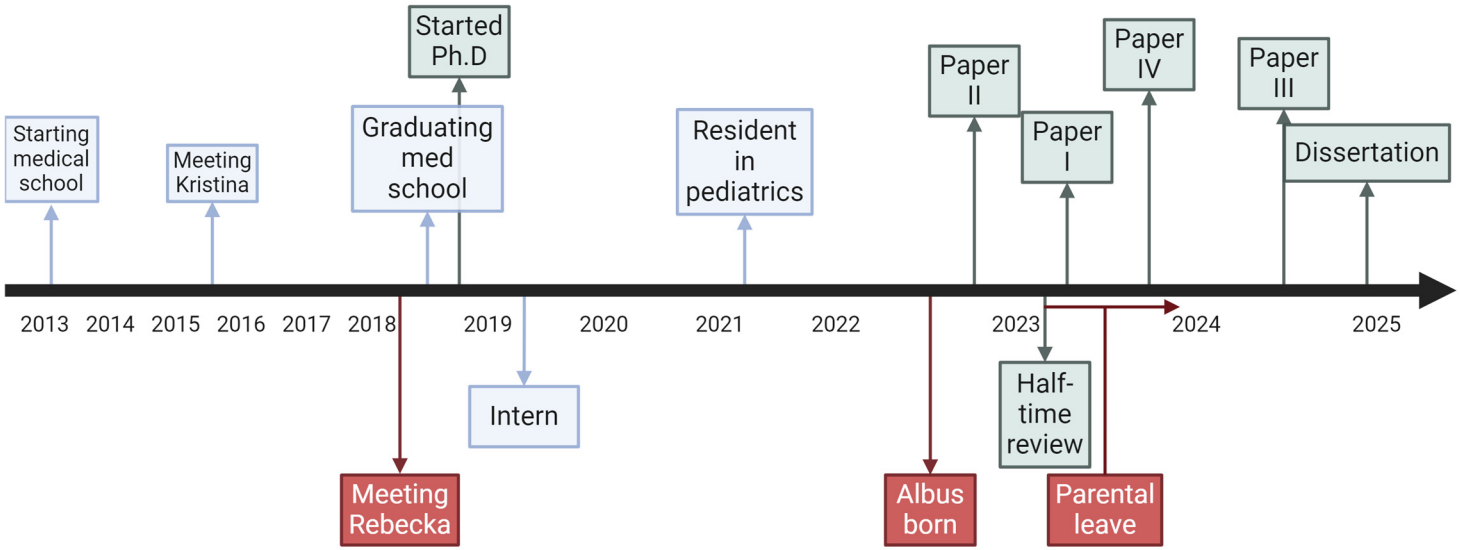


**Figure 1. Timeline of my journey from medical school to the completion of this thesis**
Created with BioRender.com.

# 1 Preface

Figure 1 depicts my professional and personal journey to the dissertation. My first contact with research occurred during my fifth term at medical school, when I wrote my bachelor´s essay. That experience sparked my desire to pursue research independently. The following summer, I met Professor Emeritus Ingmar Rosén while working as a secretary at the Department of Clinical Physiology in Karlskrona and asked him for guidance on how to proceed with my research aspirations. One of his former PhD students, Kristina Källén, was now an associate professor in Helsingborg, where I continued my studies. During my first week there, I approached her, and she offered me a project. Later, I wrote my master´s essay under her supervision, although it was unrelated to tuberous sclerosis. When I told her that I wanted to become a paediatric neurologist, she suggested the project that is now included in this thesis.

The order of the papers might initially seem confusing but follows a certain logic. The papers are presented in the intended order of publication; however, as is often the case, the plan unfolded in a way that was not planned. Paper I was submitted long before Paper II but was rejected after a long hiatus. After resubmission to another journal, the publication process was challenging. Nevertheless, Paper I is the most comprehensive study and provides a good overview of the disorder, justifying its position as the first paper in this thesis. The structure of Paper III was planned before that of Paper IV, but the data collection took longer than anticipated, leading to its later completion. However, I chose to maintain the planned order for this thesis.

# 2 Introduction

Tuberous sclerosis complex (TSC), previously known as Bourneville disease, is a genetic neurocutaneous disorder that affects multiple organs. The major manifestations are benign soft tissue tumours and neurological symptoms, including epilepsy, autism, and intellectual disability.[1] The classic skin lesion associated with TSC, adenoma sebaceum (facial angiofibromas in the modern nomenclature) was first documented in 1835. In 1862, Freidrich Daniel von Recklinghausen described the association of a tumour of the heart (rhabdomyoma) and brain '*scleroses*' in a newborn with epilepsy who unfortunately died shortly after birth.[2] However, it was not until 1880 that Désiré-Magloire Bourneville provided a coherent nomenclature for TSC in an autopsy report of a 15-year-old girl with epilepsy and 'mental retardation'.[3] The deceased girl also had skin lesions and kidney involvement, which were not described in the post-mortem report as being linked to the underlying condition of TSC. Brain lesions were described as *Sclérose tubéreuse des circonvolutions cérébrales*, coining the term 'tuberous sclerosis'. In 1908, Heinrich Vogt described the first diagnostic criteria for what was then known as Bourneville disease - a triad of seizures, 'mental retardation', and adenoma sebaceum.[4,5] Vogt was also the first to notice an association between TSC and kidney lesions.[2]

## 2.1 Tuberous sclerosis complex (TSC)

TSC is an autosomal dominant genetic disorder with a prevalence of 4.9 per 100,000 in the United Kingdom and 5.4 per 100,000 in Sweden.[6,7] Some studies have estimated the prevalence to be 8.8 per 100,000.[8] TSC is caused by a pathogenic loss-of-function variant in either the TSC1 or TSC2 gene, encoded on 9q34 and 16p13.3, respectively.[9,10] Loss of function in either of these genes causes disinhibition of the mechanistic target of rapamycin complex 1 (mTORC1) leading to benign soft tissue tumours (hamartomas). Symptoms vary with age; for example, rhabdomyoma is often present at birth but later regresses, whereas angiomyolipomas (AML) in the kidneys and subependymal giant cell astrocytomas (SEGA) in the brain develop later.[11] Focal cortical dysplasias (tubers) in the brain are present at birth and often bilateral and multiple. While tubers do not grow, they can change over time, such

as through calcification. These tubers are the main generators of seizures, which often develop before the age of one.[12]

The diagnosis of TSC is based on specific diagnostic criteria, presented in Table 1. A definitive diagnosis of TSC is made in the presence of either 2 major, 1 major and 2 minor features, or by identifying a pathogenic variant of either TSC1 or TSC2. Possible TSC is defined as 1 major or >2 minor features.[13]

**Table 1. Diagnostic criteria for tuberous sclerosis**
Adapted from Northrup et al[13] 

| MAJOR FEATURES | MINOR FEATURES |
|---|---|
| Hypomelanotic macules (≥3; at least 5 mm in diameter) | "Confetti" skin lesions |
| Angiofibroma (≥3) or fibrous cephalic plaque | Dental enamel pits (>3) |
| Ungual fibromas (≥2) | Intraoral fibromas (≥2) |
| Shagreen patch | Retinal achromatic patch |
| Multiple retinal hamartomas | Multiple renal cysts |
| Multiple cortical tubers and/or radial migration lines | Nonrenal hamartomas |
| Subependymal nodule (≥2) | Sclerotic bone lesions |
| Subependymal giant cell astrocytoma | |
| Cardiac rhabdomyoma | |
| Lymphangioleiomyomatosis[a] | |
| Angiomyolipomas (>2)[a] | |

a: The presence of only lymphangioleiomyomatosis and angiomyolipoma without other features is insufficient for a diagnosis.

### 2.1.1 Genetics and the mTOR-pathway

Using exon-only genetic sequencing, a pathogenic TSC1 or TSC2 variant is found in 85–90% of all patients with TSC.[14,15] In the remaining cases, the disease is most likely caused by a pathogenic variant in an intron, promoter region, or mosaicism.[14,15] In individuals with mosaicism, the clinical features of TSC are fewer, they often have a milder phenotype and may go undetected.[16,17] No other genes besides TSC1 and TSC2 are known to cause TSC. It is estimated that two-thirds of patients with TSC have a *de novo* pathogenic variant.[18] The majority of TSC cases are caused by TSC2 (51–82%), whereas inherited cases have an equal distribution of TSC1 and TSC2 and generally a milder phenotype.[18-22] Pathogenic variants in both genes are rare.[21,23] A pathogenic TSC2 variant is associated with a more severe phenotype than TSC1 with a higher number of tubers, earlier age of seizure onset, higher likelihood of infantile spasms, drug-resistant epilepsy (DRE), and severe kidney disease.[20,22,24-27] Therefore, pathogenic TSC1 variants are

generally diagnosed later than TSC2.[28] However, a large phenotypic variation is seen, even in inherited cases from the same family.[29,30]

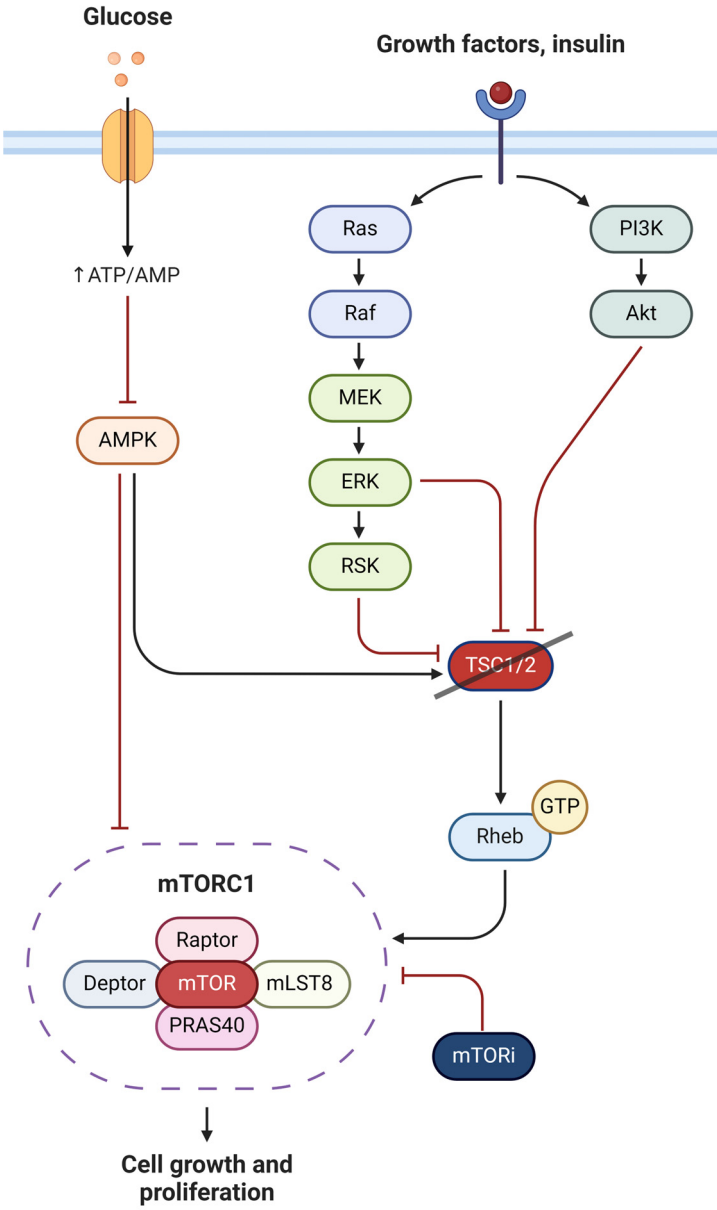


**Figure 2. The mTOR pathway**
The role of TSC1 and TSC2 in the mTOR pathway. A loss of function in these genes causes an overactivation of Rheb, which in turn activates the mTORC1-complex. mTORi include the different mTOR inhibitors, such as everolimus.
Created with BioRender.com. Adapted from Kim et al 2013.[31]

Both TSC1 and TSC2 are tumour suppressor genes that encode hamartin and tuberin, respectively. Hamartin and tuberin form a complex which inhibits mTOR through the conversion of Rheb-GTP to Rheb-GDP (Figure 2).[32] A GTPase activating protein (GAP) is present on TSC2, crucial for the TSC1/TSC2 complex function. The protein complex mTORC1 consists of the serine/threonine protein kinase mTOR and five catalytic components, including rapamycin associated protein of TOR (RAPTOR). mTORC1 responds to the extracellular metabolic environment and growth factors to control protein translation, lipid synthesis, cell growth, and neuronal differentiation, as well as limiting autophagy.[18] mTOR is also included with rapamycin-insensitive companion of mTOR (RICTOR) in mTORC2. The downstream substrates for mTORC2 are different from mTORC1 and seem to control cytoskeletal dynamics and long-term memory.[32] The TSC1/TSC2 genes and mTOR are crucial for normal myelination, axonal growth, synaptogenesis, as well as plasticity, and thereby for normal brain development.[29] Previously, tubers were thought to be the main generators of the neurological symptoms of TSC; however, recent studies have shown that glial cells contribute as well.[33] Somatic (or 'second-hit') mutations are detected in TSC-associated neoplastic lesions, such as angiomyolipomas[34] and SEGAs[35,36] but are not as frequently encountered in the largely static non-neoplastic lesions, such as tubers.[37]

### 2.1.2 Presenting features and somatic manifestations

TSC is a multi-organ genetic disorder, with epilepsy being one of the most prevalent symptoms.[1] The symptoms of TSC vary widely and tend to evolve throughout a patient's life. The condition often presents in utero with cardiac rhabdomyoma, which typically develops between 22 and 28 weeks of gestation and can be visualised through prenatal ultrasound. In most cases, rhabdomyomas regress,[11,38] but 26% persist until adulthood.[39] Some dermatological findings, such as hypomelanotic macules, are present at birth, whereas others, such as facial angiofibromas and Shagreen patches, develop over time.[38,40] Additionally, cortical malformations appearing as tubers are present at birth and are a common source of epileptic seizures in TSC.[38] One study suggests that these tubers may lack functional cortex.[41]

The age at which TSC is diagnosed varies according to various factors. One study found that for patients with a prenatal presentation of cardiac rhabdomyoma, the median age at diagnosis was 6 months (range 5 months before birth to 197 months of age), compared to 11 months for those without a prenatal presentation.[42] A prospective study[43] from 2017 revealed that 35% of infants with TSC presented prenatally with cardiac rhabdomyomas and 41% within the first month of life. Cardiac rhabdomyomas (59%) and dermatological findings (39%) were the most common signs of TSC with 85% of infants presenting with either or both.[43] The

most prevalent manifestations of TSC were hypomelanotic macules (94%), tubers (94%), subependymal nodules (90%), and cardiac rhabdomyomas (82%). No minor criteria contributed to the diagnosis. For all infants with only one major criterion, diagnosis was confirmed by genetic testing.[43] Studies have found that 50–80% of infants with cardiac rhabdomyomas have TSC.[44,45]

The TuberOus SClerosis registry to increase disease Awareness (TOSCA) was the largest international TSC registry to date and collected data regarding manifestations, interventions, and outcomes in patients with TSC of all ages. At the end of inclusion, the registry included more than 2000 patients from 31 countries,[46] with a median age at inclusion of 13 years (range: 0–71 years, 63% were <18 years of age).[21] The most frequently reported manifestations were epilepsy (83.5%), followed by hypomelanotic macules (66.8%), facial angiofibromas (57.3%), renal AML (47.2%), and cardiac rhabdomyomas (34.3%). A minority of patients had retinal (14.0%) and liver (9.1%) hamartomas.[21] Lymfangioleiomyomatosis (6.9%) almost exclusively affected postmenopausal women with TSC and is characterised by lung cysts and changes in the pulmonary lymphatic system, potentially leading to pneumothorax.[1,21] Despite the high prevalence of benign tumours in TSC, only 3% of individuals with TSC develop malignant tumours, with renal cell carcinoma accounting for half of these cases.[47]

Subependymal nodules are regarded as precursors to SEGA, a benign, slow-growing tumour of the ventricle wall that is highly associated with a TSC2 variant.[1,21,29,48] Despite being benign, SEGA may obstruct the flow of cerebrospinal fluid, causing hydrocephalus.[49] Typically, SEGA is diagnosed at the age of 8 to 9.4 years with 18% diagnosed after the age 18.[21,50] The prevalence of SEGA in TSC varies between 6–24%, increasing to as much as 27% in adults.[1,12,21,22,27,43,48]

Cerebral visual impairment (CVI) is a spectrum of disorders that cause deficits in higher-order visual processing, beyond what is indicated by structural eye examination.[51] CVI is caused by damage to the retrochiasmal visual pathways. Owing to the high prevalence of brain dysfunction in TSC, many of these patients likely have some degree of CVI, although the true prevalence remains uncertain.[51]

In conclusion, the most common symptoms of TSC are cardiac rhabdomyomas and hypomelanotic maculae, both of which tend to decrease over time. Instead, as the patient ages, neoplastic lesions (facial angiofibromas, renal angiomyolipomas, SEGA, and lymphangioleiomyomatosis) begin to appear. The prevalence of CVI in patients with TSC is highly uncertain. At the start of this project, few studies had investigated the clinical spectrum of TSC manifestations in a clinical setting and none had been conducted in Scandinavia.

## 2.2 Epilepsy

According to the international league against epilepsy,[52] epilepsy is defined as either:

(1) At least two unprovoked seizures occurring >24 hours apart
(2) One unprovoked seizure and the probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
(3) a diagnosis of an epilepsy syndrome

DRE is defined as having failed to achieve seizure freedom after a trial of two tolerated anti-seizure medications (ASM) in adequate doses.[53]

### 2.2.1 Epilepsy in TSC

The gradual development of spontaneous seizures is referred to as epileptogenesis, which in TSC is primarily driven by the presence of tubers, often multiple and bilateral.[54] Histopathological examination of TSC-associated tubers reveal cortical dyslamination, giant cells, dysmorphic neurons, and reactive astrocytes.[55] Giant cells and dysmorphic neurons are believed to induce an inflammatory response early in foetal brain development, further contributing to the process of epileptogenesis.[56,57] Some studies have suggested that the perituberal cortex may serve as the epileptogenic substrate,[58] however, it is most likely that the tubers themselves are the primary source.[59] For instance, Mohamed et al[60] found that the ictal onset zone involved tubers in 88% of cases and was confined to tubers in 57% of localised seizures. A subsequent study found a similar pattern, with some patients exhibiting a tuber with a unifocal epileptogenic zone often with features of focal cortical dysplasia type IIb and a good post-surgical outcome while others presented with a more complex epileptogenic zone that occasionally included normal-appearing cortex, resulting in worse outcomes after epilepsy surgery.[61] Histological, immunohistochemical, and molecular characteristics of tubers are also sometimes present in the perituberal cortex, albeit to a lesser extent.[62] This indicates that in certain patients a single tuber may be identified as the primary epileptogenic zone but often multiple seizure types, multiple potentially epileptogenic tubers, and multifocal epileptiform discharges are present.[63] This multifocality is, therefore, a particular challenge for epilepsy surgery in TSC potentially necessitating multiple procedures or large resections, or may yield inconsistent localising data that complicate further localizing procedures or surgery.[63] However, such hurdles should not preclude these patients from evaluation for epilepsy surgery.[64]

**Table 2. Epilepsy in TSC**
Selected major studies on the prevalence and characteristics of epilepsy in TSC.

| Author (Study group) | Year (n) | Ages | Epilepsy (%) | Seizure onset | IS (%) | DRE (%) |
|---|---|---|---|---|---|---|
| Jansen et al[65] | 2008 (61) | Range: 1.6 – 59 y, Mean 17.9 y | 85 | Mean 2.2 y (range 1 d – 37 y) | 40 | NS |
| Chu-Shore et al[66] | 2010 (291) | All ages | 85 | Mean: 29 m, median 7 m <6 m: 46 % <12 m: 63 <3 y: 82 | 38 | 63 |
| Vignoli et al[27] | 2013 (160) | 40 children 120 adults | 73 | <12 m: 57 % | 45 | 48 |
| Davis et al[43] (TACERN) | 2017 (130) | 0 – 3 y | 76 | <3 m: 17% <6 m: 39% <12 m: 57% | 57 | NS |
| Welin et al[7] | 2017 (551) | All ages, median 13 y | 70 | NS | 19 | 33 |
| Nabbout et al[67] (TOSCA) | 2018 (2216) | All ages, median 13 y | 84 | Mean: 1 y IS: 0.4 y; Focal: 2.7 y. | 39 | 38 |
| Gupta et al[68], (TSCNHD) | 2020 (1319) | Range: 0 – 81 y, Median 16 y | 88 | Median: 1 y (0-52) | 50 | NS |
| Vignoli et al[22] | 2020 (257) | Range: 18 – 87 y, median 37 y | 71 | Median: 9 m (1 day – 48 years) | 42 | 66 |
| Ihnen et al[69] | 2021 (156) | 0 – 3 y | 79 | Median: 4.7 m (range 0 – 29.5) <12 m: 93% | 57 | NS |
| Pereira et al[12] | 2022 (130) | Range: 1 – 56 y, mean 20.4 y | 82 | <6 m: 52% 6 – 12 m: 20% 1 – 2 Y: 13% <2 y: 86% | 35 | 55 |
| Licchetta et al[39] | 2024 (43) | Mean: 34.6 ± 12.3 y | 91 | Mean: 4 y SD 7.3 y | 39 | 64 |

Abbreviations: d: day; DRE: Drug-resistant epilepsy; IS: Infantile spasms; m: month; NS: not specified; y: year.

Abnormal cell proliferation is observed in the tubers of TSC as well as in focal cortical dysplasia and hemimegencephaly, which stem from non-neoplastic malformations due to cortical dysgenesis.[55] All these entities are believed to arise from dysregulation of the mTOR pathway and are collectively referred to as mTORopathies, characterised by altered cortical architecture, abnormal morphology of neurons, and severe epilepsy.[55] Dysregulation of the mTOR pathway seems to affect the maturation and functionality of the GABAergic system. Studies have shown that the cells within tubers possessed an increased density of glutamate receptors while astrocytes in the brain of individuals with TSC have an impaired capability of glutamate transport.[54] These factors contribute to an imbalance in the glutamate/GABA system, heightening the risk of seizures.[54]

As presented in Table 2, epilepsy affects 70–90% of individuals with TSC.[7,21,39,68] Focal seizures are the most prevalent seizure type, followed by infantile spasms.[66,68] Multiple seizure types are frequently observed.[43,66] The age of seizure onset differs between studies and seizure types, but approximately 60% of individuals have seizure onset before 12 months of age (Table 2). One study by Davis et al[43] including children up to 3 years of age found that 57% experienced infantile spasms, typically occurring between 3–9 months, and 36% also experienced co-occurring focal seizures. As this study only included young children, the rate of infantile spasms is probably higher compared to TSC in general. Other large studies have found that focal seizures occur in 81–84% of cases, with co-occurrence of infantile spasms in 21–24%. Additionally, 13–15% of patients present exclusively with infantile spasms.[67,68] The incidence of epilepsy in TSC has increased from 68% in the 1970s to 92% in the period of 2010–2015, likely reflecting heightened awareness among clinicians and parents.[70] Subclinical seizures may be detectable on electroencephalogram (EEG) anywhere from 1 day to 4.5 months before the onset of clinical seizures.[71-75]

Up to two-thirds of individuals with TSC develop DRE at some point during their lives (Table 2).[39,66] A study by Overwater et al[76] focused exclusively on individuals with TSC and epilepsy, revealing that 77% achieved seizure freedom for at least 1 month, and 38% remained seizure-free for 24 months, of which 43% had recurrence after 24 months. Of these children with sustained seizure freedom, 43% had seizure recurrence after a period of up to 14 years. A period of seizure freedom was achieved after the first ASM in 52% of cases, with 20% achieving it after the second.[76] DRE is associated with a history of infantile spasms, an earlier age of seizure onset, and a TSC2 variant.[20,22,24-26,66,77] A prospective, multicentre study by the TSC Autism Center of Excellence Network (TACERN) group compared early developmental patterns across 92 children with TSC based on different genotypes.[78] A pathogenic TSC2 variant was found in 68% of cases, TSC1 in 14%, while no mutation was identified in 17%; furthermore, seizures occurred in 86%, 23%, and 69% of these cases, respectively. Subsequent studies have replicated these results

and observed an overall more severe phenotype in individuals with a TSC2 variant, including earlier age of seizure onset, higher rate of DRE and SEGA, as well as more neuropsychiatric disorders and severe intellectual disability.[26-28,39,66-68,79-82] A TSC2 variant was reported to be associated with a 3-fold increased risk of epilepsy.[83] One study reported that all individuals with DRE had a pathogenic TSC2 variant.[82] The incidence of epilepsy and DRE is higher in de novo cases (91% and 83% respectively) compared to inhereted (76% and 39% respectively), due to the higher incidence of TSC1 variants in inherited cases.[22] Sudden unexpected death in epilepsy was the leading course of mortality in the Tuberous Sclerosis Alliance Natural History Database (TSCNHD), accounting for 35.5% of all decedents (n=31).[84]

One study from the TACERN group attempted to identify individual clusters of seizure patterns with machine learning.[69] The study included 156 children with TSC (76% had epilepsy) who were followed up from 3 to 36 months of age. Seizure frequency varied greatly; 36% reported <10 seizures during the study period while the maximum number of seizures was 9218. The number of seizure days ranged from 0.1–90%. Five clusters of seizure burden were identified: two favourable and three unfavourable. The group with the latest seizure onset, lowest prevalence of infantile spasms, and lowest seizure frequency also scored the highest on cognitive testing. The developmental quotient of all unfavourable groups was significantly lower than that of the favourable groups.[69]

### 2.2.2 Treatment of epilepsy in tuberous sclerosis

In general, the treatment of seizures in TSC should follow the general guidelines for epilepsy management. Recent guidelines for TSC emphasise the importance of considering epilepsy surgery, or other non-pharmacological treatments such as vagus nerve stimulation or the ketogenic diet, in cases of DRE.[64] However, there are some specific treatment recommendations for patients with TSC and epilepsy, including the use of mTOR inhibitors and vigabatrin before seizure onset.[13,64,85-89]

#### *2.2.2.1 Preventive vigabatrin*

Vigabatrin is a synthetic molecule, designed to increase the levels of GABA in the brain. It functions as an indirect GABA agonist by noncompetitively inhibiting GABA transaminase[90] and may also exert an inhibitory effect on mTOR.[91] The major adverse event associated with vigabatrin is the risk of visual field defects due to irreversible changes in retinal ganglions, which may often go unnoticed by the patient but can be detected through neuro-ophtalmic investigations.[51] Recent studies have indicated that the risk of visual field defects is most likely lower than previously believed.[92] Vigabatrin has long been known to have good efficacy on infantile spasms in tuberous sclerosis.[93-95]

Tuberous sclerosis is often diagnosed before the onset of seizures, for example by the presence of a cardiac rhabdomyoma or hypomelanotic macules.[43] This provides an opportunity for early seizure detection in this high-risk group. One study found that interictal discharges appeared, on average, 3.6 months before the onset of seizures and had a high predictive value for future epilepsy.[73] In 2011, Jozwiak et al[96] published a prospective single-centre study comparing the outcomes of standard treatment versus preventive treatment with vigabatrin after the emergence of multifocal spikes on the EEG but prior to clinical seizures in young infants. In the preventive treatment group, significantly more individuals achieved seizure freedom and significantly fewer experienced DRE or required polytherapy.[97] In the standard treatment group, the prevalence of intellectual disability was four times higher.[97] These results were maintained during the long-term follow-up (LTFU),[96] with 50% of the preventive group developing seizures compared to 96% in the standard treatment group.[96]

Two randomised multicentre studies have been published since the groundbreaking study by Jozwiak et al. The EPISTOP study was conducted in Europe, and the PREVENT study was conducted in the USA, with slightly different results. The EPISTOP trial[98] recruited 94 infants of ≤4 months of age and the PREVENT trial[99] 84 infants of ≤6 months of age with TSC before the onset of seizures. Both studies monitored the infants with EEG every 4–8 weeks until 12 months of age, and every 2–3 months from 12 to 24 months of age, randomly assigning them to receive preventive vigabatrin or standard treatment in EPISTOP, or placebo in PREVENT. EPISTOP showed that the median time to the first seizure was four times longer in the preventive group compared to the standard treatment group (614 vs 124 days, respectively) and the chance of not developing seizures was three times higher. The risk of DRE was lower in the preventive group (28% vs 64%, respectively), with none in the preventive group developing infantile spasms compared to 40% in the standard care group. Despite these findings, there were no significant differences in neurodevelopmental outcomes.[98] In the PREVENT trial, the onset of infantile spasms was delayed in the preventive group; however no statistically significant differences was found in neurodevelopment, the proportion of individuals who developed seizures, or DRE.[99]

The difference in the outcomes between EPISTOP and PREVENT may be potentially attributed to the difference in randomization procedures (the type of treatment in PREVENT, timing of treatment initiation in EPISTOP), eligible age (mean age of enrolment was 1 month in EPISTOP compared to 2.3 months in PREVENT), and the different intervals between EEG assessments. In addition, the proportion of participants with a TSC2 genotype in PREVENT was 67% in the placebo group, compared to 97% in the treatment arm.[100] The value of EEG monitoring and presymptomatic vigabatrin still remains uncertain, however, it is

recommended by international guidelines.[64,85] These guidelines were published before the results of PREVENT were made available.

*2.2.2.2 mTOR inhibitors*

Everolimus is a specific mTORC1-inhibitor.[29] Historically, surgical resection has been the standard treatment for SEGA in TSC. In 2010, Krueger et al[101] published an open-label study on the efficacy of everolimus in reducing SEGA growth in 28 patients with TSC. In addition, 9 of 16 patients with available data exhibited a reduction in seizure frequency. Since then, several randomised and observational studies have validated the efficacy of mTOR inhibitors in the treatment of SEGA,[102,103] renal AMLs,[104,105] and seizures.[23,106,107]

A phase 3, randomised, double-blind, placebo-controlled trial, EXamining everolimus In a Study of Tuberous sclerosis 3 (EXIST-3), evaluated the efficacy of everolimus in 366 patients with TSC and DRE. Over 50% reduction in seizure frequency was seen in 15.1%, 28.2%, and 40.0% of the placebo, low and high exposure groups, respectively,[106] with a higher response rate in children <6 years of age.[107] The response rate increased over time.[23]

In conclusion, epilepsy is highly prevalent in TSC and is often difficult to treat, with up to two-thirds of patients developing DRE. Early treatment with vigabatrin before the onset of seizures may delay seizure emergence, and everolimus has a better effect on seizures in children, below 6 years of age. Many patients with TSC are diagnosed with TSC in utero due to the presence of a cardiac rhabdomyoma, enabling timely interventions aimed at reducing the severity of epilepsy and promoting better developmental outcomes. The effects of everolimus on epilepsy surgery outcomes and whether intrauterine exposure to everolimus reduces the severity of TSC have not yet been thoroughly explored.

## 2.3 TSC-associated neuropsychiatric disorders (TAND)

In addition to the neurological disorders and other organ manifestations, individuals with TSC frequently experience a wide range of neuropsychiatric disorders and symptoms. These problems range from mild school difficulties to severe intellectual disabilities. In 2005, international guidelines were established to address the screening and treatment of cognitive and behavioural problems in TSC.[108] These guidelines recommend regular assessment of cognitive development and behavioural problems in children and adolescents with TSC, recognizing that neuropsychiatric manifestations can exhibit age-related expression.[109] Despite these recommendations, only a small percentage of patients received adequate assessment. Therefore, a neuropsychiatric panel at the International Consensus Conference in 2012 decided to identify strategies to reduce the treatment gap,

increase awareness of neuropsychiatric problems in TSC, and develop a simple screening tool. The panel coined the term TSC-Associated Neuropsychiatric Disorders (TAND) and developed an accompanying screening tool, the TAND checklist.[110] In 2023, guidelines were published for identifying and treating TAND.[111] These guidelines recommended lifelong monitoring of TAND, early intervention, consideration of health problems in relation to TAND, ensuring that all interventions are evidence-based, and to strive for optimal quality of life.[111] In TSC, 90% of patients have at least one symptom within the TAND spectrum.[112]

### 2.3.1 The TAND checklist

In 2015, the TAND checklist was evaluated and validated.[113] The checklist consists of 12 questions (or domains), each with various items. The first two were designed to provide the examiner with a general understanding of the patient's (1) psychomotor development and (2) abilities (e.g., dressing, language, and mobility). Questions 3–8 consisted of yes or no items related to (3) behavioural problems, (4) psychiatric disorders (including autism, attention-deficit hyperactivity disorder (ADHD), anxiety, and depression), (5) intellectual disabilities, (6) academic abilities, (7) specific cognitive difficulties (including executive function, attention, language, memory, and visuospatial skills), and (8) psychosocial problems (low self-esteem and stress within the family). Questions 9 and 12 are visual analogue scales (0–10) summarising TAND problems according to the interviewee (9) and the examiner (12). Questions 10 and 11 allow for free-formulation answers regarding priorities (10) and unaddressed TAND-related issues (11). The pilot validation used the sum of the total behavioural problems from domain 3 as a measure of severity validated against the Strengths and Difficulties Questionnaire (SDQ), with a strong correlation between the scores. A sub-score of six items, measuring difficulties within social communication as a symptom of autism spectrum disorder, was correlated with the Social Communication Score (SCQ) and the pro-social domain of SDQ with strong positive and negative correlation, respectively, as hypothesised.[113] The checklist is available in various languages (https://tandconsortium.org/checklists/), including Swedish, and is translated in a standardised matter as depicted by the TANDem consortium.[109] In 2023, an updated checklist for self-evaluation was published (TAND-SQ) with an accompanying mobile application.[114] A Swedish translation and validation of TAND-SQ have not yet been performed.

### 2.3.2 Intellectual disability

Approximately 50% of individuals with TSC are reported to have varying degrees of intellectual disabilities (Table 3). Notably, epilepsy and a pathogenic TSC2 variant are highly associated with intellectual disability.[26,65,81,115,116]

**Table 3. Intellectual disability in tuberous sclerosis**
Selected major studies about the prevalence of different degrees of intellectual disability in tuberous sclerosis.

| Year, author (group), n | Age in years | Intellectual disability, n(%) | | | | |
|---|---|---|---|---|---|---|
| | | None | Mild | Moderate | Severe | Profound |
| 2007, de Vries et al[117], 233 | <18 | 83 (36) | 31 (13) | 40 (17) | 79 (34) | |
| 2013, Vignoli et al[27], 160 | Mean: 30 range 1–74 | 87 (54) | 21 (13) | 17 (11) | 28 (18) | 0 |
| 2018, de Vries et al[81] (TOSCA) 2216 (885 with data) | Median: 13 Range: <1 – 71[a] | 393 (44) | 249 (28) | 134 (15) | 82 (9) | 27 (3) |
| 2020, Gupta et al[68], (TSCNHD) 1319 (245 with data) | Median 16 Range: 0 – 81[a] | 65 (27) | 78 (32) | 46 (29) | 38(15) | 18 (7) |
| 2021, Vignoli et al[22], 257 | Median: 37 Range: 27 – 48 | 151 (51) | 21 (8) | 22 (9) | 52 (20) | NS |
| 2022, Marcinkowska et al[118], 100 | Mean: 32 SD: 11.3 Only adults | 66 (66) | 9 (9) | 11 (11) | 6 (6) | 11 (11) |

a: The age range was only provided for all individuals in the database

### *2.3.2.1 The impact of epilepsy and genotype on development*

The relationship between epilepsy and cognitive development is encapsulated in the concept of developmental and epileptic encephalopathy. In this context, the developmental delay caused by the TSC disorder is further aggravated by the seizures.[54] Several studies have shown a higher prevalence of intellectual disability and lower intelligence quotient (IQ) in patients with TSC and epilepsy.[66,68,76,119] Epilepsy, and the age of seizure onset in particular, seem to be the strongest predictor of future cognitive development.[27,65,66,78,120,121] Continuous seizures lead to a deterioration of cognition.[73,122] Data indicate that up to 97% of individuals without epilepsy possess normal cognition, compared to 47–59% of individuals with controlled epilepsy and 24–27% of individuals with DRE.[22,67,81,118] One study found that in individuals with DRE, 60% experienced severe intellectual disability when seizure onset occurred before 12 months of age, compared to none when seizure onset occurred after 12 years of age.[22]

Although early age of seizure onset seems to be one of the best predictors of later cognitive delay, studies have shown divergent results regarding the effect of early successful medical treatment of seizures on cognitive development. While some

studies suggest that early treatment with vigabatrin before the onset of clinical seizures may reduce the risk of intellectual disability and epilepsy,[96,97] others have not found this effect,[98,99] indicating that treatment response may be an intrinsic factor.[119]

In addition to the severity of epilepsy, a TSC2 variant is also associated with higher rates of intellectual disability.[22,67,78,81,119,123] In one study, individuals with a TSC2 variant exhibited a 5–10-point reduction in intelligence equivalents, along with 73% scoring below average on neuropsychological testing, compared to 31% for TSC1 and 23% for individuals were no mutation was identified.[78] One study linked a pathogenic TSC2 variant to increased tuber load, causing an increase in seizure severity and thereby a higher degree of intellectual disability.[24,80]

The mTOR signalling pathway plays a key role in the regulation of early neural maturation, and white matter abnormalities have been observed in patients with TSC, potentially exacerbating various aspects of TAND.[33,124,125] Even after adjusting for seizures and only including individuals without intellectual disability, individuals with TSC have a lower IQ compared to their siblings.[80]

In conclusion, it is now widely established that a pathogenic TSC2 variant is associated with an overall more severe phenotype, including a higher rate of infantile spasms and DRE, as well as an earlier age of seizure onset—all of which are predictors of lower cognitive abilities. Age at seizure onset appears as a significant predictor of intellectual disability and DRE. However, a diagnosis of TSC is by itself a risk factor for lower cognitive function, as intellectual disability is present even in patients without epilepsy, albeit to a lesser extent. Dysfunction of the mTOR pathway is associated with white matter abnormalities, which by itself contributes to the symptoms of TAND. Notably, no studies have specifically addressed TAND in the Swedish population with TSC.

### 2.3.3 Other manifestations within TAND

Besides intellectual disability, TAND encompasses various other manifestations and disorders, including autism, ADHD, anxiety, and depression which exhibit variable prevalence across different studies (Table 4).

**Table 4. Prevalence of neuropsychiatric disorders in tuberous sclerosis**
Results from selected major studies which included all selected manifestations.

| Year, Author (group), n | Ages (years) | Autism | ADHD | Anxiety | Depression |
|---|---|---|---|---|---|
| 2018, de Vries et al[81] (TOSCA), 2216 | Median 13 (range 0–71) | 21.1% | 19.1% | 9.7% | 6.1% |
| 2020, Gupta et al[68], (TSCNHD),[a] | Median 16 (range 0–81) | 19.6% (192/982) | 16.5% (159/961) | 9% (91/962) | 6% (58/954) |
| 2021, Vignoli et al[22], 111, | Median 37 (range 27–48) | 33% | 4% | 23% | 7% |
| 2022, Marcinkowska et al[118], 100, | Median 32 (range not provided, only adults) | 22% | 2% | 19% | 13% |

Abbreviations: ADHD: Attention-deficit hyperactivity disorder.

a: In the study by Gupta et al[68] the number of individuals with available data differed acrossed various manifestations.

### *2.3.3.1 Autism*

According to the TSCNHD, 23% of individuals with TSC and epilepsy had autism, while none of those without epilepsy had autism.[68] Other studies have reported similar findings, demonstrating a 22-39% prevalence of autism in people with epilepsy, but no cases among those who are seizure-free.[22,118] In the TOSCA study, the total prevalence of autism was 21.1%, with a significantly higher rate among individuals with a pathogenic TSC2 variant (28.6%) compared to TSC1 (12.2%).[81] In a cohort from TACERN, 25% had autism at the age of 36 months, though many individuals had autistic features without meeting the criteria for a clinical diagnosis.[126] In the EPISTOP trial demonstrated that neuropsychological testing could differentiate individuals with a high risk of autism as early as 6–12 months, and that children with a normal development at 12 months of age did not develop autism.[127] Even though autism previously has been shown to have a higher prevalence in the epilepsy population, early epileptiform discharges are not associated with autism at 24 months of age.[74]

#### *2.3.3.2 Attention-deficit/hyperactivity disorder*

In the TSCNHD group, ADHD was diagnosed in 18% of individuals with epilepsy, compared to 7% of those without epilepsy.[68] However, in contrast to intellectual disability, ADHD was associated with a later onset of epilepsy. In individuals with epilepsy onset before 2 years of age, 13% had ADHD, compared to 22% with epilepsy onset after 2 years.[68] In the TOSCA study, 19.1% had a diagnosis of ADHD, with a significantly higher prevalence among children (22.4%) compared to adults (10.5%), indicating a higher awareness in recent years.[81] In two studies of adult patients with TSC, 2–3.6% of individuals had ADHD, all of whom had epilepsy.[22,118] Earlier studies have reported ADHD in up to 30–50% of individuals with TSC.[109] Additionally, symptoms such as overactivity, restlessness, and impulsivity are higher among individuals with intellectual disability.[117] As seen in Table 4, studies that solely focused on adults reported lower rates of ADHD.

#### *2.3.3.3 Anxiety and depression*

The relationship between epilepsy and anxiety or depression has not been investigated as extensively as other aspects of TAND. In the TOSCA study,[81] the rate of anxiety and depression was significantly higher among adults (17% and 16% respectively) than that among children (7% and 2% respectively). Furthermore, more individuals reported experiencing anxiety and depression in the behavioural domain than those with a formal diagnosis.[81] No clear relationship to genotype was seen.[81] While a diagnosis of anxiety and depression are not associated with intellectual ability,[117] they appear to have a higher reported prevalence on the behavioural level.[128] One study involving adult patients with TSC found that anxiety was more prevalent among people without epilepsy, potentially indicating underdiagnosis in that group.[22]

#### *2.3.3.4 Behavioural problems*

Behavioural problems within domain 3 of TAND may not be psychiatric disorders per se, yet they remain a significant concern for families and present in 36% of cases.[21] Sleep difficulties (43.9%), severe aggression (24.3%), and self-injury (15.5%) are some of the most common manifestations.[81]

## 2.4 Epilepsy surgery in tuberous sclerosis

The first known epilepsy surgery in patients with TSC can be traced back to a paper published in 1957, which described two patients, one of whom achieved seizure freedom.[129] Another two case reports detailing epilepsy surgery in TSC were published in 1959 by Maccagnani[130] and 1965 by Gastaut[131] with the first patient rendered free from seizures. It took another 20 years until the next report of epilepsy surgery in TSC was published in 1987.[132] The first report of patients with TSC and epilepsy surgery who underwent preoperative magnetic resonance imaging (MRI) was the Mayo Clinic series in 1993 by Bebin et al[133] Since then, the volume of publications addressing epilepsy surgery in TSC has increased steadily (Figure 3). However, most of these studies have been small, retrospective, single-centre analyses from North America with short follow-up durations (Table 5).[134] When this project was initiated, no national prospective multicentre studies had been published. The largest study to date was a retrospective national multicentre study by Liu et al[121] in 2020, with 364 individuals from 26 centres across China.

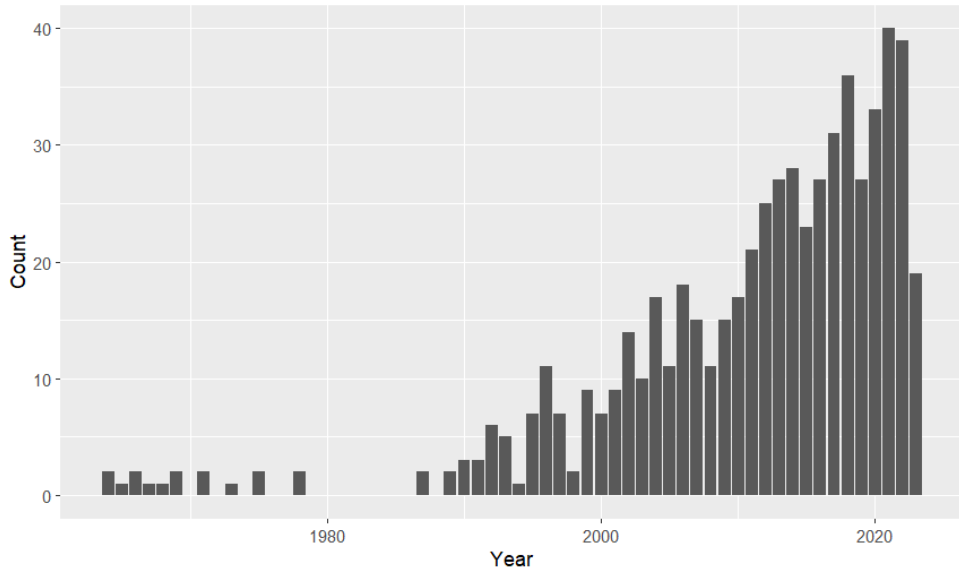


**Figure 3. Annual publication rate of studies about epilepsy surgery and tuberos sclerosis between 1960 and 2024**

Annual publications on different aspects of epilepsy surgery in individuals with tuberous sclerosis has increased steadily since 2000, peaking at 40/year in 2021. Data sourced from PubMed, collected on February 28, 2024. All types of articles are included.

**Table 5. Published series of resective epilepsy surgery in TSC with > 5 patients**
Questions (?) after "design" indicates that the study's design is not entirely clear but most likely of the type indicated.

| Author | Year, country | Design | Age at intervention (range) | Follow-up (range) | Intervention (n) | N of patients | Seizure-free, n (%) | Comments and conclusions |
|---|---|---|---|---|---|---|---|---|
| **Bebin et al**[133] | 1993, USA | Retrospective | Median: 9.5 y (10 m to 28 y) | Mean: 35 m, (10 – 72 m) | Cortical resection (2), stereotaxic lesionectomy (7) | 9 | 6 (67) | First study with pre-operative MRI |
| **Guerreiro et al**[135] | 1998, Canada | Retrospective | (20 m to 54 y) | 1 m – 47 y | Tuberectomy (12), Callosotomy (6) | 12 | 7 (58), 1 missing | |
| **Asano et al**[136] | 2000, USA | Prospective? | (13 m to 9 y) | 3 – 28 m | Resection | 7 | 5 (71) | AMT-PET evaluation |
| **Koh et al**[137] | 2000, USA and Canada | Retrospective | Mean: 4 y (0.25 – 10.7 y) | Mean: 32 m (6 – 82 m) | Resection | 11 | 8 (73) | One developed a new seizure type after surgery |
| **Karenfort et al**[138] | 2002, Germany | Prospective? | Median: 6.1 y (6 m to 34 y) | Median: 10 m (6 – 52 m) | Resection (6) Hemispherotomy (2) | 8 | 2 (25) | None with hemispherotomy sz-f |
| **Jarrar et al**[139] | 2004, USA | Retrospective | Mean: 12.5 y (1 – 54 y) | 1 y (n=20) 5 y (n=19) | Lobectomy, tuberectomy | 20 | 1FU: 13 (65) 5FU: 9 (47) | Predictors: unifocal seizure onset, no ID |
| **Kagawa et al**[140] | 2005, USA | Prospective? | Mean: 4.7 y (4 m to 12.3 y) | Median: 15 m (5 – 58 m) | Lobectomy (1), Hemispherectomy (3), resection (13) | 17 | 12 (71) | AMT-PET evaluation |
| **Lachhwani et al**[141] | 2005, USA | Retrospective | Median: 11 y (2 m to 31 y) | Median: 25 m (1 – 15 y) | Lobectomy (14), resections (3) | 17 | 11 (65) | |
| **Weiner et al**[142] | 2006, USA | Retrospective | Median: 4.0 y (6 m to 16.6 y) | Median: 2 y (0.5 – 6.2 y) | Resection | 25 | 6 m: 21 (84) Long-term: 17 (68) | Novel 3-stage procedure |
| **Jansen et al**[143] | 2007, Netherlands | Retrospective | Median: 11 y (3–36 y) | Median: 35.5 m (14 – 76 m) | Resection | 6 | 4 (66) | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Teutonico et al**[144] | 2008, USA and Italy | Retrospective | Median: 7.1 y (SD 9.15 y) | Median: 5 y (0.6 – 14 y) | Resection | 11 | 3 (27) | 10 cases excluded due to uncertain TSC |
| **Chu-Shore et al**[66] | 2010, USA | Retrospective | Missing | Missing | Resection | 39 | 10 (26) | |
| **Moshel et al**[41] | 2010, USA | Retrospective | Mean: 3.7 y (1 – 7 y) | Median: 36 m, Mean: 40 m | Perirolandic resection | 15 | 9 (60) | |
| **Wu et al**[145] | 2010, USA | Prospective? | Mean, sz-f: 4.1 SD 2.9 y. Not sz-f: 7.9 SD 4.0 | Mean 4.7 y SD 1.4 (1.75 – 8.5 y) | Resection | 18 | 12 (67) | Young age at surgery and short duration of epilepsy in sz-f |
| **Ochi et al**[146] | 2011, Canada | Retrospective | 1.1 – 16 y | Mean: 32.7 m (14 – 70 m) | Resection (12), lobectomy (1) | 13 | 8 (62) | |
| **Aboian et al**[147] | 2011, USA | Retrospective | Median: 4.4 y (0.7 – 13 y) | Median: 3.5 y (2 – 9.5 y) | Resection | 6 | 3 (50) | Evaluating SISCOM |
| **Kassiri et al**[148] | 2011, Canada | Retrospective | "Pediatric" | Mean: 2 y (1 – 6 y) | Lesionectomy (5), lobectomy (5) | 10 | 9 (90) | |
| **Mohamed et al**[60] | 2012, Australia | Retrospective | Median: 2.5 y (1.3 – 7.7 y) | Median: 19 m (12 – 62 m) | Tuberectomy | 17 | 6 (35) | EEG findings of epileptogenic tubers |
| **Liu et al**[149] | 2012, China | Retrospective | Mean: 4.23 y (1.5 – 8 y) | Mean: 3.0 y (1.2 – 6 y) | Resection (10), Resection and CC (7) | 17 | 11 (64) | Surgery for infantile spasms |
| **Kresk et al**[150] | 2013, USA | Retrospective | Mean: 6.6 y (0.1 – 17.6 y) | Follow-up at 2 y | Lobar (24), multilobar (9) | 33 | 18 (55) | Searching for predictors of outcome |
| **Kargiotis et al**[151] | 2014, Switzerland | Retrospective | Mean: 2.17 y (1 – 7 y) | Median: 2.25 y (1 – 4 y) | Lobectomy (5), lesionectomy (4), polectomy (1), cortectomy (1) | 10 | 7 (70) | The role of PET, SPECT and SISCOM |

| Author | Year, country | Design | Age at intervention (range) | Follow-up (range) | Intervention (n) | N of patients | Seizure-free, n (%) | Comment |
|---|---|---|---|---|---|---|---|---|
| **Arya et al[152]** | 2015, USA | Retrospective | Mean: 6.2 y (SD 6.0 y) | Mean: 5.7 y (SD 3.7 y) | Multi-lobar (13), Hemispherectomy (2), Tuberectomy (7), Extra-temporal lobectomy (6), Temporal corticectomy (9) | 37 | 21 (57) | Higher IQ in sz-f |
| **Fallah et al[153]** | 2015, USA and Canada | Retrospective | Median: 120 m (3 – 216 m) | 1 – 4 y | Tuberectomy, lobectomy, hemispepherectomy | 74 | 1FU: 48 (65)<br>2FU: 37 (50)<br>3FU: 33 (45)<br>4FU:32 (43) | Greater extension of resection predictor of sz-f |
| **Kannan et al[59]** | 2016, Australia | Retrospective? | Median: 3.8 y (2.4 – 13.3 y) | Median: 39 m (10 – 55 m) | Tuberectomy | 10 | 4 (40),<br>3 (30) free from targeted seizure | Epileptic discharges arise from the tuber centre |
| **Liang et al[154]** | 2017, China | Retrospective? | Median: 11 y (5 – 28 y) | 1 – 10 y | Tuberectomy (26), lobectomy (15), tuber resection and lobectomy (10). 11 with adjunctive callosotomy | 51<br>51<br>23 | 1FU: 38 (75)<br>5FU: 30 (59)<br>10FU: 11 (48) | 8 patients refused surgery<br>Improved IQ if sz-f |
| **Koptelova et al[155]** | 2018, Russia and Finland | Retrospective | 6 y 1 m (4 y 0 m to 16 y 9 m) at time of MEG | Median: 24 m (12 – 48 m) | Tuberectomy (2), multilobar (2), disconnection (2), ATL (1) | 7 | 4 (57) | The use of MEG in identifying epileptogenic tubers |
| **Fohlen et al[156]** | 2018, France | Retrospective | Median: 16 m (5 – 54 m) | Mean: 4.7 y (1.9 – 7.2 y) | Tailored surgical resection (15) | 15 | 9 (60) | No ID if surgery <20 m of age |
| **Grayson et al[157]** | 2020, USA | Prospective | Median: 17 m (3.7 – 21.3 m) | Median: 22.8 m (12 – 48 m) | Tuberectomy (15), partial lobectomy (4) | 19 | 10 (53) | Neuro-developmental gains after epilepsy surgery |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Liu et al**[121] | 2020, China | Retrospective | Median: 8.45 y (0.5 – 47 y) | 1 – 10 y | Resective surgery with (46) or without (318) callosotomy | 364<br>196<br>71 | 1FU: 258 (71)<br>4FU: 118 (60)<br>10FU: 36 (51) | More seizure-free after larger resection.<br>IQ improved if seizure-free |
| **Chivukula et al**[28] | 2020, USA | Retrospective | Mean (SD):<br>TSC1: 5.6 (3.8) y<br>TSC2: 8.1 (5.1) y | NS | Resective surgery (TSC1: 32, TSC2 110) | 142 | TSC1: 21 (65.7)<br>TSC2: 54 (49.1) | No significant difference in outcome between TSC1 and TSC2, p=0.09. |
| **Huang et al**[158] | 2021, China | Retrospective | Median: 228 m (IQR: 95 – 312 m) | Median: 84 m (IQR: 48 – 132 m) | Tuberectomy (53), lobectomy (23), resection with callosotomy (5) | 81 | 48 (59) | Investigating predictors of seizure freedom |
| **Vannicola et al**[159] | 2021, Italy | Retrospective | Median: 6 y (IQR: 3 – 13 y) | Mean: 7.5 y (1 – 21 y) | Lesionectomy (16), +cortectomy (13), Lobectomy (5), Hemispherecomy (1) | 35 | 18 (51) | Results improved in the last decade |
| **Stomberg et al**[160] | 2021, Germany | Follow-up questionnaire of 85/133 who had a presurgical evaluation | Median: 2.6 y (IQR 1.6 – 6.2 y) at presurgical evaluation | Mean: 7.1 y (SD 3.8 y) | Unilobar (24), Multilobar (10) | 34 | 18 (53) | Sz-f had improved cognition |

| Author | Year, country | Design | Age at intervention (range) | Follow-up (range) | Intervention (n) | N of patients | Seizure-free, n (%) | Comment |
|---|---|---|---|---|---|---|---|---|
| **d'Orio et al**[161] | 2022, Italy | Retrospective | Median: Sz-f 7 y (IQR 4.75 – 13 y),<br>Sz: 6 y (IQR 3 – 13 y) | Median: 115 m (IQR: 63 – 168 m) | Tuberectomy | 51 | 28 (55) | Investigating predictors of unfavourable outcome |
| **Melikyan et al**[162] | 2023, Russia | Retrospective | Median: 5.4 y (range missing) | Median 4.2 y (7.5 m to 16 y) | Tuberectomy (21), lobectomy (8), callosotomy (3), disconnection (6) | 33 | 18 (54) | Article in Russian. Only abstract available. |
| **Gauer et al**[163] | 2024, France | Registry study | Median: 42 m (2 – 161) m | 1 – 10 y | Tuberectomy (8), Tuberectomy+ (4), Lobectomy (3) | 14 | 1FU: 8 (57)<br>10FU: 3 (43) | Depicting the pathway to surgery in patients with TSC |

Abbreviations: AMT, α-[11C]-Methyl-l-tryptophan; ATL, anterior temporal lobectomy; CC, corpus callosotomy; FU, follow-up (the preceding number indicates year of follow-up); ID, intellectual disability; sz-f, seizure-free; PET, positron emission tomography; EEG, electroencephalogram; MEG, magnetoencephalography; SISCOM, subtraction ictal SPECT coregistered to MRI; SPECT, single-photon emission computed tomography

### 2.4.1 Resective surgery

The most commonly described surgical procedure for TSC is resection, often in the form of tuberectomy; however, tuberectomy with resection of the perituberal cortex (tuberectomy plus), lobectomy, and hemispherotomy have also been used (Table 5). Since the year 2000, the use of epilepsy surgery in TSC has seen a marked increase.[70] The published literature on resective epilepsy surgery in TSC with at least five study participants is summarised in Table 5.

Previous systematic reviews indicate that 56–59% of patients achieve seizure freedom after resective surgery.[63,164-166] Predictors of good outcomes identified in these reviews were the absence of intellectual disability, absence of tonic seizures, epilepsy onset after 1 year of age, lobectomy, EEG/MRI concordance, and focality on the EEG.[164-166] A previous review by Ibrahim et al[134] from 2012 showed that the rate of seizure freedom had increased in the last 15 years and that children were undergoing surgery at a younger age. After epilepsy surgery, the patient may achieve seizure freedom for the targeted seizure type; however, previously dormant tubers can begin to generate seizures.[129] In a systematic review and meta-analysis by Wei et al,[167] tuberectomy plus (involving the removal of 1–2 cm of the surrounding cortex) was associated with a greater chance of seizure freedom at 76.6%, compared to a rate of 58.1% for tuberectomy alone. When multiple tubers were resected, the rate of seizure freedom in the tuberectomy group was 38.1% compared to 67.7% in the tuberectomy plus group, further emphasising the complexities and challenges of epilepsy surgery in TSC due to the intricate relationship between the tubers and the surrounding cortical tissue.[61]

Despite the importance of patient and caregiver satisfaction with epilepsy surgery, no studies have specifically investigated this aspect in the TSC, either before or after the commencement of this thesis; however, satisfaction rates after epilepsy surgery in general tend to be high.[168,169]

#### *2.4.1.1 Outcomes before the start of this thesis*

Before the start of this project in October 2018, seizure freedom after epilepsy surgery in TSC varied widely: 26–27%[66,144] to 70–85%,[142,151,154] depending on several factors, including the number of participants, procedure, and duration of follow-up (Table 5).

In 2000 Asano et al[136] published the first report of increased uptake on α-[11C]methyl-L-tryptophan positron emission tomography (AMT-PET) in the epileptic lobe of individuals with TSC. In their study, five out of seven individuals achieved seizure freedom after surgery.[136] In 2005, AMT-PET was further evaluated in 17 children that underwent epilepsy surgery, of which 12 achieved seizure

freedom.[140] In patients with increased uptake in multiple tubers, the highest uptake was consistently localised within the EEG-defined seizure onset zone. All seizure-free patients had tubers with an increased AMT uptake.[140] Subtraction ictal single-photon emission computed tomography co-registered to magnetic resonance imaging (SISCOM) has also shown usefulness in the preoperative evaluation of patients with TSC.[147] Of six patients, three achieved seizure freedom; all those with continuous seizures had incomplete resections of the SISCOM-defined foci.

In 2006 Weiner et al[142] described a new invasive surgical approach that involved invasive monitoring and removal of primary and secondary foci. Five patients were previously rejected due to multifocality, four of whom were rendered seizure-free using Weiner's new approach. At a mean follow-up of 28 months, 17/25 (68%) patients were seizure-free.[142] Another study found that new ictal onset zones may emerge after the removal of the presumed epileptogenic tuber.[170]

A few studies conducted before the start of this thesis attempted to identify the predictors of outcomes after epilepsy surgery. The results varied among studies, but some identified unifocal seizures on preoperative EEG,[139,150] large/complete resection,[139,150,153], young age at surgery,[145,153] and concordant EEG and MRI findings[141] as predictors of good outcomes.

In 2015, Arya et al[152] published the first study with adequate power to evaluate the effect of epilepsy surgery on cognitive development in individuals with TSC, revealing that those who achieved seizure freedom had significantly higher IQ scores compared to those who did not (IQ: 68 and 56, respectively). In 2017, Liang et al[154] showed that full-scale, verbal, and performance IQ, as well as quality of life, increased after surgery but decreased over time in the non-surgical group.

#### *2.4.1.2 After the start of this thesis*

Before this thesis was initiated, most studies were too small to reliably identify predictors of outcome and often focused on the rate of seizure freedom after surgery. Following the works of Arya et al[152] and Liang et al,[154] the focus seemed to shift from small descriptive studies to larger analytical studies that explore the effects of epilepsy surgery on the development and identify the predictors of outcome. In addition, fewer studies were conducted in the USA (Table 5).

The first prospective study that evaluated the cognitive effect of epilepsy surgery in 19 young children was published in 2020 by the TACERN group.[157] The 160 children were categorised into surgical, DRE, controlled seizures, and no seizures groups. The surgery group scored the lowest on all cognitive tests but also had seizure onset at an earlier age than the other groups. The seizure-free group maintained average cognitive test scores, but all other groups showed a decrease in standardised test scores over time. Stabilization in the language domain was observed after surgery with favourable outcomes (Engels I and II). There was no

difference in the rate of autism among the four groups.[157] In 2021 Stomberg et al[160] reported similar results. In their study, 18/34 (53%) patients achieved seizure freedom at the 1-year follow-up (1FU), compared to 15/50 (30%) of the individuals who were deemed not eligible for surgery. The developmental level was higher among seizure-free individuals, especially in the surgical group.[160] To date, the largest study (n=364) to evaluate epilepsy surgery was published in 2020 by Liu et al[121] and included 26 centres in China (Table 5).

Since the start of the thesis project in 2018, various studies have aimed to identify predictors of good and bad outcomes after epilepsy surgery in TSC.[121,158,159,161] Despite an increase in studies, no definitive predictors of outcomes have been found, although findings suggest that larger resection and unifocal discharges on preoperative EEG are predictors of good outcomes in numerous studies and are clinically reasonable.[121,158,159,161]

### 2.4.2 Corpus callosotomy

Corpus callosotomy, first introduced in the 1940s as a palliative procedure, was one of the earliest described surgical interventions for epilepsy. This procedure aims to interrupt the primary pathway for the spread of focal to bilateral seizures, primarily to reduce debilitating drop attacks.[171] In some cases, a corpus callosotomy may precede a focal resection to reduce multifocal interictal activity and better delineate the epileptogenic zone.[172-174]

Corpus callosotomy can be total, anterior, or posterior with the first two being the most common.[171] In an anterior corpus callosotomy, the corpus callosum is severed from the rostrum to the junction off the body and isthmus, while a total corpus callosotomy extends the disconnection to include the splenium.[175] Complications tend to be more prevalent after total callosotomy compared to anterior callosotomy,[175] with transient disconnection syndrome occurring in 12.5% of children after total procedures but absent in those undergoing anterior callosotomy.[176]

To my knowledge, only one study from 2019 has specifically evaluated the efficacy of corpus callosotomy for TSC. The study involved seven patients, aged 2–21 years at surgery, who were followed up for 9 months to 3.5 years, 5/7 patients achieved remission of the targeted spasms.[177] In 1998, Guerreiro et al[135] evaluated 18 children with TSC who underwent epilepsy surgery for intractable epilepsy, of whom six underwent corpus callosotomy, with 8 months to 13 years of follow-up. None of the patients achieved seizure freedom, but four had at least a 75% seizure reduction.

The definition of a good outcome after corpus callosotomy varies across studies.[176] One study including 50 patients with epilepsy of different aetiologies found that 40% experienced complete resolution of drop attacks after anterior or total

callosotomy.[178] Younger age was significantly associated with a better seizure outcomes.[178] In a systematic review and meta-analysis including 1644 patients with at least 1FU, 12.4% achieved complete seizure freedom,[179] with higher rates associated with total compared to anterior callosotomy.[179,180]

In conclusion, since the start of this project, various large studies have significantly expanded our understanding of the manifestations and treatment of TSC, emphasising the importance of early referral for epilepsy surgery evaluation. There is a need for large, prospective, multicentre studies on epilepsy surgery in TSC, as well as the quest to find more reliable predictors of surgical outcomes. Identifying a single epileptogenic tuber is challenging, as patients often present with multiple and bilateral tubers, along with morphologically normal-appearing perituberal cortex that can also have epileptogenic potential.[63] After surgery, new epileptogenic zones and distinct types of seizures may emerge, underscoring the importance of LTFU.[129,170] Epilepsy surgery appears to have a more favourable impact on development compared to medication; while studies of preventive vigabatrin have indicated a delay in the onset of epilepsy, this delay has not consistently translated into improvements in cognitive function. In contrast, epilepsy surgery has consistently demonstrated positive effects on cognitive outcomes. However, it remains unclear whether early surgery increases the likelihood of seizure freedom and what barriers clinicians and caregivers face in proceeding with epilepsy surgery.

# 3 Rationale

When this project commenced in 2018, the TSC research landscape flourished. However, research on epilepsy surgery has been predominantly retrospective and largely confined to single-centre studies, most often in North America. To date, no national, prospectively collected studies exist, and various previous investigations presented short follow-up durations. Research on TSC has primarily focused on the disease-modifying properties of medications like everolimus and vigabatrin, which are costly, require lifelong administration, and are not curative. Although these therapies hold promise, epilepsy surgery remains the only intervention that can potentially render patients free from ASM.

Since the beginning of the project, I have identified ten studies addressing different aspects of epilepsy surgery in TSC, though few have included prospectively collected data. To date, only one retrospective study with more than 100 participants has been conducted. Increasing awareness regarding the potential benefits of epilepsy surgery in TSC has emerged, highlighting not only the possibility of seizure freedom but also the importance of seizure freedom for cognitive development and quality of life. However, most studies have been performed in specialised centres and have retrospective data, reinforcing the need for comprehensive national prospective studies. The possibility of new epileptogenic foci arising after surgery necessitates long follow-up durations to evaluate outcomes effectively.

No previous studies have evaluated patient-related outcome measures beyond seizure frequency with regard to epilepsy surgery in TSC. Is seizure freedom the sole objective? Are the challenges families face before surgery justified by even a modest reduction in seizures? Is it worthwhile if only a brief period of seizure freedom is achieved? And is it worthwhile if only the number of ASM can be reduced? Each of these questions must be addressed to optimise care for these patients, making it essential to identify what truly matters to the patients and their families.

# 4 Aims

This thesis aimed to evaluate the outcomes of epilepsy surgery in individuals with the rare and disabling condition of TSC.

The specific objectives of this thesis are outlined as follows, with Roman numerals corresponding to the different papers included in the section *List of papers* of this manuscript:

I. To describe the clinical spectrum of symptoms in children with TSC in Southern Sweden, including the presentation of diagnostic manifestations, epilepsy manifestations, treatment interventions, and changes over time.
II. To present long-term seizure outcomes and reported satisfaction from patients and caregivers following epilepsy surgery in individuals with TSC during LTFU.
III. To investigate the differences in TSC-associated neuropsychiatric comorbidities between individuals with TSC who did and did not undergo epilepsy surgery, while controlling for other clinical factors.
IV. To analyse the evolution of seizure outcomes and clinical characteristics in individuals with TSC and previous epilepsy surgery over time.

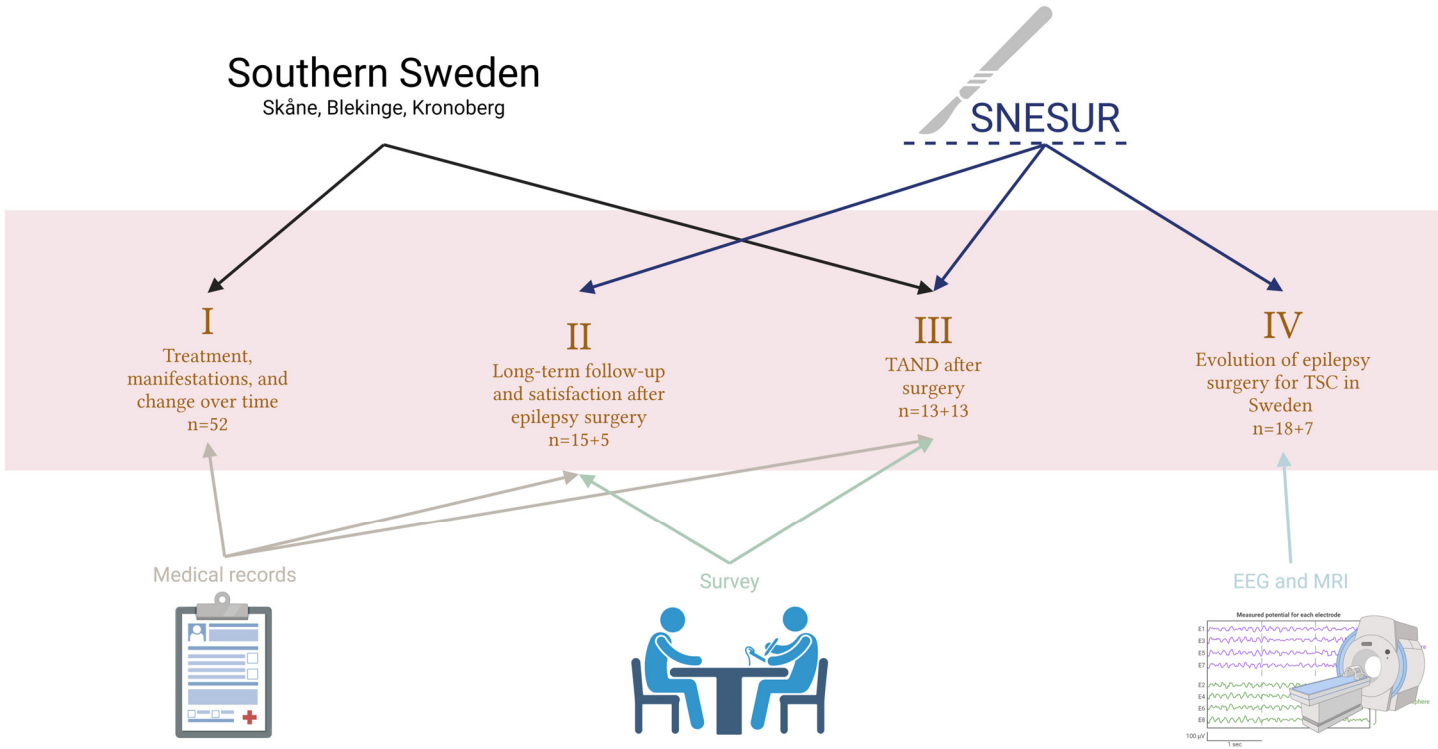


**Figure 4. A graphic overview of the included papers**

Survey data included satisfaction in paper II and neuropsychiatric disorders in paper III. Abbreviations: EEG: electroencephalogram; MRI: magnetic resonance imaging; SNESUR: Swedish National Epilepsy Surgery Register; TAND: Tuberous sclerosis associated neuropsychiatric disorders.

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# 5 Methods

This thesis is based on two cohorts: (1) individuals identified through a comprehensive medical record search at Skåne University Hospital who were treated at hospitals and habilitation centres in Skåne, Blekinge, and Kronoberg and (2) individuals with a history of epilepsy surgery, identified through the Swedish National Epilepsy-Surgery Register (SNESUR). All the included patients had a definitive diagnosis of TSC. Papers I and III use cohort (1) and papers II–IV use cohort (2). While the different included papers tackle epilepsy surgery in TSC in different ways, this thesis focuses on providing a narrative review of how the dynamics of epilepsy surgery in TSC has evolved in Sweden, focusing on who underwent surgery and the outcomes achieved, as well as long-term outcomes in seizures, neuropsychiatric comorbidities, and patient satisfaction. This thesis also describes trends in diagnosis, epilepsy, and surgery in TSC in southern Sweden. Table 6 and Figure 4 provide an overview of the included studies.

**Table 6. Overview of the four studies included in the thesis**

| | Paper I | Paper II | Paper III | Paper IV |
|---|---|---|---|---|
| **Design** | Retrospective Observational study Descriptive | National registry study Cross-sectional long-term data Descriptive | National registry study Cross-sectional long-term data Analytic | National registry study Cohort study Descriptive |
| **Number of participants** | 52 | 15 resections 5 callosotomies | 13 surgery 13 no surgery | 18 resections 7 callosotomies |
| **Data** | Disease manifestations Discussion about epilepsy surgery | Pre-operative epilepsy data, postoperative outcome, satisfaction | Seizure-data, TAND | Pre-and postoperative seizure data, pre-operative investigations |
| **Data collection methods** | Medical records | SNESUR, medical records, survey (Satisfaction after surgery) | SNESUR, medical records, survey (TAND) | SNESUR, medical records, re-evaluation of preoperative investigations |

## 5.1 Patient selection

Figure 5 depicts a flowchart of the patient selection process for the different papers.

### 5.1.1 Non-surgical cohort (1) from southern Sweden

Eligible individuals were identified by searching medical records using the International Classification of Diseases 10th revision code for TSC (Q85.1) during outpatient visits at Skåne University Hospital. The study period extended from 1st January, 2000 to 31st December, 2020.

The inclusion criteria were as follows:

- Patients with a definitive diagnosis of TSC, fulfilling the diagnostic criteria of the 2012 guidelines.[181] The 2021 diagnostic criteria[13] had not yet been established at the time of the search; however, only minor differences were introduced between 2012 and 2021, which should not have affected the patient selection.
- Patients aged <18 years at the beginning of, or born during, the study period.
- Patients that were followed up at the hospitals or centres for the habilitation of children and adolescents in Southern Sweden (Skåne, Blekinge, and Kronoberg).

The experts on TSC in Southern Sweden are all based at Skåne University Hospital in Lund and should be contacted for all newly diagnosed children. Even if they do not meet all the children personally, they are consulted, and the consultation is documented.

Patients from Hallands were excluded because these hospitals sometimes sent their patients to Gothenburg, which might have introduced selection bias.

### 5.1.2 Surgical cohort (2)

The surgical cohort was identified through the SNESUR, a national register with almost complete coverage of all epilepsy surgeries in Sweden since 1990. The register collected data retrospectively and prospectively between 1990 and 1995; thereafter, inclusion was fully prospective. Invasive EEG recordings and epilepsy surgeries (excluding neuromodulation, such as vagus nerve stimulation) are reported to the register either at the presurgical evaluation or at the time of surgery. Data were collected for each patient at baseline and at subsequent follow-up.

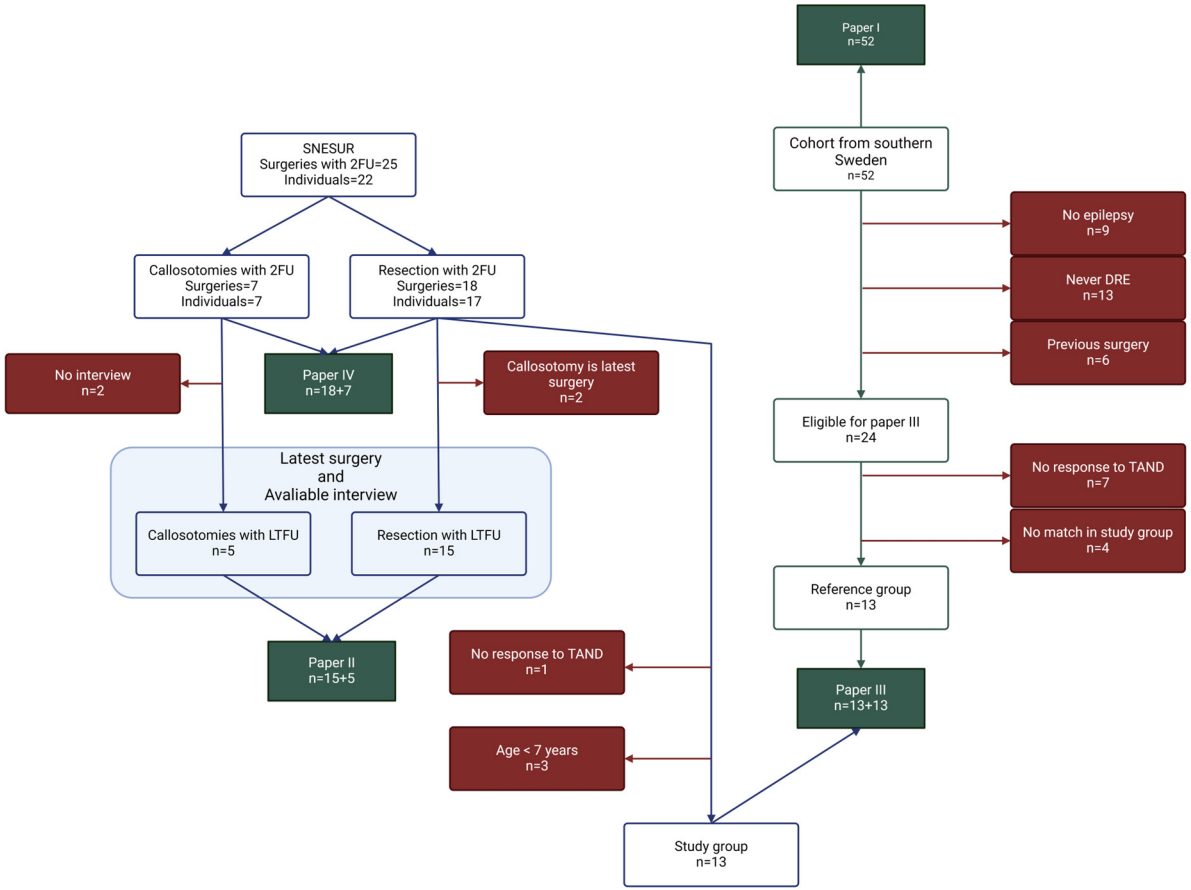


**Figure 5. Flowchart of the patient selection process for the different papers**
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The baseline data included medical history, ASM (current and previous), seizure situation (seizure types and mean monthly seizure frequency in the year before surgery), preoperative investigations and results, surgical data (site, technique, histopathology, and complications), and psychosocial data. Follow-up data were collected two years after surgery, and for surgeries since 2000, LTFU was performed every 5 years after surgery. Follow-up data included seizure status, ASM, and psychosocial data. LTFU data were collected via the telephone.

The inclusion criteria were as follows:

- Patients with a definitive diagnosis of TSC, fulfilling the diagnostic criteria of the 2012 guidelines[181]
- Patients that had undergone at least one previous epilepsy-related surgical procedure
- Patients of all ages

The search in the SNESUR was performed at the end of 2018, and the search criteria were surgical treatment of epilepsy between 1990 and 2018, a diagnosis of TSC in the register, and a post-resective histological examination. To ensure complete national coverage, that no patients who had not yet been registered were missed, and to collect contact information for the study participant, all six epilepsy surgery centres in Sweden were approached by phone. Information about the study was also provided at the family gathering of the TSC national meeting in Stockholm in May 2019, and written information was published in two consecutive issues of the TSC Patient Organization magazine. Three additional patients who were not included in the register at the time of the search were identified by contacting the surgical centres. One patient with a previous callosotomy was identified through information in the patient's organisation magazine, who had not been classified as having TSC in SNESUR due to the absence of histological tissue sampling.

Medical records were obtained from all identified individuals to confirm the diagnosis of TSC and to collect data that were not available in the register.

## 5.2 Data collection

Data from cohort (2) and survey data from both cohorts were collected and managed using RedCAP before being exported to the Statistical Package for the Social Sciences (SPSS) (IBM Corp., Armonk, NY, USA). Information obtained from the SNESUR and medical records for individuals in Cohort (1) were managed in Microsoft Excel before exportation to SPSS.

All data were pseudonymized; each study participant was assigned an identification number connected to their personal identity number, which was stored in a separate

password-protected file stored on a secure USB drive. Complete anonymisation was not possible due to the necessity of accessing medical records.

### 5.2.1 Medical records

Medical records were obtained for all study participants in both cohorts. For patients managed locally in Skåne, records were obtained electronically, while for patients treated at a hospital outside Skåne or for those with older records that were not digitally accessible, records were requested in paper format.

For access to the local electronic medical records, a formal request was submitted to the local quality registry (*Samråd KVB*, *Kvalitetsregister, Vårddatabaser och Beredning*), and medical record searches were conducted using the electronic database Melior© using a separate account for traceability. Paper records from before the introduction of electronic records and those from the centres for habilitation for children and adolescents were retrieved from the regional archive.

#### *5.2.1.1 Non-surgical cohort (1)*

Data extraction was primarily performed by a subspecialist in the area from which the data were extracted.

Data retrieved from the medical records of the non-surgical cohort included presenting symptoms, age at first seizure, epilepsy treatment, presence of DRE, discussion of epilepsy surgery, and presence of manifestations in different organs.

To evaluate the presence of DRE and how epilepsy surgery was discussed and performed, the cohort was divided into four age groups (<5 years, 5–9 years, 10–14 years, and 15–18 years). To avoid introducing bias, only participants with available medical record data who met the upper age limit for inclusion in each age group were considered.

Data regarding epilepsy surgery included (1) discussions among colleagues without further referral, (2) discussions with parents without further referral, and (3) discussions and results of a structured multidisciplinary epilepsy surgery round. Within each age group, individuals could only be categorized according to the highest-ranking category but would still, if possible, be included in one of these categories for each available age group.

The cohort was divided into individuals born between 1983–2009 and 2010–2020 to study changes over time. The year 2009/2010 was chosen as the dividing point because everolimus was introduced for TSC in Sweden in 2010.

*5.2.1.2 Surgical cohort (2)*

Medical records were obtained for all study participants, either electronically (managed in the same way as in cohort (1)) or in paper format. These records were used to confirm the data from the SNESUR. The following data were collected: vigabatrin and everolimus treatment and duration, confirmation of TSC diagnosis, and presence of infantile spasms.

Seizure freedom was used as the outcome at the LTFU to secure the validity of the data, as the reported seizure frequency in medical records for each seizure type was uncertain and difficult to obtain.

The following data were obtained for confirmation from the SNESUR: age at seizure onset, intellectual disability, and incidence of autism.

### 5.2.2 Swedish national epilepsy surgery register (paper II-IV)

Data extracted for cohort (2) from the SNESUR included participants' date of birth, date of surgery, age at seizure onset, age at surgery, epilepsy type, preoperative seizure frequency for each seizure type, ASM used previously and at the time of surgery, intellectual disability, autism, the centre that performed the surgery, type of surgery, localisation of resection, results of histological examination, complications, seizure outcome, and ASM usage at 2, 5, and 10 years after surgery.

The seizure outcomes in the SNESUR were presented using a modified Engel Scale, which was also used throughout this thesis (Table 6). Seizure status is based on the year before follow-up and compared with the year before surgery. In this thesis, the seizure outcome at 2FU is presented using the modified Engel classification, while LTFU outcome is categorised as seizure-free or not.

**Table 6. Modified Engel classifications system used in SNESUR and this thesis**

| Engel | Outcome |
|---|---|
| I | Free from seizures, with or without auras. Seizures only within 14 days of surgery, thereafter seizure-free. |
| II | > 75% seizure reduction |
| III | 50-74% seizure reduction |
| IV | 0-50% seizure reduction |
| V | Increased seizure frequency |

### 5.2.3 Neurophysiological, functional imaging, and morphological data (paper IV)

Neurophysiological, functional imaging, and morphological data were retrieved and re-examined for the surgical cohort.

Data from neurophysiological investigations and functional imaging were retrieved in two steps and evaluated by an experienced clinical neurophysiologist.

First, data were extracted from SNESUR regarding the type and the results from functional imaging and neurophysiological investigations.

Second, the results from preoperative video-EEG (intra- or extracranial) and functional imaging reports were retrieved from the epilepsy surgery centres and examined by a clinical neurophysiologist for EEG foci (mono- or multifocal) and location on the lobar level for the major interictal focus and seizure onset zone. Only resective surgeries were included in this step, as medical records from callosotomy cases did not indicate focal epilepsy, and these surgeries aimed to relieve patients from drop attacks.

Pre- and postoperative MRI scans were retrieved for all study participants, if available, for interpretable quality. Computed tomography (CT) images were retrieved when available to identify the calcified tubers; if not available, MRI images were used. Preoperative and postoperative images closest to the surgery with acceptable quality and sequences were retrieved and re-examined by an experienced neuroradiologist.

Data collected from the MRI re-examination for all participants included the number of supratentorial and cerebellar tubers, presence of SEGA at the time of surgery, and the field strength of the MRI camera used preoperatively.

For participants that underwent resective surgery, the following additional parameters were assessed: the site of resection, volume of the resected tuber on postoperative MRI, whether it was the largest tuber overall, whether the resected tuber was cystic or calcified, whether the resected tuber exhibited any unique qualities compared to most other tubers (unique tuber), and the presence of radial migration lines adjacent to the resected tuber. These parameters were obtained for each tuber when more than one tuber was excised.

The volume of the resected tuber was calculated on T2 weighted and fluid-attenuated inversion recovery images if available preoperatively. SEGA was defined according to international guidelines[182] as either (1) serial growth of a subependymal lesion, with or without contrast enhancement, or (2) a lesion at the caudothalamic groove with a size of >1 cm in any direction.

### 5.2.4 Survey data (papers II and III)

*5.2.4.1 Patient satisfaction (paper II)*

All individuals who had previously undergone epilepsy surgery were contacted by phone to receive information about the study and a structured questionnaire regarding their satisfaction after surgery. The following three questions were asked:

1. "How satisfied are you with the operation as a whole?" from "very satisfied" (score=5) to "not at all satisfied" (score=1).
2. "Do you think the surgery, as a whole, was beneficial, neutral, or harmful?"
3. "Would you recommend others with tuberous sclerosis and epilepsy to undergo epilepsy surgery?" Yes, or no.

All 15 individuals with a previous resective surgery responded, and 5 of 7 individuals who had a previous corpus callosotomy responded.

*5.2.4.2 TAND (paper III)*

All of the individuals who responded to the satisfaction survey by phone, as well as those individuals with current or past epilepsy in the non-surgical group of cohort (2), were approached to complete the TAND checklist, which was sent by mail.

The following domains from TAND were selected for the analysis in paper III:

- A summary of the number of "yes" responses in domain 3 (behavioural problems), as a proxy for the severity[113]
- Total score of the social communication problems sub-score of domain 3 (items 3h–3m)[113]
- A diagnosis of autism in domain 4
- Intellectual disability in domain 5 was categorised as normal, borderline/mild, or moderate/profound.
- Overall subjective difficulties in TAND from domain 9 (0–10 on a visual analogue scale)

These domains were chosen based on previous studies and clinical reasoning.[22,67,68,81,118,160] Domains 1 and 2 evaluated general psychomotor milestones; these were excluded due to the high risk of recall bias. The current abilities of domain 2 were mainly used in the clinical setting and were therefore not included. Psychiatric disabilities in domain 4 (ADHD, anxiety, depression, obsessive compulsive disorder, and psychosis) were excluded because of a lack of association with epilepsy in previous studies. Furthermore, the diagnoses in domain 4 are reflected as symptoms in domain 3, and are therefore included in the summary score. Domains 6–8 (academic skills, specific cognitive abilities, and psychosocial problems) were reflected in the overall score of domain 9. Including all these

domains and items was deemed to be too detailed for the sample size and was excluded to minimise the risk of type I errors. The decision to use a summary score for domain 3 was based on the same rationale, and all the included domains were predefined.

### 5.2.5 Statistical analysis

Data from the questionnaires and medical records were obtained from the Research Electronic Data Capture database hosted by Lund University, Sweden. SPSS version 27 (IBM Corp., Armonk, NY, USA) was used to analyse and generate descriptive data. Owing to the small sample size, the data were considered non-parametric and presented as medians and ranges at the group level. Differences between groups were assessed using the Mann–Whitney U test for continuous variables and Pearson's chi-square or Fischer's exact test, as applicable, for two dichotomous variables in papers I and III. The level of significance was set at $p < 0.05$. Due to the small sample size and heterogeneity of the data, statistical comparisons within or between groups were not feasible in papers II and IV.

In paper III, adjusting for confounders using multiple regression was not feasible because of the sample size. Instead, a procedure was employed for balancing the groups based on previously determined factors. Only individuals with current or previous DRE were included. Children aged <7 years were excluded because their TAND symptoms might not have been recognised. The balancing factors were chosen based on their putative effect on TAND and were, in hierarchical order, as follows: DRE at follow-up, age at seizure onset (cutoff, 12 months), age at survey (cutoff, 18 years), and sex. Through this balancing procedure, we established the reference and study groups. Due to the limited sample size, we chose not to adjust for multiple testing which would have increased the likelihood of type II errors.

Figures 1, 2, 4, 5 and 6 were created using BioRender. Boxplots (Figures 10 and 11) were generated in RStudio 2023.12.1 + 402 for Windows using the *ggplot2* package.

## 5.3 Ethical considerations

Three permits were obtained from the Swedish Ethical Review Authority. The first permit allowed access to medical records for paper I (diary number 2020-05201). The second facilitated data retrieval from SNESUR for papers II–IV (diary number 078-09). The third pertained to the questionnaires and contact with study participants for papers II–IV (diary number 2019-00518).

Individuals with TSC generally represent a vulnerable group with a high prevalence of intellectual disability, frequently requiring representation by another person when responding to a questionnaire. In this thesis project, individuals with TSC did not respond directly to the questions and may therefore not reflect their views but rather those of the caregiver. This discrepancy may have been more pronounced in the satisfaction questionnaire compared to the TAND, which employs more objective items regarding symptoms and diagnoses. The patient may not be satisfied with the pre-surgery process or the surgery itself, while the caregiver often feels a sense of satisfaction, believing that they have done everything possible to help. It is the patient, not the caregiver, who endures postoperative pain and invasive investigations using intracranial electrodes. However, due to the mental state of most patients, direct questioning was not feasible. Instead, we had to rely on caregivers and guardians to accurately represent the patient's best interests.

The studies included sensitive data, such as psychiatric diagnoses. Personal identification numbers were necessary for collecting data from medical records and linking them to data from SNESUR. However, personal identification numbers were pseudonymized as required by the authorities and each participant was assigned a unique ID. The connection to personal identification number was preserved in a password-protected file on a secure USB drive that was also password-protected.

A retrospective study of medical records most often assumes a breach of integrity when the data are not fully anonymised and involve sensitive information, as was the case in this thesis. It was not feasible or required by the Ethical Review Authority to obtain informed consent from the study participants for the collection of retrospective data. In a sample of this size, the risk of selection bias increases substantially if only a few individuals cannot be contacted. The included questionnaire was considered an intervention, therefore, informed consent was necessary for its inclusion, as stipulated by the law of Ethical Review of Research Involving Humans (2003:460). The contact with patients and caregivers may also in itself be an ethical problem as exemplified in two cases in the surgical cohort. Some individuals were contacted who had not been diagnosed with TSC but were classified as such in SNESUR. This could have caused undue distress for those later excluded. Furthermore, some individuals who had poor experiences with surgery found the questionnaire to be distressing, which was reported to the treating

physician who was not part of the project. Some participants in the project had their treating physicians involved, which may have increased their motivation to respond to the questionnaires out of concern for receiving inadequate treatment. This possibility persists despite assurances to the contrary provided in the written patient information.

Given the rarity of the disorder studies, involving a small number of individuals, it was unavoidable that some participants could be identified. However, as far as possible, efforts were made to present all data at the group level; where this was not possible, the minimum amount of information necessary was disclosed.

# 6 Results

This section summarizes the key findings from the four studies included in this thesis. Roman numerals within parentheses refer to specific papers.

## 6.1 Manifestations and treatment of tuberous sclerosis in Southern Sweden (I)

In total, 52 children (25 female) with TSC in Southern Sweden were identified. The median age at the end of the study period (30th December, 2020) was 17 years (range: 0–37 years). Among individuals with available genetic testing, a pathogenic variant of TSC1 was identified in 10 (19%) participants, TSC2 in 12 (23%), no mutation was identified in 4 (8%), and 1 (2%) had a mutation in PTPN11 indicative of Noonan syndrome but fulfilled the clinical diagnostic criteria for TSC. Genetic testing was not performed for 27 (52%) patients.

### 6.1.1 Presenting features and age of epilepsy onset

The first presenting feature of TSC varied notably between individuals born in 1983–2009 compared to those born in 2010–2020. Before 2010, 72% (28/39) of the patients had seizures as the first presenting symptom of TSC, compared with 31% (4/13) in 2010–2020 (p=0.001). Of the nine patients who presented with cardiac rhabdomyoma after 2010, six were followed up with regular EEG. One patient did not develop epilepsy or EEG changes and two were administered preventive vigabatrin after subclinical seizures and remained seizure-free. Three patients received vigabatrin treatment after the onset of clinical seizures, and one patient was seizure-free at the LTFU.

Forty-three (83%) patients developed epilepsy, with a median onset of 11 (range: 2–85) months, with no significant difference between the periods of 1983–2009 and 2010–2020 (p=0.214). Among patients with epilepsy, 23 (53%) had seizure onset before the age of one year. Infantile spasms were present in 15 (29%) patients: three after the onset of focal seizures and 12 had hypsarrhythmia on EEG. Of the nine individuals without epilepsy, only one (11%) had an intellectual disability and two

(22%) had autism. In the entire cohort, 56% (n=29) had an intellectual disability (45% mild, 48% moderate, and 7% moderate), and 38% had autism.

### 6.1.2 Epilepsy treatment

Twelve (28%) of the 43 individuals with epilepsy achieved seizure freedom for ≥2 years on ASM. Eight patients received everolimus; one achieved seizure freedom and four had >50% seizure reduction at 3 months follow-up. The individual who achieved seizure freedom was the youngest, starting treatment at four months. The other patient was administered everolimus between the ages of 2 and 14 years.

Vigabatrin use increased significantly (p=0.004), rising from 13 out of 32 patients before 2010 to 10 out of 11 after. Of the 23 individuals treated with vigabatrin, 10 underwent ophthalmological examination of peripheral vision using electroretinography. Three patients underwent electroretinography, necessitating dose reduction or cessation, all of whom experienced some degree of recovery.

### 6.1.3 Drug-resistant epilepsy and epilepsy surgery discussion

Of the 43 patients with epilepsy, 27 (63%) developed DRE in at least one age group. Five patients had DRE in the first age group after seizure onset (four <5 years, one between 5 – 9 years) but became seizure-free thereafter. Three had controlled seizures in the age group of <5 years but later developed DRE.

Among individuals above 18 years of age (n=25), six had missing data for certain age groups. Four patients (16.0%) never developed epilepsy, three (12%) developed epilepsy but never DRE, while 10 (40%) had DRE across all available age spans.

Table 7 presents the data regarding DRE and epilepsy surgery in different age groups. Epilepsy surgery was discussed at some level in 13/14 (93%) individuals with DRE in at least two age groups compared with 7/13 (54%) individuals with DRE in only one age group. Of the 27 patients with DRE, 14 (52%) were evaluated for surgery in a multidisciplinary epilepsy surgery round, of which five (36%) underwent surgery. Three of the five surgeries were performed at <5 years of age. Among individuals with DRE, for 11/14 (79%) individuals with DRE in two different age groups and 3/13 (23%) individuals with DRE in only one age group epilepsy surgery was discussed at a multidisciplinary epilepsy surgery round. One individual in each age group interrupted the epilepsy-surgery evaluation owing to a decrease in seizure frequency.

**Table 7. Drug-resistant epilepsy and epilepsy surgery evaluation**

| Epilepsy surgery discussion at different levels, n (% of individuals with DRE) | < 5 years | 5 – <10 years | 10 – <15 years | 15 –18 years |
|---|---|---|---|---|
| **Drug-resistant epilepsy, n (% of all epilepsy cases)** | 20 (56) | 14 (42) | 12 (48) | 11 (55) |
| **Discussed at the multidisciplinary epilepsy surgery round, n (%)[a]** | 6 (30) | 4 (29) | 4 (33) | 2 (18) |
| **Epilepsy surgery performed, n (%)** | 3 (15) | 1 (7) | 1 (8) | 0 |
| **Epilepsy surgery declined at a multidisciplinary epilepsy surgery round, n (%)** | 2 (10) | 2 (14.3) | 1 (8) | 1 (9) |
| **Other, n (%)** | 1 (5) | 1 (7.1) | 2 (17) | 1 (9) |
| **Epilepsy surgery not discussed on any level, n (%)** | 8 (40) | 5 (35) | 6 (50) | 8 (72) |
| **Other, n (%)** | 4 (20) | 4 (29) | 1 (8) | 1 (9) |
| **Missing data, n (%)** | 2 (10) | 1 (7) | 1 (8) | 0 |

[a] One individual was discussed in the multidisciplinary epilepsy surgery round in the first and second age groups, and another in the second and third age groups.

### 6.1.4 Other organ manifestations

A summary of the manifestations in different organs is shown in Figure 6. All individuals with prenatal rhabdomyomas showed renal cysts on ultrasonography at 12 months of age. Renal lesions were found significantly earlier after the year 2010 compared to that before (4 months vs 116 months, respectively, p=0.0001).

None of the study participants exhibited CVI. No pulmonary manifestations or malignant tumours were observed.

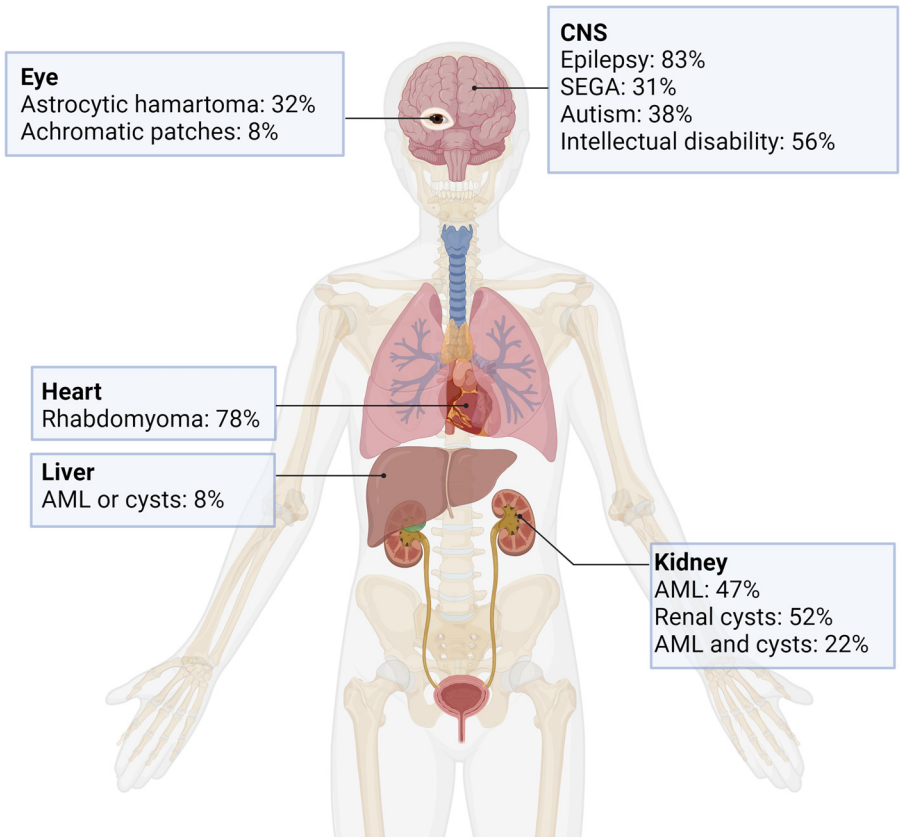


**Figure 6. Overview of organ manifestations in children with tuberous sclerosis**

Created with BioRender.com.

Abbreviations: AML: angiomyolipoma; CNS: Central nervous system; SEGA: Subependymal giant cell astrocytoma

## 6.2 Epilepsy surgery in tuberous sclerosis (II–IV)

In total, 22 individuals with a history of epilepsy surgery were identified using the SNESUR. Five individuals had undergone callosotomies, 15 underwent resective surgery, and two underwent a corpus callosotomy several years after an unsuccessful resective surgery. Three individuals had more than one resective surgery, but only one (female, without intellectual disability) had more than two years between the surgeries; therefore, the 2FU was available for both operations. Consequently, data from the 2FU was presented for 18 resective surgeries in 17 patients, when applicable.

Table 8 presents demographic data for the different cohorts. All individuals in the callosotomy group had at least moderate intellectual disability. Median age at surgery was 5 years in the tuberectomy group and 14 years in the callosotomy group. Of the 17 patients with resective surgery, 12 had frontal resections.

**Table 8. Demographics for the two groups**
Two individuals first had resective surgery and later a callosotomy before and are therefore included in both groups.

| | Resective surgery n=17 | Callosotomies n=7 |
|---|---|---|
| Female, n (%) | 10 (58.8) | 4 (57.1) |
| Age at seizure onset in months, median (range) | 5 (0 – 24) | 4 (2 – 24) |
| Infantile spasms, n (%) | 5 (29.4) | 5 (71.4) |
| Seizure/month, median (range)[a] | 150 (6–1180) | 200 (36–924) |
| Intellectual disability, n (%) | | |
| None | 2 (11.8) | 0 (0) |
| Mild | 5 (29.4) | 0 (0) |
| Moderate to severe | 10 (58.8) | 7 (100) |
| Autism, n (%) | 11 (64.7) | 6 (85.7)[b] |
| SEGA, n (%) | 5 (29.4) | 2 (28.6)[b] |
| N of tubers, median (range) | 16.5 (2–31) | 18.5 (13–35)[c] |

Abbreviations: SEGA: Sub-ependymal Giant Cell Astrocytoma

a: Seizure/month at the start of preoperative investigation. b: one missing. c: two missing.

The number of surgeries increased each decade, from 3 in 1990–1999, to 6 in 2000–2009, and 9 in 2010–2018.

### 6.2.1 Resective surgery

*6.2.1.1 Seizure outcome and change over time (II, IV)*

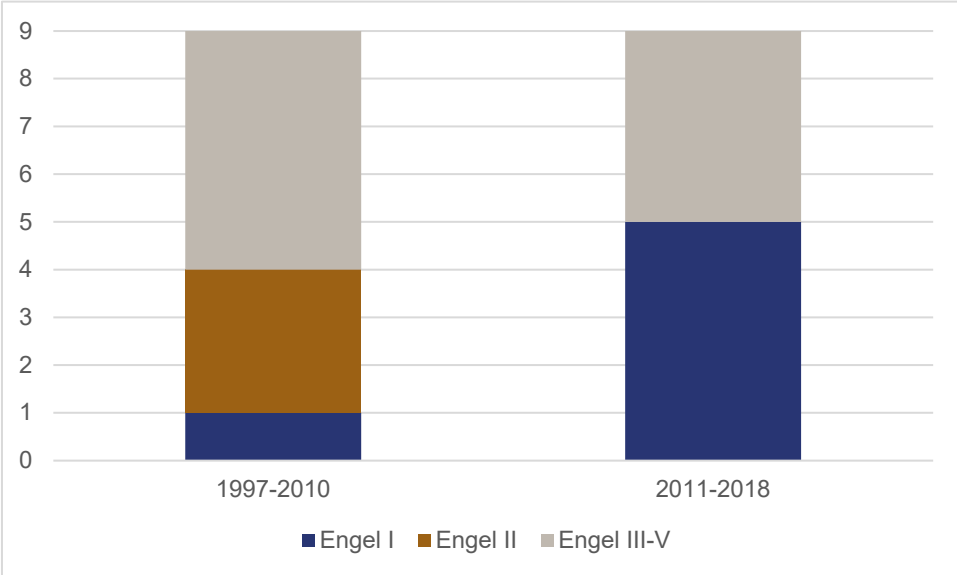


**Figure 7.** Outcome at 2-year follow-up for 18 resective surgeries in 17 patients

The first resective surgery was performed in 1997, with the first patient achieving an Engel I outcome at the 2FU in 2006. At the 2FU after the latest surgery, 6/17 (35.3%) patients achieved Engel I status. Figure 7 illustrates the differences in seizure outcomes between the periods of 1997–2010 and 2011–2018. Of the nine surgeries in 1997–2010, only one (11%) achieved Engel I, compared to five (56%) during 2011–2018. Between 1997 and 2010, three achieved Engel II, all of whom managed to reduce their ASM with 1–2 drugs at the 2FU. Four individuals were medication-free at the 2FU.

The median time from surgery to LTFU for the 15 patients who underwent resective surgery as their last surgery was 6 years 8 months (range: 3 years 1 month to 15 years 11 month). There was no seizure relapse between 2FU and LTFU. One patient began treatment with everolimus prior to the 2FU (seizure-free), and three patients between 2FU and LTFU (two of whom were seizure-free); all four patients were 4 years of age or younger. Therefore, at LTFU, 8/15 (53%) of patients achieved seizure freedom.

Of the patients who experienced >200 seizures/month preoperatively (n=3), had a SEGA detectable on MRI (n=5), or had a history of infantile spasms (n=5), none

achieved Engel I at 2FU. Monofocal EEG foci were identified in 3/6 (50%) of Engel I cases compared to 1/10 (10%) of Engel II–V cases. The number of tubers was comparable between Engel I (median: 20.5; range: 2–31) and Engel II-V (median: 15.5; range: 2–26). Preoperative SPECT was performed on 2/6 patients in the Engel I group and 9/12 patients in the Engel II–V at the 2FU.

*6.2.1.2 Patient satisfaction with the surgery and adverse events (II, IV)*

The interviews were completed by caregivers in 12/15 cases. Notably, 6/8 individuals that achieved an Engel I outcome at LTFU rated satisfaction as high and thought that the surgery was beneficial (Figure 8). Two individuals that underwent two and one surgery rated satisfaction as 3 and 2, respectively, on a five-point Likert scale and expressed uncertainty about the utility of the surgeries. These were the only two patients who did not recommend epilepsy surgery to others facing similar circumstances.

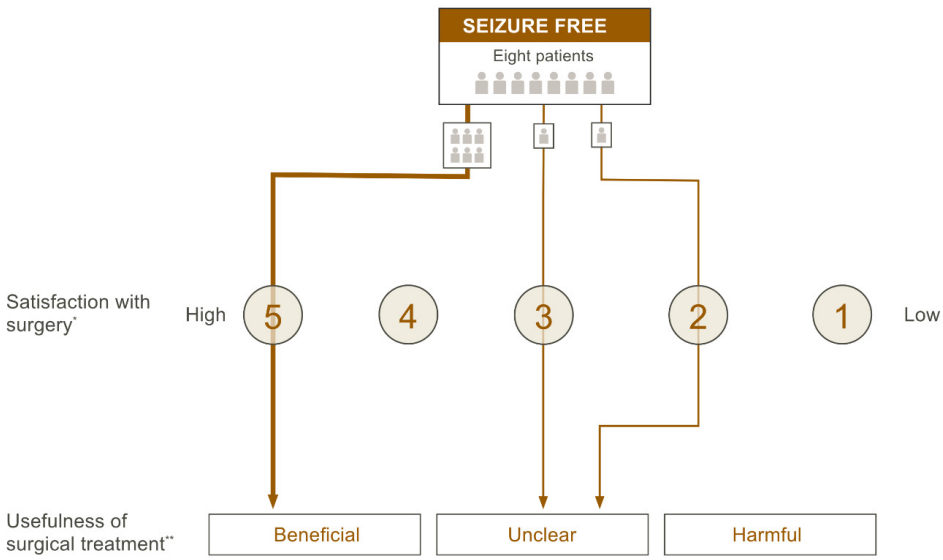


**Figure 8.** Satisfaction with the surgery in seizure-free individuals at long-term follow-up

Of the seven patients with continuous seizures at LTFU, three (43%) rated satisfaction as high and thought the surgery to be beneficial. Other satisfaction ratings ranged between 1 and 4 (Figure 9). The two individuals who rated satisfaction as 2 and 3 thought the surgeries were beneficial, whereas those who rated satisfaction as 1 and 4 thought the benefit of the surgery was unclear. None of the patients rated the surgery harmful. All those who thought the epilepsy

surgery was beneficial recommended it to others. Two individuals had undergone previous resective surgeries and rated their satisfaction as 2 or 4.

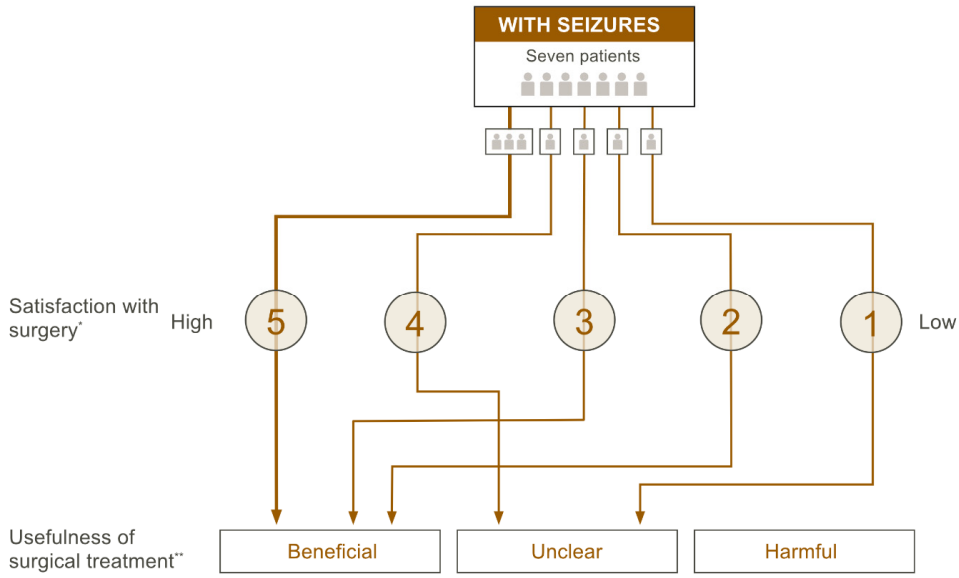


**Figure 9.** Satisfaction with the surgery in individuals who did not achieve seizure freedom at long-term follow-up

No complications were reported after resective surgery.

*6.2.1.3 Disease characteristics, preoperative investigations, and changes over time (IV)*

Disease characteristics and preoperative investigations during the two time periods are presented in Table 9. Notably, none of the five patients with infantile spasms underwent surgery after 2011. All three patients who experienced >200 seizures/month had their surgeries between 1997–2010.

The four largest and two smallest resections were conducted between 2010–2018. Additionally, one individual underwent preoperative FDG-PET (Engel III) and three underwent AMT-PET scans (two Engel I, one Engel IV) after 2013. The first 3T MRI scans were performed in 2011.

**Table 9. Disease characteristics and selected preoperative investigations for individuals who had resective surgeries in the two time periods**

| | 1997 – 2010 (n=9) | 2011 – 2018 (n=9) |
|---|---|---|
| Age at seizure onset in months, median (range) | 9 (1 – 18) | 5 (0 – 24) |
| Age at surgery in months, median (range) | 86 (39 – 306) | 48 (20 – 251) |
| Seizures/month pre-op, median (range) | 175 (30 – 1180) | 102 (6 – 200) |
| Resected tuber-size, median (range) | 3130 (1545 – 7175)[a] | 3735 (342 – 14 104) |
| Intracranial video EEG, n(%) | 3 (38)[b] | 6 (67) |
| SPECT, n(%) | 5 (63)[b] | 6 (67) |

Abbreviations: SPECT: Single-photon emission computed tomography; EEG: encephalography

a: four missing, b: one missing

### *6.2.1.4 Tuberous sclerosis associated neuropsychiatric disorders (III)*

A comparison was made between 13 individuals with TSC who had undergone previous resective surgery (study group) and 13 individuals with TSC and previous DRE who did not undergo epilepsy surgery (reference group). The disease characteristics used for balancing—DRE at the time of the survey, age at seizure onset, age at the time of the survey, and sex—were similar between the groups. There were no significant differences in behavioural problems, social communication, proportion of patients with autism spectrum disorder, intellectual disability, or perceived overall rating of TAND problems (Figure 10) between the reference and study groups.

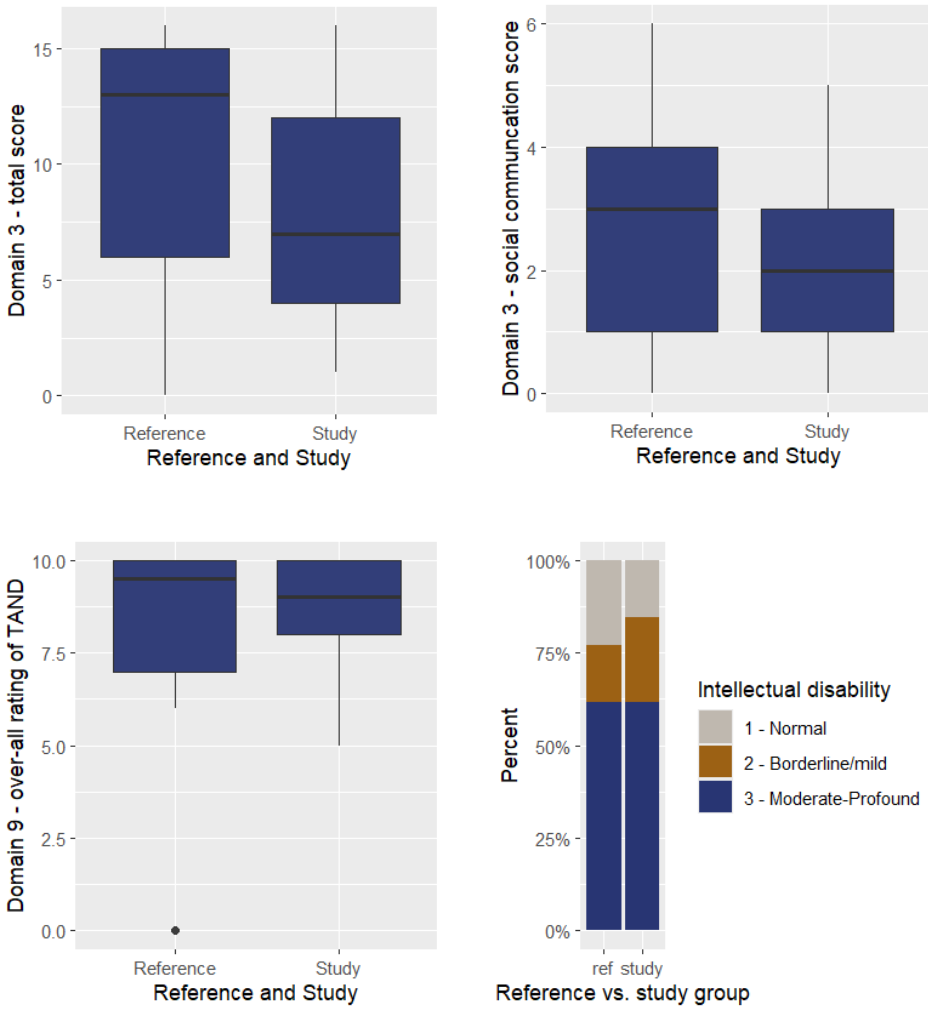


**Figure 10. Difference in the values of the selected TAND domains between the two balanced groups**
There were no significant differences between the reference (n=13) and the study (n=13) group.

In a pooled analysis of all 26 individuals, a comparison of the subgroups of individuals with seizures (n=15) and those without seizures (n=11) at the time of the survey showed that problems in the domains of social communication (p=0.016), intellectual disability (p=0.029), and overall rating of TAND problems (p=0.005) were higher among individuals with seizures (Figure 11).

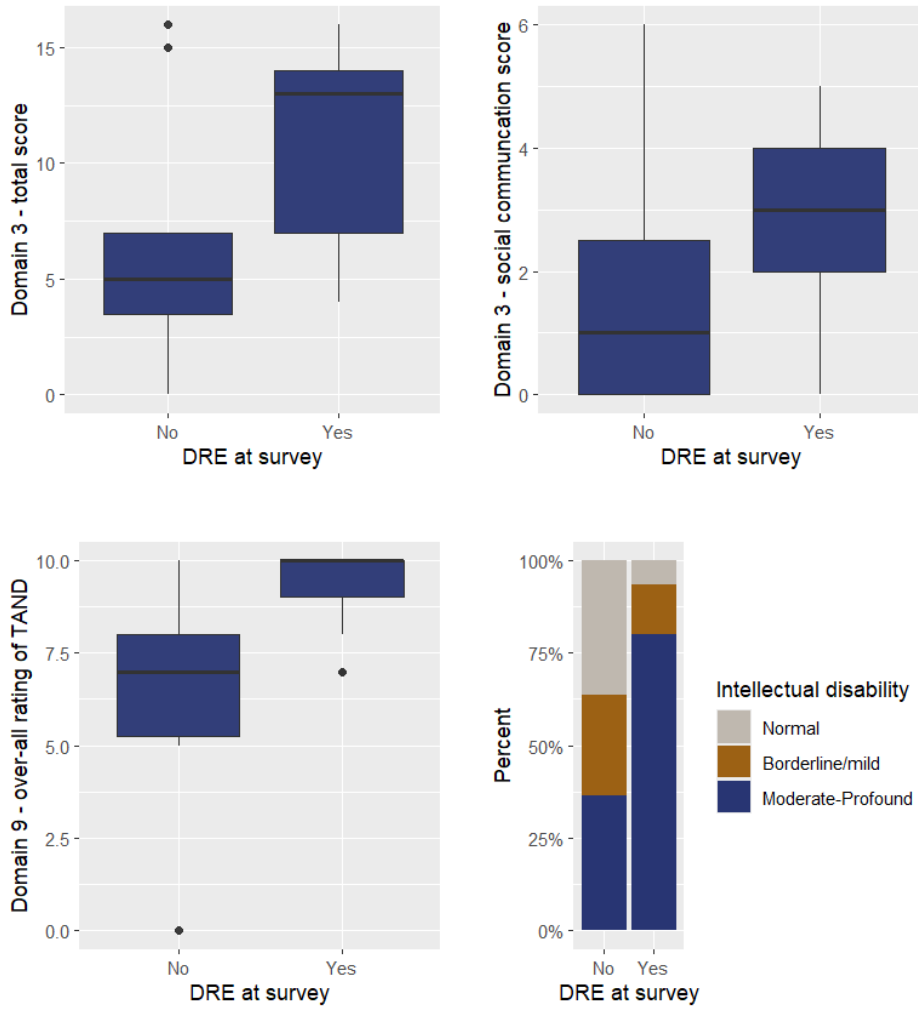


**Figure 11. Difference in the values of the selected TAND domains between the two groups**
Significant difference were observed in Domain 3 – social communication score (p=0.016), intellectual disability (p=0.029), and Domain 9 (p=0.005) between the individuals with DRE at the time of the survey (n=15) and those who were seizure-free (n=11).

### 6.2.2 Corpus callosotomy

*6.2.2.1 Seizure outcome and change over time (II, IV)*

The first two callosotomies were performed in 1992 and 1994, both of which were anterior callosotomies and rendered the patients free from drop-attacks at 2FU. LTFU could not be obtained for these two patients as it had not been implemented in the SNESUR at the time, and they did not respond to the questionnaire.

There was a hiatus of 17 years before five additional callosotomies (all total callosotomies) were performed between 2011–2013, all at the same centre; of which, only one individual was rendered free from drop attacks at 2FU. This individual was still seizure-free at LTFU 10 years after surgery, and another individual who was not seizure-free at 2FU had gained seizure freedom at LTFU 5 years after surgery. At the latest available follow-up, 4/7 were free from drop attacks.

*6.2.2.2 Disease characteristics, preoperative investigations, and changes over time (IV)*

After 2010, all patients had experienced infantile spasms, and the two most recent patients had SEGA. The number of tubers ranged from 13 to 35. Six patients underwent vagus nerve stimulation implantation: three before and three after callosotomy.

None of the patients in the callosotomy group underwent preoperative PET, only one underwent preoperative intracranial video EEG, and three underwent ictal SPECT.

*6.2.2.3 Satisfaction with the surgery and adverse events (II, IV)*

Five of the seven participants in the callosotomy group completed the questionnaires (Figure 12). None of the participants reported high levels of satisfaction. Notably, the caregiver of one participant who experienced an increased frequency of drop attacks perceived the surgery as harmful. Two complications were reported after callosotomy: one patient developed new-onset neglect of the right arm, while another had new-onset urine incontinence and could not walk straight.

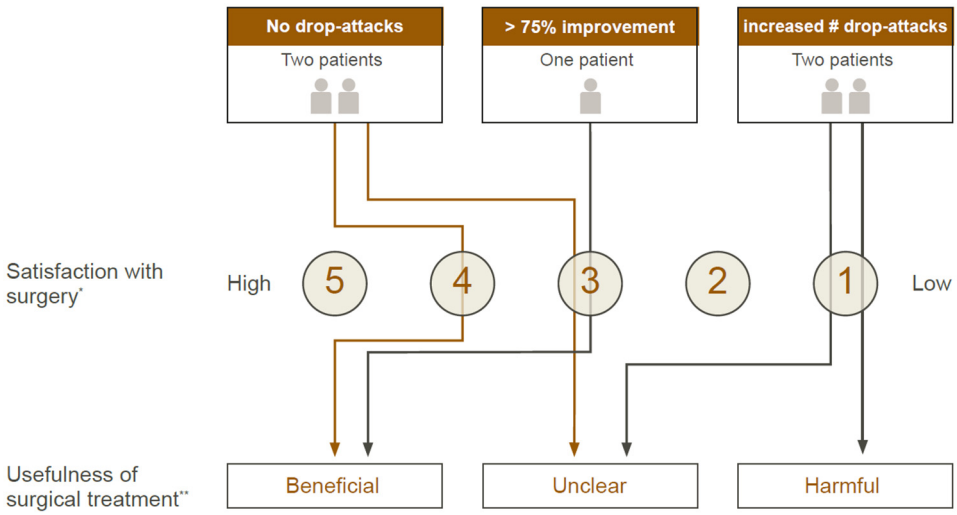


**Figure 12. Satisfaction with the surgery at long-term follow-up among individuals that underwent corpus callosotomy as the latest surgery**

Brown arrows indicates individuals free from drop attacks, and black arrows indicates individuals with continuous drop attacks.

# 7 Discussion

## 7.1 Main findings

In the last decade, there has been an increase in the number of infants diagnosed with TSC prior to the onset of seizures, as well as a rise in the rate of sustained seizure freedom after epilepsy surgery. Of the patients evaluated, two achieved seizure freedom, while none achieved seizure remission between 2FU and LTFU (3–15 years) after resective epilepsy surgery. Overall, satisfaction with resective surgery was high, and it was higher than expected among those who did not achieve seizure freedom. Almost all patients who underwent resective surgery would recommend surgery to other patients. None of the patients in this group thought that surgery was harmful, compared to one of five in the callosotomy group. For three-fourths of individuals with DRE, the possibility of epilepsy surgery was discussed at some level, and 52% were evaluated at the highest level, i.e., the multidisciplinary epilepsy surgery round. Individuals who underwent surgery in the last decade seemed to have undergone surgery at a younger age and with a less severe phenotype, indicating that it is now seen as a viable treatment option rather than as a last resort for patients with severe epilepsy.

## 7.2 Clinical manifestations and genotype

This thesis demonstrates a significant shift in the symptoms of TSC between two periods: 1983–2009 and 2010–2020. This change is likely attributed to increased awareness among clinicians and improved prenatal ultrasound quality. Before 2010, almost three-quarters of the patients had seizures as the presenting symptom, compared to less than one-third in the later period. The rate of prenatal diagnosis has increased in the general literature.[43,183] In a study from 2024, the rate increased from 3% before 2012 to 51% in or after 2012.[184] In individuals aged <10 years in the TOSCA cohort, 50% had a history of a rhabdomyoma, comparable to the 69% found after 2010 in our study.[21]

Although we did not include adults, the incidence of SEGA in paper I was 31% compared to 6–27% in previous studies.[1,12,21,22,27,43,48]

Surprisingly, we found an equal distribution of TSC1 and TSC2 variants. Previous studies have primarily linked this distribution to inherited cases, whereas in terms of the overall distribution, TSC2 variants accounted for three-fourths of cases.[21,43,163,185] Of the nine patients who presented with rhabdomyoma in the period of 2010–2020, 4/5 with an identified mutation had a pathogenic TSC2 variant. This discrepancy may arise from older individuals with TSC being tested only if the diagnosis was uncertain, which may have skewed the findings towards TSC1 variants associated with a milder phenotype. One such type most likely include the individual with a mutation in PTPN11, whose phenotype were more similar to that of TSC than Noonan syndrome.

## 7.3 Epilepsy

In this thesis, 83% of the children with TSC were diagnosed with epilepsy, 35% had infantile spasms, and 28% had infantile spasms as presenting seizures. As outlined in Table 2, page 26 our findings of epilepsy rates is similar to that in previous studies.[7,12,22,27,39,43,65-69] The rate of infantile spasms has varied greatly in previous studies, from <20% in a Swedish national registry study by Welin et al[7] to almost 60% in two studies that only included children of <3 years of age.[43,69] Our results are similar to the 38–39% reported in larger cohorts.[66,67] In the TOSCA cohort,[70] the rate of infantile spasms increased over time, most likely due to increased awareness among clinicians and caregivers rather than because of a more severe phenotype. Unfortunately, we did not test for differences in infantile spasms over time .

In the later period of paper I, seizure onset occurred before TSC presentation in 30% of the cases, compared to 15% in another study of approximately the same period.[43] Seizure onset occurred before 1 year of age in 53% of participants, similar to most previous studies of epilepsy in TSC.[7,12,22,27,39,43,65-69] An early diagnosis of TSC, as seen in most patients after 2010 in paper I, is important as some studies have shown that presymptomatic vigabatrin may inhibit seizure progression[98] and that everolimus has a better effect at earlier ages.[107,186] Despite the increase in prenatal diagnosis in our cohort, there was no significant difference in the age of the first seizure between the two study periods.

In paper I, almost two-thirds of the individuals with epilepsy had a DRE at some point in life, but only 40% of individuals above 18 years of age had a DRE across all available age groups. Previous studies have reported varying degrees of DRE within TSC populations. In a study by Vignoli et al[27] in 2013, 48% of children had DRE compared to 66% in a follow-up study,[22] the highest prevalence ever reported. However, the 2013 study[27] also included children who were diagnosed late in life, at a mean age of 7.6 years. The number of seizure-free individuals did not differ between the two studies, but individuals with DRE had a significantly earlier age of

seizure onset compared to those that were seizure-free.[22] In our study, 55% had DRE in the last age group (15–18 years of age) but data were unavailable after that. Vignoli et al[22] reported that the median age for achieving seizure freedom was 18 years (IQR: 10–29), indicating that despite the presence of DRE in childhood, there is still a chance of seizure remission later in life. Two other studies showed rates of DRE similar to our results.[12,66] In a study by Chu-Shore et al,[66] 19/155 (12.3%) individuals with DRE later achieved spontaneous seizure freedom.

All three studies[12,22,66] with DRE rates of >50% were single-centre studies from tertiary TSC clinics, similar to ours. A Swedish national register study by Welin et al[7] defined refractory epilepsy as having more than two simultaneous ASM for at least 91 days, as was observed in 32.9% of the cases reported. The register approach combined with a different definition of DRE may have contributed to the low level of DRE in this study. In TOSCA, the rate of DRE remained relatively stable at 40% from 1940 to 2015, despite advancements in new therapies.[70]

Previous studies have found a higher efficacy of everolimus if initiated at an early age.[107] Despite our sample size, our findings support this observation in cohort (1), as the patients who achieved seizure freedom were the youngest, with an average age of just 4 months. In cohort (2), three individuals who experienced seizures after surgery started everolimus treatment and interestingly two of them became seizure-free. However, given our sample size, this may reflect a random effect as the rate of seizure freedom differs from the EXIST-3 study, where 5% (15/275) were seizure-free after 12 months.[23] Another plausible reason is that surgery somehow disrupts the epileptogenic pathways, although it is not always sufficient enough to achieve seizure freedom, and everolimus further enhances this antiepileptic effect. However, in a previous study of 34 children with TSC that underwent epilepsy surgery, four started everolimus after surgery, of which none achieved seizure freedom.[160] A post-hoc analysis of the EXIST-3 study showed that the efficacy of everolimus was higher in patients under the age of 6 years.[107] This might also have influenced the high rate of seizure freedom in our study, as all patients in cohort (2) were less than 6 years old at the time of everolimus initiation compared to a median of 10 years in the extension of EXIST-3.[23]

Of the 23 children treated with vigabatrin in cohort (1), only 10 were monitored for vigabatrin-attributed visual field loss, of which three developed a peripheral vision defect, similar to some older studies.[187-189] Fortunately, all three individuals in our study exhibited some amount of recovery after either discontinuation or dose reduction of vigabatrin (this was described more thoroughly in another study that was not included in this thesis).[190] In contrast to our study, some recent large prospective studies have shown that the rate of vigabatrin-attributed visual field loss may be less common than previously ssumed.[92] As none were evaluated for CVI, the prevalence is still uncertain.

## 7.4 Epilepsy surgery

### 7.4.1 Epilepsy surgery discussions

Several studies underscore the significance of early epilepsy surgery, especially regarding neurodevelopmental outcomes.[156,157,160] During the study period for paper I, five patients underwent epilepsy surgery as children and three of these underwent surgery before 5 years of age. In paper IV, we also observed indications of decreasing age at the time of surgery after 2010, suggesting a growing awareness of early intervention. However, only approximately half of the patients with DRE in one age group had been considered for epilepsy surgery compared to nearly all patients with DRE in more than one age group. Of all individuals with DRE, half were evaluated at a multidisciplinary epilepsy surgery round; 36% of them were considered eligible for surgery and consented to it. Previous studies have shown that 59–78% of patients with TSC who undergo preoperative evaluation undergo surgery.[154,163]

### 7.4.2 Resective surgery

A study from 2017 by Welin et al[7] found that 386 individuals in Sweden were diagnosed with TSC and epilepsy. If we apply the results of our and previous studies and assume a DRE of two-thirds, it would result in approximately 260 individuals with TSC and DRE in Sweden. Our study of the national cohort (2) found that only 17 of these individuals underwent potentially curative resective surgery, indicating a severe treatment gap. However, at the national level, the number of surgeries in TSC increased each decade but remained stable overall.[191] Liu et al[121] and the TOSCA cohort[70] revealed similar findings; in TOSCA, only a single individual had surgery for infantile spasms and 6–7% for focal seizures between 1980 and 2000 compared to 7–8% for infantile spasms and 9–10% for focal seizures between 2001 and 2015.[70] A recent study reported a rate of surgery of 19% in individuals with TSC and DRE.[163] In 2018, the international treatment guidelines for epilepsy in TSC stressed the importance of early referral for presurgical evaluation in cases with DRE.[85] This recommendation was retained in the updated 2023 guidelines, however, the difficulties in performing the surgery for patients with multiple seizure types and EEG foci was emphasised.[64] Our results suggest that the number of individuals who are referred to epilepsy-surgery evaluation is rather high but with room for improvement, as we found that almost everyone with a DRE in at least two age groups and half the patients with DRE in one age-group had a discussion about epilepsy surgery on some level. However, the earliest individuals were born in 1983 and whether the referral level increased during the study period was not investigated. In our study, one patient in each age group stopped the evaluation for surgery due to seizure remission, and in total, six patients were deemed ineligible in

the multidisciplinary epilepsy surgery round. In a recent study[163] of 39 individuals with TSC who were evaluated for epilepsy surgery, 23 did not undergo surgery. Six were due to spontaneous remission and six parents refused. At the last follow-up, 12/23 had controlled seizures with ASM.[163] Previous studies have found that 6–10% of patients or caregivers of individuals with TSC declined surgery[154,160] and 12% were rejected after preoperative evaluation.[154]

This thesis shows that the rate of seizure freedom at the 2FU after epilepsy surgery has increased substantially in the last decade, from over 10% to over 50%. After 2010 epilepsy surgery was performed at an earlier age in patients with less severe epilepsy (as indicated by the lower monthly seizure frequency and rate of infantile spasms). There were also indications for a more tailored approach as both the largest and smallest tubers were resected, and the use of intracranial video EEG doubled in the later period. This shift may reflect the changing perception of epilepsy surgery, moving from a last-resort option to an early intervention strategy, in line with recent international guidelines advocating for early surgical consideration following DRE onset.[64,85] As seen in Table 5 (page 38) the rates of seizure freedom rafter epilepsy surgery in patients with TSC have varied between 50–60%, consistent with our results in the recent decade,[63,121,164-167] and comparable to those reported in specialised TSC centres.[152,154] Moreover, Vannicola et al[159] demonstrated similar results to ours in a cohort of 35 patients with TSC who underwent previous resective surgeries between 1997 and 2019 across seven Italian centres. In that study, the rate of seizure freedom increased from 11% in individuals with >10 years of follow-up to 65% in patients who had surgery in the last 10 years. There were no significant differences in the phenotype between these groups.[159] A review analysing the historical perspective of epilepsy surgery in TSC noted that infantile spasms were previously seen as a contraindication for surgery,[129] a notion not supported by our data, which included five individuals with infantile spasms who all had undergone surgeries before 2011.

The individuals with TSC that underwent epilepsy surgery in our study exhibited generally more severe phenotypes, characterized by a larger number of tubers and higher seizure frequency than some previous large-scale studies with similar outcomes.[154,161] The cohort analysed by Liang et al[154] had a later age of seizure onset (median age: 1 year) compared to ours (5 months), with fewer tubers (maximum 13; range: 8–13 tubers in 57% of individuals) compared to our study (median age: 16.5 years) and lower monthly seizure frequency (median: 22, range: 3–80) compared to ours (median: 150, range: 6–1180). While the seizure-free rate of 58.8% at the 5FU and 47.8% at the 10FU was somewhat similar to our 53% at LTFU, their cohort had a milder phenotype and underwent surgery at a single centre with four times the number of epilepsy surgeries in patients with TSC compared to all six centres in Sweden combined during the same time frame. Another study from a single TSC centre in Cincinnati with a high rate of epilepsy surgeries on TSC had a similar phenotype to that of our cohort and achieved a similar rate of seizure freedom (57%)

at a mean follow-up of 5.7 years.[152] However, the surgeries were performed between 2007 and 2012, at a time when Sweden was experiencing lower seizure-free rates.

Various studies and systematic reviews have been conducted on the predictors of favourable or poor outcomes after epilepsy surgery in patients with TSC. However, to date, no definitive presurgical factors have been determined to include or exclude patients from surgery.[64] Because of the limited sample size of our cohort, no statistical analyses were performed to identify predictors. However, we observed that none of those with prior infantile spasms, a SEGA diagnosis, or preoperative seizure frequencies exceeding 200 seizures/month at presurgical evaluation achieved seizure freedom from surgery. All three of these variables are associated with a TSC2 variant and a more severe phenotype. It is therefore reasonable to assume that they are predictors of a more severe disease overall and do not directly influence seizure freedom; however, multivariate analysis is needed to confirm this. As observed in previous studies[139,159,161] and meta-analyses,[165,166] unifocal EEG-foci appeared to be associated with Engel I outcomes in our study also. In contrast to our results, Vannicola et al[159] demonstrated that the number of tubers was significantly higher in the Engel II–IV group (median: 12, IQR: 4–30) than in the Engel I group (median 2, IQR: 1–8.25), however, the authors found no significant difference in the presence of SEGA, infantile spasms, or seizure frequency. In a multivariate analysis, only the number of tubers was associated with Engel I.[159] Another predictor of good seizure outcome in some[121,145] but not all[150,153,158,161] studies were age at surgery. Despite these somewhat conflicting results, a consensus emerged that an early age at surgery, as seen in the most recent cohort of our study, tends to yield better cognitive outcomes, at least in seizure-free patients.[121,152,154,156,157,160] Previous studies and meta-analyses showed that a larger resection was associated with better seizure outcomes.[61,121,158,167] In a retrospective multicentre study by Fallah et al[153] of 74 resective surgeries, the only predictor of seizure freedom in a multivariate analysis was a larger resection (lobectomy or more) compared to tuberectomy alone. However, we were unable to reliably ascertain the extent of the resection in our dataset, and therefore, this data was deemed unreliable and was excluded.

In some cases, MRI and video EEG are sufficient to identify the presumed epileptogenic zone.[64] When further presurgical investigations are needed for its identification, ictal SPECT or SISCOM followed by intracranial EEG monitoring is a common choice for gathering supplementary information. In our cohort, the rate of seizure freedom seemed to be lower among individuals who underwent presurgical SPECT, most probably because these individuals had several potential epileptogenic foci, making it harder to delineate the epileptogenic zone. The number of SPECT procedures performed was equal between the two time periods, suggesting that the observed outcomes did not stem from an increase in SPECT evaluations over time.

In contrast to previous studies, the rate of seizure freedom increased from 35% at the 2FU to 53% at LTFU in our cohort, largely attributed to the initiation of everolimus treatment. However, all individuals who were seizure-free at the 2FU remained seizure-free at LTFU. In a previous study by Liang et al[154] the rate of Engel I outcome decreased from 75% at the 1FU to 48% at the 10FU. While Engel II rates remained stable at 13–14%, Engel III–IV rates increased. Similar results have been observed in most studies with LTFU.[121,153,163] In concordance to our results, Vannicola et al[159] demonstrated that seizure recurrence often occurs before the 2FU; however, patients generally remain stable at the Engel class thereafter. In a Chinese study[158] of 81 resective surgeries, the mean duration of remaining seizure-free was 7 years, with an inversely proportional relationship between the duration of seizure freedom and the likelihood of seizure recurrence.

*7.4.2.1 Complications*

Our study contrasts with earlier literature by reporting no complications after resection. Previous studies have reported transient neurological deficits as well as more severe permanent complications in a small proportion of surgical cases.[154,157,159,163] In the largest study to date of 364 resective surgeries, 20 participants (5.5%) had transient complications (paralysis and aphasia), four had permanent hemiplegia, and three developed hydrocephalus.[121] One study of resective surgery in 20 children reported no complications.[139] One study of 15 children who underwent tuber resection in or near the central sulcus reported transient postoperative motor deficits in four children but all had returned to preoperative motor functioning at 3 months-FU.[41]

### 7.4.3 Corpus callosotomy

A corpus callosotomy is a palliative procedure, primarily aimed at reducing drop attacks. In our study, 4/7 patients achieved remission of drop attacks after callosotomy. The same results were found in a study of seven individuals with TSC and epileptic or tonic spasms; 5/7 achieved remission of spasms after total callosotomy.[177] However, the follow-up period was <4 years (range: 9 months to 25 years). In this study, a higher rate of seizure freedom from drop attacks was observed after anterior callosotomies than that after total callosotomies. The opposite has been demonstrated in previous meta-analyses.[179,180] Thus, the outcomes in our study could be attributable to the small sample size, as only two individuals with a short follow-up periods underwent an anterior callosotomy.

### 7.4.4 Patient satisfaction

We demonstrated that satisfaction after resective surgery in TSC was high, even among individuals who did not achieve seizure freedom. Due to our relatively small sample size and methodological considerations, the seizure outcomes were dichotomous (seizure-free or not seizure-free). This may partly explain some of the high satisfaction in the group that did not achieve seizure freedom, as some of these individuals achieved at least 75% reduction in seizure frequency.

The data regarding satisfaction after epilepsy surgery is generally scarce and the tools available for measuring satisfaction are limited.[192] To my knowledge, no study before or after the initiation of this thesis project has specifically investigated the satisfaction of patients TSC following epilepsy surgery. However, after the start of the project, some self-evaluation measures of satisfaction after epilepsy surgery have been developed.[168] A systematic review from 2011 showed overall high satisfaction with epilepsy surgery and, not surprisingly, higher satisfaction among seizure-free individuals.[193] A Swedish study[169] of epilepsy surgery, in general, found similar results to our study; satisfaction and perceived benefit from surgery were generally high, even among individuals who did not achieve seizure freedom. In that study, a greater percentage of participants perceived themselves as harmed from surgery compared to ours: 20% perceived themselves as harmed by the surgery across the entire cohort, approximately 10% among seizure-free individuals, and 25% among those with ongoing seizures.[169] Nguyen and Porter[194] published a study in 2020 on the caregiver's impression of the path to epilepsy surgery in TSC, demonstrating that all of them were happy that their child underwent surgery and were willing to accept a lower chance of seizure freedom than initially anticipated by preoperative assessments. Similarly, a study by Engelhart et al[195] on 111 children with previous resective surgeries for various aetiologies, found that only 1/54 of the children and 2/103 parents would probably or definitely not re-opt for surgery. In that cohort, surgery was deemed successful by 98% of seizure-free children and 99% of their parents, as well as in 70% of the children who did not achieve seizure freedom and 89% of their parents. Interestingly, 52% of parents of children experiencing seizures were willing to consider surgery again after a period of seizure freedom.[195] Similar sentiments may also explain the high satisfaction rates in our cohort, as some individuals that did not achieve seizure freedom in our study may still have experienced seizure freedom between surgery and the 2FU, which was not captured in the available data. Verdinelli et al[196] showed similarly high rates of satisfaction as ours after hemispherotomy, as follows: 8/9 seizure-free individuals or their caregivers and 11/17 individuals with seizures rated their satisfaction after surgery as 6–7 on a seven-point Likert scale.[196] The reasons for satisfaction after epilepsy surgery, in general, are linked to themes such as independence and ability to drive, seldom possible even in seizure-free patients with TSC.[197]

In our study, satisfaction rates following callosotomy were generally lower than those observed after resective surgery, with no patients reporting high satisfaction after surgery. Only 2/5 individuals perceived callosotomy as beneficial, and one thought it was harmful. To our knowledge, no previous study has evaluated satisfaction with callosotomy in TSC, but some studies have done so for callosotomy in general. In contrast to our results, Engelhart et al[195] reported that the parents of two children with previous callosotomies rated the surgeries as a great success despite continued seizures. Two studies on callosotomy in general showed that satisfaction was similar to our results and highly correlated with seizure outcomes.[198,199] A Swedish qualitative study[200] of the parents' perception of callosotomy found that the families lived in a chaotic bubble before surgery but that callosotomy provided an initial glimpse of hope. Although, the reduced seizure frequency improved the situation of the families, the situation challenges persisted and, in some cases, led to divorce.[200]

## 7.5 TAND

This thesis includes the first nationwide LTFU comparison of TAND symptoms from different domains, contrasting individuals with TSC and DRE against those who did not undergo previous resective surgeries. No significant differences were observed between the groups. However, we demonstrated the importance of seizure freedom in TAND symptoms, as almost all evaluated domains of TAND were less severe in seizure-free individuals. No previous study has used the TAND questionnaire to investigate the neuropsychiatric effects of epilepsy surgery in patients with TSC.

Numerous studies have shown that epilepsy surgery has a positive effect on cognitive development in patients with TSC. One study showed a higher IQ (68) in individuals who achieved seizure freedom after surgery than in those who did not achieve sustained seizure freedom (IQ 56).[152] Another study found that individuals with postoperative seizure freedom had an IQ improvement of 10 compared to 3 in those who did not, and -6 in the medicine-only group.[154] Liu et al[121] found an average improvement of 6 IQ points after surgery. Postoperative improvement was seen in 28% and associated with seizure freedom and preoperative IQ < 70.[154] Fohlen et al[156] showed that 9/11 patients that underwent surgery before 20 months of age achieved seizure freedom, while none had a diagnosis of autism, and four improved from having a mild developmental delay to normal intelligence. Two subsequent studies on young children by Grayson et al[157] and Stomberg et al[160] showed similar results. Both studies analysed the developmental progress of children with TSC who underwent epilepsy surgery compared to those who did not. In Grayson et al's[157] study, all children with continuous seizures showed a longitudinal decline in neurodevelopment; however, those with a favourable surgical outcome experienced

improvement, especially in the language domain. Stomberg et al[160] showed that the developmental level was highest in seizure-free individuals, especially after epilepsy surgery. However, selection bias may impact findings in Stomberg's[160] study because the surgical group was compared to non-candidates, who may have had more potential epileptogenic foci and a more severe phenotype. However, there was no difference in age at seizure onset, and the seizure frequency before surgery was higher in the surgical group.[160]

The lack of difference between the groups with and without previous resective surgeries in our study may be owing to the relatively small sample size or the blunt nature of the TAND questionnaire. However, the boxplots of Figure 10 exhibit IQR overlap and with nearly identical numbers of people with intellectual disabilities. The balancing procedure also ensured that the number of individuals with DRE at the time of the survey was similar between groups. These results indicate that epilepsy surgery does not seem to directly influence TAND, however, seizures likely contribute to deterioration in TAND symptoms compared to the reference group.

In concordance with paper III, paper I showed that only 1/9 individuals who never had epilepsy had an intellectual disability, compared to 56% of the whole cohort. Similar results have been replicated in various studies showing that epilepsy is highly associated with intellectual disability.[12,27,66,119] Age at seizure onset[27,65,66,74,77,78,119-121] or epilepsy severity in the first year of life[122] are often the major factors in predicting developmental delay. In one study, two-thirds of patients with seizure onset before 1 month of age had intellectual disability.[66] In the EPITOP trial, none had an IQ score of < 70 when the first epileptiform discharge occurred at >160 days of age.[74] A cognitive decline can be observed in individuals with TSC and epilepsy while cognition remains stable in seizure-free individuals.[73,77,122] One large prospective study from the TACERN group showed that the presence of seizures was correlated with declines of 9 to 23 points across different domains of cognitive testing, with the most obvious effect on early learning composite (-23 points), and receptive language (-14 points).[78] Others have found that non-verbal skills may be one of the first cognitive domains impacted by TSC.[122] This may help explain why the rate of moderate to profound intellectual disability in cohort (2) was relatively high compared to previous studies on the general TSC population (Table 3, page 32) as all individuals in this group had early seizure onset and severe epilepsy, and underwent epilepsy surgery.

In the general epilepsy population, individuals with intellectual disabilities were previously viewed as unsuitable candidates for epilepsy surgery.[201] However, the number of individuals with intellectual disability evaluated for surgery has increased.[202] In a study based on SNESUR, IQ score of <70 was associated with significantly worse seizure outcomes after epilepsy surgery compared to matched controls.[203] Some TSC studies have shown that intellectual disability is a predictor of seizure recurrence[164] but if seizure freedom is achieved, these are the

individuals most likely to have an increase in IQ.[121] In our cohort of individuals with TSC that underwent epilepsy surgery, the rate of intellectual disability was higher than that seen for the general TSC population;[81] however, the rate of seizure freedom was similar to previous studies on epilepsy surgery in TSC[121,154,158,161] and higher than that for individuals with an IQ score of <70 in the general population.[203] Further, there were no significant differences in any of the chosen TAND domains between the surgery and reference groups, although fewer issues were seen in the seizure-free group. This indicates that while epilepsy surgery does not seem to negatively affect TAND, achieving seizure freedom is crucial. All individuals with TSC and DRE, regardless of the severity of TAND, should be referred to a tertiary centre for evaluation of potential epilepsy surgery.

## 7.6 Limitations of the studies and methodological considerations

First, the primary limitation of this thesis is the sample size, limiting us to employ descriptive statistics for the most part. However, it is most likely that all available study participants were approached, and all individuals who underwent resective surgery completed the satisfaction questionnaire; one did not respond to the TAND questionnaire. Furthermore, selection bias may be present among the callosotomy group, as 2/7 individuals could not be approached; both had an anterior callosotomy in the 90s' and were rendered seizure-free. The national prospective register enabled a nationwide population without selection bias in the surgery cohort, though it did lead to discrepancies with an earlier Swedish study citing that 25 individuals with TSC had underwent epilepsy surgery.[7] After personal communication with the authors, it was revealed these patients were likely misidentified, indicating that the correct count is 22. In the SNESUR, several individuals were misclassified as having TSC, however, further examination did not lead to a definitive diagnosis (Figure 1 in paper II). Owing to the retrospective nature of paper I, potential selection biases were inherent, as limitations in medical record data could introduce reporting errors, particularly during the early years of the study when some patients may not have undergone documented cardiological examinations. Conducting the search for eligible patients at a tertiary centre might also have resulted in a risk of exclusion of the milder cases, and inaccurate documentation of diagnosis code could have occurred during potential telephone consultations. Due to the long follow-up period of patients with previous surgery, morphological data for some of the individuals who underwent surgery in earlier years were unattainable.

Second, the short questionnaire on satisfaction has not yet been validated. Owing to the small sample size, we aimed to maximise the number of responses to our satisfaction questionnaire. At the project's inception, no validated questionnaire

regarding satisfaction after epilepsy surgery was available.[197] However, by the time of paper II's publication, a study found that a global rating scale on a seven-point Likert scale had high validity and reliability and correlated well with other measures of satisfaction in epilepsy surgery.[168] This indicates that a global rating scale may be a satisfactory measure of satisfaction. However, the validated scale differed, not only in being a seven-point scale instead of our five-point one, but it was also skewed to the positive side with a non-neutral midpoint. The TAND questionnaire applied in paper III was originally not intended for self-evaluation but has previously been used that way.[112] It was not until 2023 that the TAND self-evaluation checklist was published,[114] and it is still not available in Swedish.

Third, despite our efforts, it was not possible to obtain reliable genotypic data from the surgical cohort. However, we had extensive phenotypic data for that cohort; therefore, the lack of genotypic data should not have affected the results substantially.

Fourth, only postoperative TAND data were available, which prevented a prospective evaluation and made a comparison to a reference group necessary.

Fifth, the sample size precluded further subgroup analysis of the different Engel classes. However, because seizures are reported by patients and their caregivers, these data may be unreliable in some cases, particularly in individuals with high monthly seizure frequencies.

Sixth, the dichotomous approach applied when comparing changes over time in papers I and IV may distort findings, as the cutoff dates were based on presumed years of notable change in TSC treatments. However, we cannot be certain that these dates exactly correspond to those changes, and the results could have varied had alternative years were used. A continuous data approach was deemed impossible.

Finally, not all the domains of TAND were included in the analysis presented in paper III, leading to the use of a summary score for domain 3 to reduce the number of analyses. The selected domains were based on previous studies[22,67,68,81,118,160] and on clinical reasoning. Various symptoms in the excluded domains are included as manifestations in domain 3 (behavioural problems) and are therefore included in the summary score; however, the diagnosis is not specifically included. Furthermore, domain 9 provides an overall measure of the severity of TAND, which has previously not been studied, and we therefore believe that it holds greater relevance than individual symptoms. Furthermore, we chose not to adjust for multiple testing, as doing so would have increased the likelihood of type II errors in this limited sample.

# 8 Conclusion and future perspectives

This thesis explored the different aspects of epilepsy surgery in TSC. Despite the small sample size, this study provides valuable knowledge to the field owing to two key reasons: (1) it employs unique, prospective, national register data that offers comprehensive coverage and (2) it is the first study of epilepsy surgery for TSC in Scandinavia.

In the last decade, we have shown that most patients with TSC are identified prenatally by cardiac rhabdomyomas visualised on ultrasound. This can be of great importance, as close postnatal monitoring and early ASM treatment may prohibit or delay the onset of seizures and improve cognitive abilities.

In our cohort from southern Sweden, i.e., cohort (1), most of the patients eligible for epilepsy surgery were considered for surgery at some level; however, future studies should evaluate physicians' and caregivers' attitudes toward surgery to increase the rate of referrals for epilepsy surgery in TSC. Our outcome data provide an encouraging source to guide counselling for patients and caregivers.

Notably, many individuals who underwent resective surgery expressed satisfaction with the procedure, even if they did not achieve complete seizure freedom. While seizure outcomes are the most straightforward metrics to assess post-surgery, other patient-reported outcomes, particularly those related to satisfaction, remain significantly understudied. Future research should prioritize these patient-related outcome measures to better capture the overall experience of those undergoing the procedure. Additionally, a qualitative approach is warranted to identify the aspects that patients and caregivers prioritize. We also advocate for a more thorough integration of diverse patient-related outcomes, beyond seizures, into the evaluations of epilepsy surgery follow-ups.

The rate of seizure freedom at the national level has increased substantially over time. Recent long-term outcome data in Sweden indicate results comparable to specialized centres that treat more than four times as many individuals as the combined total of all Swedish centres.[154] This underscores the importance of seriously considering epilepsy surgery, even without access to highly specialised TSC centres. The increased rate of seizure freedom likely results from multiple factors: improvements in preoperative investigational methods, increased awareness, knowledge of the potential of epilepsy surgery in these patients, and the emergence of a more tailored resection due to better invasive EEG methods and

high field strength MRI. Despite the advancement of everolimus in the treatment of epilepsy in TSC, the number of epilepsy surgeries in TSC has increased each decade, whereas the total number of surgeries has remained relatively stable at the national level. Our study revealed that patients in recent years are undergoing surgery earlier and seem to have a less severe phenotype, indicating that surgery is no longer seen as a last resort for the most severe cases but as a viable option for achieving seizure freedom. Therefore, as observed in previous studies,[64,160] I emphasise that surgery should be considered early in the treatment process rather than as a final option. Future studies should also explore how different modalities may improve the identification of epileptogenic tubers[204] and how best to tailor surgery for each patient. Less invasive methods, such as laser ablation and thermocoagulation with stereo EEG, are available in Sweden, but have yet to be studied in TSC.

Our data reveal that seizure freedom after the introduction of everolimus was substantially higher after epilepsy surgery than that in the general TSC population. Future prospective studies should evaluate whether everolimus or other disease-modifying drugs,[205] could have additive effects on surgery.

Patients or caregivers of individuals with severe TAND problems may find presurgical investigations challenging and therefore may be inclined to withdraw from consideration. However, our results indicate that individuals with these problems should not be excluded from presurgical evaluation because they have a reasonable chance of seizure freedom, and the families in our study could successfully undergo presurgical evaluations. Instead, frequent screening using the TAND checklist and early intervention should be performed. The TAND checklist is now available as a self-evaluation questionnaire (TAND-SQ) with an accompanying mobile application, making screening even easier.[114] However, TAND-SQ is not yet available in Swedish. Future studies should translate and validate TAND-SQ into Swedish and explore whether the mobile application can enhance the clinical usefulness of the TAND checklist to motivate clinicians to use it more extensively. A future qualitative study is needed to explore the obstacles that physicians and families of individuals with TSC perceive on the road to epilepsy surgery. Addressing these obstacles will hopefully reduce the treatment gap for epilepsy surgery in patients with TSC.

# 9 Acknowledgements

First and foremost, I would like to express my sincere gratitude to all the individuals with TSC and their families who shared their stories with me and participated in the studies. I would also like to wholeheartedly thank all of the people, friends and colleagues who, in any way, have contributed to this thesis.

I am extremely grateful to **Kristina Källén**, my main supervisor. Thank you for always sharing your knowledge and for introducing me to research, epilepsy, and your colleagues around the world. Thank you for all the feedback you have given me. I might not be a queen, but you have still helped to fix my crown. **You are an inspiration!**

I would also like to express my deepest appreciation for my co-supervisors. **Maria Compagno Strandberg**, **Erik Eklund**, and **Olof Rask** for sharing your knowledge and for all the support you have given me through this process.

I am also extremely grateful to my clinical supervisor, **Lisen Ignell.** Without the support and encouragement you have given me this thesis would not be possible. I will forever be your padawan.

**Katarina Stedt**, **Simon Heissler** and **Ulla-Britt Karlsson** for all of your support and administrative help.

Special thanks to **Zivile Bekassy, Johan Lundgren, Lotta Gränse, Josefin Björk Werner, Ingmar Rosén,** and **Håkan Sjunnesson** for our rewarding collaborations and for sharing your knowledge with me.

I am also grateful to **Kirsten Holmberg, Claes Ignell,** and **Ioannis Orfaris** for encouraging me and sharing your research experiences.

A special thanks to **The Stig & Ragna Gorthons Foundation, The Margaretahemmet Foundation,** and **Vera & Carl J Michaelsens donation fund** who provided financial support.

Last, but not least, I would like to express my love for my family. My future wife **Rebecka,** my son **Albus,** and of course our future, as of yet, unnamed kid, for helping me realise that there are more important things in life, and to **Bosse** and **Gösta** for furry support.

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Printed by Media-Tryck, Lund 2024 NORDIC SWAN ECOLABEL 3041 0903

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**Kevin Pearsson** (born in 1993) is a resident in paediatrics at Helsingborg general hospital since 2021 and started his doctoral studies in 2018.

This thesis explores different aspects of epilepsy surgery in tuberous sclerosis complex, from referral to long-term follow-up.

LUND UNIVERSITY

FACULTY OF MEDICINE

Department of Clinical Sciences, Lund

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2024:140
ISBN 978-91-8021-638-8
ISSN 1652-8220