Sagittal synostosis – surgical outcomes and long-term follow up

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ABSTRACT

The overall aim of this thesis was to evaluate and compare surgical outcomes in patients with sagittal synostosis operated with the most commonly used surgical methods in Sweden: craniotomy combined with springs, pi-plasty, or H-craniecomy.

Paper I is a systematic review that identified the evidence showing that spring-assisted surgery is as efficient as more extensive cranioplasties to be of very low quality, thereby emphasizing the need for more rigorous studies. The aims of the other papers were to determine intracranial volume (ICV) in a large cohort of children with sagittal synostosis and compare ICV and cephalic index (CI) between sagittal synostosis patients operated with either craniotomy combined with springs, pi-plasty, or H-craniecomy. Additionally, they compared the effect using two versus three springs on the ICV and CI. Paper II indicated that ICV is normal in infants with sagittal synostosis, Paper III determined that craniotomy combined with springs represents an equally effective surgical method to modified pi-plasty in terms of improving ICV and CI, and Paper V showed that craniotomy combined with springs is a better surgical method than H-craniecomy for correcting CI. Moreover, Paper V showed that craniotomy combined with springs resulted in a lower risk of comorbidities, such as blood loss and need for blood transfusion. Furthermore, Paper IV showed that three springs were more effective at improving CI than two springs, even in the long-term.

Keywords: sagittal synostosis, craniofacial surgery, spring-assisted surgery, intracranial volume, cephalic index

SAMMANFATTNING PÅ SVENSKA

Under de första levnadsåren är skallens suturer mjuka och eftergivliga så att hjärnans tillväxt kan ske utan hinder. Prematur sutursynostos innebär att suturerna slutits för tidigt, vilket sker i fosterlivet och drabbar ca 100 levande födda barn per år i Sverige. Den vanligaste synostosen är sagittal synostos som drabbar den sagittala suturen vilken är belägen i medellinjen högst uppe på skallen. Då kan kraniet inte växa lika bra utåt sidorna utan utvidgar sig istället framåt och bakåt. Pannan och nacken blir bullrig och utstående medan huvudformen blir långsmal, vilket benämns skäfocefali, och huvudet kommer därför att efterlika kölen på en båt och kallas därför ibland ”bätskalle”.

Ungefär 50 levande barn föds årligen med sagittal synostos i Sverige, och tillståndet är klart vanligast hos pojkar. Oftast upptäcks de tidigt av BVC-sköterskan och barnet blir via barnläkar remitterat till något av de två kraniofaciala centra som handlägger kraniofacial vård i Sverige, Plastikkirurgiska klinikerna vid Sahlgrenska Universitetssjukhuset, Göteborg eller Akademiska Sjukhuset, Uppsala.

Indikationer för behandling av sagittal synostos är av funktionella och utseendemässiga skäl och utförs kirurgiskt. Det har rapporterats att barn som ej opereras utvecklar neuropsykyologiska problem.

Runt om i världen används flera olika operationsmetoder till skillnad mot i Sverige där i huvudsak tre olika kirurgiska tekniker används. Dessa är kraniootomi med fjädrar, pi-plastik eller H-kranioektomi. Val av metod är beroende på barnets ålder samt vilken teknik som används på det behandlande sjukhuset.

Fjäderoperationen introducerades i slutet av 1990-talet av det kraniofaciala teamet på Sahlgrenska Universitetssjukhuset i Göteborg och tekniken har sedan spridits runt om i världen. Metoden syftar att minimera ingreppet i skallbenet och istället för stora omformningar med förflyttningar av ben sågas den stängda suturen upp och hålls sedan isär av två eller fler dynamiska fjädrar, vilka avlägsnas efter ca sex månader.


Delarbete I
Som start på denna avhandling gjordes en systematisk litteraturöversikt för att bedöma kvaliteten på kunskapsläget avseende fjäderoperationens effekt på behandling av sagittal synostos. Studier på patienter med diagnosen sagittal synostos som opererats med fjäderoperation och som jämförts mot en kontrollgrupp samt hade definierade utfallsmått, t ex cefaliskt index och också blödningsmängd, operationstid och vårdtid, söktes via Pubmed, EMBASE och The Cochrane Library. Studiernas kvalitet och evidensgrad graderades med hjälp av tre olika skalar. Resultatet blev att nivån på evidensen att fjäderoperationen skulle vara lika effektiv som större operationer i tidigare genomförd studier var låg ("very low"). Resultatet visade på ett behov av bättre studier.

Delarbete II
Kunskapen om vilket mått på intrakraniell volym barn med sagittal synostos har var svårtolkad på grund av till exempel dåligt gjorda jämförelser eller få studerade fall. I detta delarbete utfördes en volymmätning på 143 barn med sagittal synostos vilka opererats på Sahlgrenska Universitetssjukhuset i Göteborg. Dessa varden jämfördes med lika många barn som inte hade sagittal synostos. Resultatet visade att sagittal barn har normal intrakraniell volym. Till dags dato har inget större material publicerats kring detta.

Delarbete III
I delarbete III jämfördes skallformen hos de barn med sagittal synostos som opererats med fjäderoperationen med de som opererats med ett större ingrepp, pi-plastik. Fjäderoperationen sker när barnen är 5-6 månader gamla medan Pi-plastik utförs vid senare ålder, upp till att barnet är 1,5 år. Barnen följes till tre års ålder och jämfördes med barn i samma åldrar utan sagittal synostos. Mätten på jämförelsen var cefaliskt index och intrakraniell volym. Resultaten visade att fjäderoperationen är lika bra som pi-plastiken på att förbättra cefaliskt index och intrakraniell volym, givet att de opereras vid de i studien aktuella åldrarna. Ingen av operationsmetoderna normaliserade helt skallens form.

Delarbete IV
Ju mer avläg huvudformen är hos patienten desto fler fjädrar sätter kirurgen in. I studie IV utvärderades om operationer som utförs med två fjädrar (55 patienter) skiljer sig från operationer med tre fjädrar (57 patienter). Jämförelsen innefattade mätningar av den absoluta och relativa förändringen från tiden före operation till dess att fjädrarna togs ut (till ca ett års ålder) samt vid tre års ålder. Det kunde visas att tre fjädrar ökade cefaliskt index mer än vid två och att den effekten kvarstod vid tre års ålder.
Delarbete V
Det slutliga delarbetet var ett samarbete med Akademiska Sjukhuset, Uppsala, där en större operationsmetod kallad H-kraniektomi används. Patienter i Uppsala opererade mellan 2012 och 2015 matchades ihop med patienter opererade med fjäderhaft på Sahlgrenska Universitetssjukhuset, Göteborg avseende kön, cefaliskt index och ålder före operation och följdes i tre år. Resultaten visade att fjäderhaften ökade cefaliskt index mer än H-kraniektomi och att blödningsrisken samt behov av blodtransfusion var mindre hos barnen opererade med fjäderhaften. Denna jämförelse är unik i sitt slag i världen och var möjlig tack vare såväl samarbete som koordinering av uppföljningsprogram.

Sammanfattning
Denna avhandling visar att operationsmetoden kranioptomi i kombination med fjädrar är en säker teknik som ökar skullformen lika bra som mer omfattande kirurgi. Förhoppningen är att bra studier i framtiden kan utföras som styrker dessa resultat. Det är viktigt att barn med sagittal synostos remitteras tidigt till Kraniofaciala centra så att den mindre invasiva tekniken kan användas.
LIST OF PAPERS

This thesis is based on the following papers referred to in the text by their Roman numerals (I–V). Reprints were made with permission from the publishers.


IV. Fischer S, Maltese G, Tarnow P, Wikberg E, Bhatti Søfteland M, Kölbty L.
    Comparisons of Intracranial Volume and Cephalic Index After Correction of Sagittal Craniosynostosis With Either Two or Three Springs. J Craniocac Surg 2021 Jul; 7
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<td>Two-dimensional</td>
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<tr>
<td>3D</td>
<td>Three-dimensional</td>
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<td>CI</td>
<td>Cephalic index</td>
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<tr>
<td>CS</td>
<td>Craniosynostosis</td>
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<td>CT</td>
<td>Computed tomography</td>
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<td>CVR</td>
<td>Cranial vault remodeling</td>
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<tr>
<td>FGFR1</td>
<td>Fibroblast growth factor receptor 1</td>
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<tr>
<td>GRADE</td>
<td>Grades of recommendation, assessment, development and evaluation</td>
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<td>HU</td>
<td>Hounsfield unit</td>
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<td>ICP</td>
<td>Intracranial pressure</td>
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<td>ICU</td>
<td>Intensive care unit</td>
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<td>ICV</td>
<td>Intracranial volume</td>
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<td>IH</td>
<td>Intracranial hypertension</td>
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<td>IQ</td>
<td>Intelligence quotient</td>
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<td>MINORS</td>
<td>Methodological index for non-randomized studies</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>PICO</td>
<td>Population intervention control outcome</td>
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<td>SD</td>
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### 1 INTRODUCTION

#### 1.1 CRANIOSYNOSTOSIS

The human brain is relatively large in size as compared with other mammalian species. The head and neck of an infant constitutes of ~20% of the total body surface relative to 10% in the adult.¹ The human skull has adapted to be able to fit through the pelvis during childbirth, and most human brain growth occurs after birth and during the first years of life. The skull comprises the cranium and the mandible, with the cranial vault constituting the roof of the cranium, and including the frontal, parietal, temporal, sphenoidal, and occipital bones (Figure 1). Cranial sutures are the fibrous joints where these bones articulate with each other. During infancy, the cranial sutures are open and compliant (except for the metopic suture that starts to fuse at ~4-8 months of age) allowing the brain to grow without obstruction. Craniosynostosis (CS) is a congenital condition associated with the fusion of one or multiple sutures. The relationship between abnormally closed cranial sutures and the resulting shape of the head was first described by Hippocrates in 400 B.C.²

Depending on which suture is affected, characteristic deformation of the skull develops due to compensatory growth of the other skull bones in directions unrestrained by the fused suture (Figure 2). This phenomenon was stated by Virchow in 1851.³ Craniosynostosis can be isolated or associated with other extracranial malformations and often as part of a syndrome,⁴ ⁵ with descriptions related to nearly 200 different syndromes.²

**Management in Sweden**

Sweden was populated with 10.3 million inhabitants in 2020, with ~113,000 children born in Sweden that year.⁶ Preventive care is performed in Child Health Centers that are nurse-led and reach almost all newborns (99%). Sweden demonstrates excellent child health statistics for several reasons, including a long history of peace and the presence of a parliamentary democracy throughout the 20th century. The country’s health care system is publicly financed based on local taxation and children receive care from family physicians and Child Health Center nurses free of charge.⁷ The definitive treatment of sagittal synostosis (SS) is surgical expansion of the fused suture or the cranial vault. Craniofacial surgeons and neurosurgeons are employed by the public sector and work at university hospitals that provide a high quality of inpatient care for children.
In Sweden, care for all craniosynostosis patients is managed by two national centers within a multidisciplinary team setting: the Gothenburg Craniofacial Center and the Uppsala Craniofacial Center. The two centers have carried a license since 2012 for specialized care similar to the National Health Service contract for craniofacial service in England. Family physicians and Child Health Center nurses often discovers cases of craniosynostosis and, with the help of pediatricians, refer patients to one of the National craniofacial centers. In 2019, the two centers managed ~110 new patients with non-syndromic craniosynostosis.
1.1.1 EPIDEMIOLOGY
The incidence of craniosynostosis reportedly ranges from 1 in 1600 to 4000 live births,\textsuperscript{11-14} although this appears to be increasing. Approximately 80% of craniosynostosis is of the isolated, non-syndromic variety without major associated malformations. Sagittal synostosis is the most common non-syndromic craniosynostosis and accounts for 41% to 68% of non-syndromic cases, with an incidence of ~1 in 4000 children.\textsuperscript{13} An Australian study from 2021 investigated alterations in the incidence between 1982 and 2008, but found that the incidence for sagittal synostosis was unchanged.\textsuperscript{15} A recent study in the Netherlands showed a significant annual increase in scaphocephaly of 11.7% relative to the incidence from 1997 to 2013,\textsuperscript{11} with the explanation for the increase a combination of an actual rise in incidence and improved awareness. The same phenomenon was found in Norway, where a study from 2020 showed one of the highest incidence rates reported to date and with the primary increase observed in non-syndromic midline craniosynostosis.\textsuperscript{15}

1.1.2 ETIOPATHOGENESIS
Normal cranial sutures allow spatial separation of the cranial bones during growth. The cranium develops from outspread bone islands within the ectomeninx, a fibrous membrane surrounding the brain. Cell proliferation in the periphery of the islands (called the osteogenic front) promotes the movement of two osteogenic fronts to form a suture at ~18 weeks of embryonic development.\textsuperscript{16,17} New bone is produced by bone growth when the plates are pushed apart by displacement movements due to the growing brain.\textsuperscript{18}

Historically, different theories have been presented regarding craniosynostosis pathogenesis. Virchow\textsuperscript{1} suggested that the suture itself was the site of the abnormality and independent of the underlying dura mater, which secondarily affected the cranial base. By contrast, Moss\textsuperscript{19} reported that the cranial base was the primary site for abnormality and transmitted pathological tension to the cranial vault via the dura mater. Others suggested intrauterine constraint as a hypothetical cause, although this was later contradicted by animal studies.\textsuperscript{4} Subsequent research indicated the presence of not only intrinsic bone abnormalities but also multiple factors responsible for the condition, including metabolic conditions, genetic variations and environmental causes, as well as maternal smoking and use of anticonvulsants.\textsuperscript{20-23}

Synostosis of the sagittal suture may originate from a mesenchymal disorder involving the intramembranous ossification and could suggest dysregulation of the osteogenic process, resulting in calvarial ossification via hyperactive mesenchymal cells and leading to early ossification and premature closure of the suture.\textsuperscript{24} Studies suggested that the middle section of the sagittal suture fuses first, followed by the frontal or posterior regions.\textsuperscript{25,26}

1.1.3 GENETICS
A complex set of genetic processes regulates membranous bone formation.\textsuperscript{14} Mutation of \textit{BMP2} gene (chromosome 20), the intronic sequence of \textit{BBS9} (chromosome 7) and \textit{IGF1R} (chromosome 15) have been identified in isolated sagittal synostosis.\textsuperscript{14,27,28} These genes are involved in skeletal development, although their clinical significance as prognostic factors for premature fusion have yet to be determined.

Genetic variants associated with syndromic craniosynostosis include those in \textit{DPH1}, \textit{ERF}, \textit{MSX2}, \textit{TWIST} and genes associated with fibroblast growth factor receptor (FGFR).\textsuperscript{4,27} \textit{ERF} variants can induce late-onset sagittal synostosis.\textsuperscript{27} Additionally, it is reported that patients with sagittal synostosis as part of a cardiofaciocranial syndrome harbored variants in \textit{BRAF}, with the authors proposing a possible interaction between the RAS/MAPK signaling pathway and \textit{FGFR}.\textsuperscript{27} Apert, Crouzon, Muenke, and Pfeiffer are syndromes associated with \textit{FGFR} mutations.

A study of 93 patients with sagittal synostosis identified \textit{FGFR1} and \textit{TWIST1} variants, although in a very small proportion of patients (1%). The authors further on concluded that sagittal non-syndromic synostosis exhibits complex genetic heterogeneity.\textsuperscript{29} A genetic panel was considered for familial cases of non-syndromic craniosynostosis following identification of \textit{SMAD6} mutations in 18% of familial cases of sagittal/metopic craniosynostosis.\textsuperscript{30} Additionally, inclusion of a geneticist as part of the multidisciplinary team surrounding craniosynostosis patients has been proposed in order to determine the need for genetic testing.\textsuperscript{31} An update by Goos et al. in 2019 investigating new causes of the most common craniosynostosis syndromes argued for performance of next-generation sequencing rather than gene-specific testing, given that recently identified mutations were less specific, and that genetic causes were potentially increasing.\textsuperscript{27} It is likely that the importance of genetic mechanisms will continue to increase in the future.\textsuperscript{2}
1.1.4 SAGITTAL SYNOSTOSIS

This thesis focuses on patients diagnosed with sagittal synostosis, the most common form of craniosynostosis. Premature fusion of the sagittal suture can occur as early as the late first trimester, resulting in restricted transverse bitemporal growth and causing compensatory expansion in the anteroposterior direction. This results in scaphocephaly (the characteristic “boat-shaped” head) with an elongated skull, frontal bossing, narrow biparietal diameter, and prominent occiput (Figure 3).

There are morphologically variations in the severity of the deformity depending on how much of the sagittal suture that is fused and on the individual degree of the compensatory growth. Diagnosis can be made by clinical evaluation or often using combined low-dose computed tomography (CT) scan with three-dimensional (3D) reconstructions of the skull.

The male-to-female ratio of occurrence ranges from 3:1 to 4:1. The risk of recurrence is high in affected families (6-10% of cases are considered familial). Risk factors for sagittal synostosis include low parental education, preterm gestation (<37 weeks), low birth weight (<1500 g), cesarean delivery (both elective and emergency), and macrosomia defined as birth weight >4000 g and large weight for gestational age (>90th percentile). Among the different types of craniosynostosis, sagittal synostosis showed the strongest association with maternal smoking. No association between maternal age and sagittal synostosis has been found. A study investigating nutrient intake found that maternal use of riboflavin and vitamin B6 resulted in a significantly lower risk for sagittal synostosis in the infants.

1.1.5 CONSEQUENCES OF CRANIOSYNOSTOSIS AND INDICATIONS FOR SURGERY

Intracranial hypertension

The cranium contains mainly the brain, cerebrospinal fluid, and blood. Because the cranium is a rigid structure, any increase in one of the three components increases the intracranial pressure (ICP), which can potentially cause visual impairment, brain damage, and adversely affect psychomotor development.

In single-suture craniosynostosis, bossing and bulging of the unfused bone plates compensate for craniofacial disproportion. It is difficult to clinically determine whether this compensatory mechanism is sufficient to maintain normal ICP. A controversial theory suggests that sagittal synostosis patients experience craniofacial disproportion with volume restriction, resulting in intracranial hypertension (IH), due to the fused sagittal suture.

Suture diastasis, papilledema, and a bulging anterior fontanelle are signs of intracranial hypertension, which has been identified in patients with craniosynostosis; however, its effect on brain development and correlation with intracranial volume remain unclear. Previous reports identified intracranial hypertension in up to 19% of patients with non-syndromic craniosynostosis, and ~50% of syndromic patients. Wall et al. identified an...
incidence of increased intracranial pressure in 44% of 39 patients with late-presenting non-syndromic sagittal craniosynostosis, and who underwent intracranial pressure monitoring. Some of these patients suffered from persistent headache, two showed developmental delay, but none showed signs of papilledema. Additionally, the authors found no evidence of more common symptoms or radiological signs (e.g., copper-beaten appearance of the calvaria, reduction of subarachnoid spaces, or destruction of sulci) in the patients with increased intracranial pressure. The definition of increased intracranial pressure used in that study was 15 mm Hg, an upper normal threshold commonly used in chronic conditions, whereas other authors use 20 mm Hg as a high threshold (use of the higher threshold would have identified increased ICP in 15% of the 39 patients). 42 The definition of normal intracranial pressure in small children is unknown, making it difficult to interpret results. 41

Neuropsychological outcomes associated with sagittal synostosis
There are few studies on neuropsychological development in untreated patients with sagittal synostosis. Bellwi et al. 43 found that untreated children with sagittal synostosis showed poor gross motor skills relative to children without sagittal synostosis. The function deficit was subsequently reversed in patients that underwent surgical treatment but remained in untreated children. 43 A follow up at 5 years of age showed that the untreated patients still showed deficits in gross motor function along with impaired fine motor function. These results suggest that surgical treatment is important not only for cosmetic reasons. 44 Studies on operated children with sagittal synostosis reported average cognitive profiles 45-47 and normal school performance level. 48

Indications for surgery
The need for surgery is primarily to address functional issues, promote normal brain growth, and restore appearance. There are few untreated patients in developed countries, given that the recommendation for craniosynostosis is surgical treatment. If left untreated, the condition could result in psychosocial concerns for the patient and family. 20 Several different surgical methods are used worldwide to correct the malformation, and often depend on local traditions, as well as the experiences and philosophy of the surgeon. There is an ongoing debate regarding which technique to use, and the treatment has evolved to maximize patient outcome while minimizing morbidity. The goal of surgery is to normalize the skull shape and achieve normal neurological development. The challenge is in using minimally invasive techniques, and optimize anesthetics and blood-conservation methods in order to minimize blood loss and the need for analgesics. 3,20

1.2 SURGICAL METHODS
In 1890, Lannelongue performed the first described surgical treatment of sagittal synostosis, 39 which involved bilateral strip craniectomies of the fused sagittal suture. 30 Approximately 50 years later, the American neurosurgeon Ingraham published results of surgical treatments of the cranium for cosmetic reasons. 51 Paul Tessier, considered a pioneer of modern craniofacial surgery and descriptions of craniofacial deformities, published treatment suggestions for craniofacial deformities in 1971, including meticulous, step-by-step descriptions of the surgical procedures. 52

Over 20 different surgical methods for correcting sagittal synostosis have been described. 53 The techniques include minimally invasive methods such as strip craniectomy, endoscopic strip craniectomy with helmet molding, spring-assisted craniectomy, and distraction osteogenesis, and more extensive calvarial reconstruction techniques, such as pi-plasty/modified pi-plasty, H-craniectomy, and total cranial vault remodeling (CVR). 34,55 A general distinction can be made between minimally invasive methods and open surgery. Among minimally invasive methods, an osteotomy is typically performed to open the fused suture (sometimes the fused suture is removed by osteotomies), followed by insertion of springs or distractors to actively widen the skull or use of a helmet postoperatively to mold the skull shape. For open surgery techniques, the skull is formed into the desired shape by reshaping a large part of the skull. Randomization of the different methods for comparison has never been performed. 54

For anesthesiological safety reasons, it is not recommended to operate on patients before 3 months of age. However, because increased ossification of the skull makes it less moldable after 6 months of age, minimally invasive surgery is ideally performed before that age. By contrast, extensive open cranial vault surgery is normally performed after 6 months of age due to the risk of inducing a growth limitation on the skull, and the increased risk of needing major surgical revisions if performed too early. 54,56

A recent review stated that parents of children with non-syndromic synostosis prefer surgery at an early age, as they find the surgery burdensome; however they agree to surgical treatments based on the potential improvements in aesthetic results, neurocognitive functions, and vision. 54

The health- and socioeconomic factors related to surgery are frequently debated, especially in the United States, where hospital- and surgical costs are sometimes paid through private insurances or by the families themselves. 57,58
Comparison of cranial vault remodeling to the use of the less extensive open sagittal strip and endoscopic strip craniectomy showed that the endoscopic patients experienced lower morbidity, higher cost savings, shorter lengths of stay in the hospital, and fewer subsequent surgical revisions.58

The indication for surgical treatment of sagittal synostosis is based on expert opinions. Timing of when to operate and the choice of surgical method is an ongoing debate, but the general professional perspective is that minimally invasive methods are preferred for correction of sagittal synostosis. The arguments for this are simpler anesthesia, lower risk of blood loss and thereby less need for a blood transfusion, less prominent scars, and the aesthetic results in the short-term appears similar to those following a open cranial vault corrections.54,59,60 However, it remains unclear whether long-term neurocognitive, visual, and aesthetical results are similar.54

The surgical methods evaluated in this thesis are craniotomy combined with springs, pi-plasty and H-craniecotomy. Further explanations of these methods follow.

1.2.1 SPRING-ASSISTED SURGERY

In 1986, Persing et al.61 used a rabbit model to demonstrate the possibility of enhancing growth across a linear craniectomy by using implantable stainless-steel spring expanders. In 1998, Lauritzen et al.62 published the first description of spring-assisted correction. The method has since evolved, and several other craniofacial centers world-wide have adopted and developed the technique.63-66 During this procedure the fused sagittal suture is cut open and sometimes even removed, followed by placement of springs on the cut edges of the parietal bone (Figure 4).

![Illustration of the craniotomy combined with springs technique.](image)

The springs gradually expand the bi-parietal diameter via a distracting force, and the skull is remodeled. Due to the requirement that the skull should be malleable, the spring technique is performed before 8 months of age.67-71 The effect of the springs is greatest immediately after insertion, and as the springs unfolds the force decreases.72 Analysis of spring kinetics showed that the springs reached a plateau of expansion 10 days after insertion.69
Re-ossification of the removed suture occurs, and the springs are removed during a second surgery, at ~3 to 6 months after insertion.\textsuperscript{67,68,70}

In general, two springs are inserted, although one, three, or even four have also been used.\textsuperscript{63,68,73,74} Arko et al.\textsuperscript{63} reported that 54.5% of their patients received three springs, and the others two.

Several craniofacial centers have published outcome analyses of surgical results when using spring-assisted craniectomy to correct sagittal synostosis. A recent study comparing perioperative outcomes between spring-mediated cranioplasty and cranial vault remodeling in sagittal synostosis found low complication profiles for either technique. The authors stressed on future focus of long-term outcomes within the research field.\textsuperscript{75}

Spring-assisted surgery is also employed by smaller centers world-wide for sagittal synostosis (e.g., Moldova) based on the cost-effectiveness of the method and its benefits for countries with limited health system resources.\textsuperscript{76}

Supporters of this technique highlight its low blood loss and short operation time, as well as the subsequent short durations in the intensive care unit (ICU) and hospital. Compared with helmet molding, spring-assisted surgery involves no need for adjustments during frequent visits, which interfere with daily life. Conversely, critics of the method note the potential for spring dislodgment, extrusion through the scalp, and the need for a second surgery.

1.2.2 PI-PLASTY

Pi-plasty (or modified pi-plasty) is an open-surgery, calvarial-reconstruction technique often performed at between 6- and 12 months of age. Pi-plasty was first described by Jane et al.\textsuperscript{77} in 1978, and is named after its osteotomy pattern, which resembles the Greek letter π. The procedure immediately corrects the anterior-posterior dimension and widens the skull via multiple craniotomies, which release proximally-based parietal bone flaps that are out-fractured and rounded. The midline is left intact, and the parietal flaps are fixed to the midline by resorbable plates, thereby promoting an immediate widening of the skull. If desired, the skull can be shortened by a small resection of the midline bone (Figure 5). The dura needs to be separated from the bone. Several modifications of the technique have been developed.\textsuperscript{71,78} The temporal muscle and periosteum remain attached to the skull. Published results report low complication rates, a postoperative cranial shape close to normal, and good parental satisfaction.\textsuperscript{79,80}

![Figure 5. Illustration of the pi-plasty technique used at Sahlgrenska University Hospital, Gothenburg.](image-url)
1.2.3 H-CRANIECTOMY

The H-craniectomy technique is also an open-surgery, calvarial-reconstruction technique that was first described by Marchac and Renier\textsuperscript{4} in 1981. During this technique, the sagittal suture is removed in a central strip ~4 cm wide, and biparietal, transverse bone strips are removed anteriorly and posteriorly, resulting in an osteotomy pattern imitating the letter “H”. The temporal bone-flap bases remain attached, and the flaps are “green-sticked” and shortened. Bone grafts from the central strip are replaced over the superior sagittal sinus. The H-craniectomy technique offers good surgical visibility of the sagittal sinus and direct anterior-posterior shortening and immediate biparietal widening (Figure 6). The drawbacks include risk of secondary closure of the coronal suture and severe blood loss, with the majority of patients requiring blood transfusion. A revision rate of 7.9% has been reported and there was no statistical difference in the postoperative CI comparing to patients following endoscopic or open surgery.\textsuperscript{50,71}

![Figure 6. Illustration of the H-craniectomy technique used at Akademiska, Uppsala.](image)

1.3 EVALUATIONS OF SURGICAL METHODS

**Overview**

To date, craniofacial surgeons have not established a gold standard for or agreed upon objective means of assessing potential post-surgical changes in cranial morphology. A recent systematic review investigating outcome measurements in craniosynostosis revealed that only ~40% of outcomes were clearly defined.\textsuperscript{81}

Evaluation tools for measuring outcomes of craniosynostosis surgery can be divided into objective and subjective evaluations. The Whitaker scoring categorization is a subjective tool that is based on the need for secondary surgery and has been used in several studies.\textsuperscript{82} It divides the patients into four categories, according to their need for revision surgery: ranging from no revision surgery necessary (category I), soft-tissue or minor bone-contouring revision desirable (II), major procedures needed (e.g., osteotomies or bone grafting) (III), and a need for a duplication of primary surgery or even extended treatment (IV).\textsuperscript{83} Subjective evaluation suffers from observer bias, either from the patient, parent or surgeon.

Several other more objective measurement tools are used in craniofacial surgery and orthodontics, including landmark-based alignment in CT or cephalograms. Landmarks can through mathematical analysis allow for precise measurements of inter-landmark variations; however, landmarking is time consuming and requires an operator. Moreover identification of every landmark can be difficult (e.g., if a landmark lies on flat, broad curve rather than a sharp, pointy curve) and it is very important to describe definitions in detail in order to minimize errors.\textsuperscript{84,85} There are also techniques for generating a surface of 3D CT scans without landmarks. Surfaces from preoperative scans can be compared to postoperative scans and the vectors- and distances-outputs mapped accordingly. Amm et al.\textsuperscript{85} reported these techniques as being easily reproducible and useful in craniofacial surgery, although landmark-based analysis is more suitable for delicate surgery areas (e.g., the periorbital area). Additionally, three-dimensional photogrammetry is a relatively newer technology and a tool that enables objective visualization of surfaces to allow measurement of cranial shape.\textsuperscript{86}

A recent study on parents and patients reporting outcomes for head shape in children undergoing surgery for single suture synostosis showed that such a questionnaire highlights the clinical usefulness of patient-reported outcome measures (PROMs) and can discover potential areas of concern among parents and patients.\textsuperscript{87}
1.3.1 CEPHALIC INDEX

Cephalic index (CI) is a two-dimensional (2D) measure of the skull form applied to living individuals, whereas the cranial index is used when referring to dry skulls. Cephalic index was introduced in 1843 by the Swedish anatomist Anders Retzius, who used the description *gentes brachycephalae* for individuals with a short skull shape and *gentes dolichocephalae* for those with elongated skulls. Numerical values were assigned later.59

The CI is the maximal cranial width divided by the maximal cranial length and multiplied by 100, and used for indexing the severity of scaphocephaly, which enables comparison with normal skulls. The CI is easy to obtain from a CT scan and is widely used to compare surgical outcomes in scaphocephaly.

A CI ranging from 76 to 80.9 is defined as “normal” (normocephaly or mesocephaly), whereas dolichocephaly (scaphocephaly) describes a CI of ≤75.9 and brachycephaly as ≥81.56,59-62 The average CI of children with isolated sagittal synostosis is reportedly between 60 and 67.56,59,63 A CI >70 has been described as unlikely to be noticeable as a deformity, while a CI < 66 is usually noticeable.54

1.3.2 INTRACRANIAL VOLUME

*History*

Measurements of intracranial volume in healthy children from the 1960s through the 1980s were calculated from 2D roentgenograms.66 The most frequently used data for normal intracranial volumes were produced by Lichtenberg in his thesis in 1960.66 He measured skull length on 2D roentgenograms from 226 children aged 0 to 8 years and created volume curves mathematically, based on an elliptical approximation of the brain form and a shape-correcting factor of adult skulls.67,68 Almost two decades later, a larger study of >1000 “Caucasians” aged 7 days to 20 years, reported manual measurements of cranial width, length, height, and circumference to allow creation of a database of volume curves.62 However, these measurements were not calibrated to real intracranial volumes, resulting in criticisms related to the use of these curves versus ICV measurements derived from modern techniques.69

CT

CT has been the primary imaging modality used for craniosynostosis in order to understand pathology and evaluate the changes imposed by craniofacial surgeries.100 Measurement of ICV using CT scans is accomplished through segmentation and image processing, and can be performed manually outlining the intracranial area within each image slice from foramen magnum to vertex. A more common method uses semiautomatic software that applies thresholding of Hounsfield units (HU) and region growing.101 There are multiple sources of such software with craniofacial teams often developing in-house versions.102,103 There are also fully automatic techniques. A review comparing the three different modalities found no gold standard but rather similar results of measured volume regardless of the method used.101 Deep learning and artificial intelligence aims to improve measurement efficiency by automating objective segmentation and represents a rapidly developing field.104,105

Ionizing radiation

The harmful ionizing radiation from CT is an ongoing concern, with previous studies showing an increased cancer risk associated with pediatric CT scans.106,107 A nationwide Dutch pediatric CT study found a statistically significant dose-effect relationship for brain tumors from head CTs indicating the possibility of one case of brain tumor in 10,000 head CT scans during the first 10 years after exposure to a head CT.106 Individuals experience exposure to natural background sources of ionizing radiation, such as radiation from solar-, cosmic-, water, and air sources, rocks, and radon gas, as well as food. In the United States and Sweden, the average person is exposed to background radiation on the order of 1 mSv to 6.2 mSv annually.108-112 The effective radiation dose from radon gas in an average American household is 2.3 mSv, that from a mammography is 0.4 mSv and a flight from Stockholm to New York results in exposure of 0.05 mSv.113-115 A recent study on cumulative medical radiation exposure in patients with craniosynostosis showed that patients with sagittal synostosis underwent an average of two head CTs, corresponding to an effective total dose of ~8 mSv.109 Other craniofacial centers report effective doses of ≤0.31 mSv per CT, or equivalent to 2 months of background radiation.107,108 Previous studies highlight the importance of following the “as low as reasonably achievable” (ALARA) principle, with low-dose head CT protocols capable of decreasing the dose by up to 40% while preserving image quality.107,108 thereby enables a compromise between radiation risk and image quality.108
Magnetic resonance imaging and “black bone” imaging

Magnetic resonance imaging (MRI) has been used to calculate ICV in healthy children. Already in 1999 Sgouros et al. reported that at 2 years of age, MRI suggested that the ICV in healthy children reached ~75% of the adolescent ICV. Additionally, a recent study described that MRI in previous 10 years has become a routine imaging modality in craniosynostosis, and that “black bone” MRI has demonstrated good accuracy relative to CT imaging. Conventional MRI provides a weak signal in cortical bone and is, therefore, used secondary to CT for visualizing craniosynostosis pathology. “Black bone” imaging technique, first described in 2012, maximizes the contrast between bone, soft tissue, and air and has shown accuracy in detecting fused sutures, with demonstrated applications in virtual craniofacial surgical planning. A major obstacle to “black bone” imaging is the excessive manual processing necessary to yield 3D images of the cranium for visualizing the sutures; therefore, CT scans are still needed for volume measurements.

Head-circumference

Measurements of head-circumference are easily obtained, harmless, fast, and low cost. Full maturation of head-circumference values has been determined as 13 years in females and 15 years in males. Several studies report a strong correlation between head circumference and ICV in craniosynostosis patients, although this was lower in relation to scaphocephaly. The authors argued that the proportion between skull base and cranial vault was altered in sagittal synostosis patients to a greater degree relative to that of other types of craniosynostoses. A study of Asian craniosynostosis patients found a similar growth curve when comparing ICV, obtained via CT, with head circumference, revealing that ICV values in Asian sagittal synostosis patients corresponded to healthy Asian children. Additionally, Martini et al. determined whether head-circumference in children ≤ 12 months of age (in addition to the ear-to-ear distance over the vertex and head length from glabella to opisthocranium over the top of the head) was a good predictor of cranial volume, revealing that this method improved the determination of cranial volume relative to previous measurements that included circumference only.

3D photogrammetry

3D photogrammetry allows visualization of the skull (Figure 7) and has become increasingly popular within pediatric settings due to its fast speed, the lack of need for anesthetics or ionizing radiation, and its non-invasiveness. These images can also be used to measure skull shape. A multi-camera system with a synchronized flash is both fast and efficient, which is advantageous when working with young children. The patients often wear a nylon cap to flatten their hair. A previous study reported determination of the relationship between CT-measured cranial volume and that determined by 3D photogrammetry. Additionally, a study on sagittal synostosis patients concluded that volume measurements obtained via 3D photogrammetry were a valuable alternative to ICV measurements derived by 3D CT, based on the easily reproducibility of the 3D photogrammetry measurements and their high correlations with CT measurements. Moreover, abnormalities in cranial shape in patients with sagittal synostosis have been evaluated by 3D photogrammetry combined with principal component analysis. Drawbacks to 3D photogrammetry include the effect of soft tissue overlying the cranium, which can diminish the precision of measurements. Therefore, the technique might be more useful and reliable in severe cases as compared with milder deformities and better used for evaluating overall head shape and aesthetics rather than cranial bone morphology. Other shortcomings include the cost of the equipment required for 3D photogrammetry and the fact that CT or MRI can reveal additional diagnostic information beyond ICV.
1 INTRODUCTION

1.3.3 SYSTEMATIC REVIEW

A systematic review should include all scientific literature that contributes to answering the pre-determined research question(s) and describe the sampling strategy and pre-defined quality criteria, as well as present the results in a transparent and reproducible manner. In this way, a systematic review should summarize current existing evidence and allow clinicians to utilize the best available evidence in their clinical work.

The research question can be specified through the choice of patient group and treatment whether there should be a comparison with a placebo group or control group, and define the outcomes of importance. A strategy for determining a well-constructed clinical question involves application of the PICO format (population, Intervention, control and outcome), which helps ensure that relevant information can be identified in the selected studies.

The quality of published studies is assessed based on study design and possible systematic errors. Following the review of the quality of all included studies, an overall assessment is made and grading of evidence levels across studies for each outcome accomplished using the GRADE system (grades of recommendation, assessment, development and evaluation).122,123

The GRADE-system describes four levels of evidence (high – moderate – low – very low) that depend on the consistency between studies, precision, directness, overall quality of the studies, and risk of publication bias (Table 1). This system does not rate the quality of individual studies, but rather the overall body of evidence and reflects the correctness of the estimates of the effects. Additionally, GRADE accounts for study methodology (e.g., where randomized trials are graded as high and observational studies as low) and applies lower grades in the event of identified inconsistencies, indirectness, imprecision, or publication bias. Conversely, the studies are rated higher if there is a large reported effect and/or dose response or if residual confounding is eliminated.122,123
Table 1. The GRADE system

<table>
<thead>
<tr>
<th>Quality levels for a body of evidence</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>High ★★★★</td>
<td>High confidence in the correlation between the true and estimated effect</td>
</tr>
<tr>
<td>Moderate ★★★★</td>
<td>Moderate confidence in the estimated effect; possibility that the true effect is different from the estimated effect</td>
</tr>
<tr>
<td>Low ★★★☆</td>
<td>Limited confidence in the estimated effect; the true effect may vary markedly from the estimated effect</td>
</tr>
<tr>
<td>Very low ★★★★</td>
<td>Very little confidence in the estimated effect; the true effect probably very different from the estimated effect</td>
</tr>
</tbody>
</table>

2 AIMS

The aims of each paper were as follows:

- To determine the quality of evidence of the efficacy of spring-assisted surgery in the scientific literature. (Paper I)
- To determine intracranial volume in children with sagittal synostosis as compared with that in unaffected children. (Paper II)
- To compare intracranial volume and cephalic index following craniotomy combined with springs to pi-plasty for sagittal synostosis, as well as to unaffected children. (Paper III)
- To compare the effect on intracranial volume and cephalic index using 2 springs versus 3 springs in patients operated with craniotomy combined with springs for sagittal synostosis. (Paper IV)
- To compare perioperative outcome, intracranial volume and cephalic index following craniotomy combined with springs versus H-cranietomy in sagittal synostosis patients. (Paper V)
3 PATIENTS AND METHODS

3.1 SYSTEMATIC REVIEW
The PICO inclusion criteria for the articles included in Paper I were:

P. Patients were diagnosed with sagittal synostosis.
I. The intervention was surgical treatment with strip craniectomy of the sagittal suture combined with springs placed across the osteotomy line.
C. There was a control group that included patients with sagittal synostosis operated with an alternative surgical technique.
O. The perioperative parameters and outcomes were objectively evaluated, and the primary outcome was CI as an objective measurement that reflected the effects of surgery on the skull shape.

A literature search of PubMed, EMBASE and The Cochrane Library was performed, with the help of a librarian, for articles published between 1997 and September 2013, using the following search string: “spring AND craniosynostoses OR craniosynostosis OR sagittal synostosis OR scaphocephaly OR cranial sutures OR suture OR cranial OR skull OR calvaria OR calvarium OR cranium”. From the articles identified, additional papers fulfilling the inclusion criteria of the pre-defined PICO were manually searched from within the reference lists.

Because no randomized clinical trials were identified, the validity of the individual studies was evaluated through a specific index developed for non-randomized studies (MINORS). An additional scale, specifically developed for pediatric surgery, was used to assess the quality of the retrospective studies.

The rating of evidence across the studies for each outcome was determined using the GRADE system.

3.2 STUDY POPULATION

The Gothenburg Craniofacial Registry
All retrospective studies (Paper II, Paper III, Paper IV and Paper V) used for this thesis involved patients surgically treated for sagittal synostosis at the Department of Plastic Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden. The Gothenburg Craniofacial Registry was developed in the 1990s and includes information on every patient referred to the department for treatment of craniofacial malformations since 1978. To date >3000 patients with craniofacial diseases have been registered, including ~1450 with craniosynostosis patients, of which ~700 patients were diagnosed with sagittal synostosis. At inclusion, demographic data was collected, including a personal identification number, age, gender, diagnosis of the specific type of craniosynostosis and specifics regarding comorbidities (e.g., syndromes). Details of the surgical treatment are also registered, including type of surgical procedure, number of springs inserted, duration of surgical procedure, body weight on the day of surgery, estimated perioperative blood loss, amount of blood transfusion given, counts of time spent in the ICU, as well as at the ward. Any complication is also registered.

Information from pre- and postoperative radiological examinations is stored digitally in the medical records at Sahlgrenska University Hospital. CT scan with springs still in place is mostly conducted within a few days before spring extraction. The CT scan at follow up at 3 years of age is often done the day of the follow up visit to the out-patient clinic, at Sahlgrenska University Hospital. The department’ photographer photographs every patient at all visits to the out-patient clinic, including at follow up, and in the operating room during surgery. The 3D photos are also stored digitally in the medical records.

3.2.1 PAPER II
The 143 patients (74% male) included in Paper II were untreated consecutive patients with isolated sagittal synostosis identified in the Gothenburg Craniofacial Registry from 2005. All patients had been diagnosed using CT, use of which began to increase in 2005. Study inclusion ceased on 31 December 2012.

The control group was identified among patients undergoing head CT scans for post-traumatic or neurological reasons at Sahlgrenska University Hospital. Only controls with expected normal head shapes and sizes were included.
They were matched by gender and age. Age-matching between patient and unaffected child was within ± 30 days.

We sub-grouped the patients according to gender and age (±180 days), with the 180-day cut-off chosen to correlate to a clinical application where patients ≤180-days old were to be operated with craniotomy combined with springs, and those >180 days old operated with pi-plasty.

**Statistical analyses**
Student’s paired-sample *t*-test was used to compare ICV between patients and matched controls, with a *p* < 0.05 considered significant.

### 3.2.2 PAPER III

Paper III included 143 patients (74% male) with a preoperative CT scan (these were the same patients as those described in Paper II) and 103 patients (76% male) with a postoperative CT scan conducted at 3 years of age. The study included untreated, consecutive patients diagnosed with isolated sagittal synostosis identified in the Gothenburg Craniofacial Registry from 2005 until 31 December 2012. The patients underwent surgery with either craniotomy combined with springs (≤ 6 months of age) or modified pi-plasty (> 6 months of age). By the summer of 2015, most patients had undergone their follow up postoperative CT scan at 3 years of age.

For each case, a control was identified among patients without sagittal synostosis, and undergoing head CT scans for post-traumatic or neurological control at Sahlgrenska University Hospital. Only controls with expected normal head shapes and sizes were included, and matched by gender and age. Age-matching between patients and controls without sagittal synostosis, was within ±30 days for preoperative CT and within ±90 days for postoperative CT.

**Statistical analyses**
Student’s paired-sample *t*-test was used to compare CI and ICV between patients and matched controls. Independent-sample *t*-test was used to compare the two surgical techniques. A *p* < 0.05 was considered significant.

### 3.2.3 PAPER IV

The inclusion criteria for Paper IV were sagittal synostosis patients operated between 1 January 2008 and 31 December 2017 with craniotomy combined with springs and who had undergone a preoperative CT scan and two postoperative CT scans (one at 6 months after spring insertion and conducted within a few days before spring extraction and one at 3 years of age). 130 consecutive patients were identified in the Gothenburg Craniofacial Registry, of which 18 were excluded due to motion artifacts in their CT scan, use of an external spring, or complementary surgery (e.g., barrel stave osteotomies or diadema-shaped bone resection). The remaining 112 patients were divided into two groups: those operated with two (49.1%) or three springs (50.9%).

**Statistical analyses**
An independent-sample *t*-test was used to compare width, length, CI, and ICV between the two- and three-spring groups at the preoperative stage, at the time of spring extraction (~6-months post spring insertion) and at follow up at 3 years of age, respectively.

Absolute and relative changes in width, length, CI, and ICV were calculated between all 3 paired variables:

- From the preoperative scan to spring extraction
- From spring extraction to at 3 years of age
- From the preoperative scan to at 3 years of age

Student’s paired-sample *t*-test were used to compare changes between the two- and three-springs groups. Additionally a mixed model analysis was performed that adjusted for possible effects of age at surgery. A *p* < 0.05 was considered significant.

### 3.2.4 PAPER V

Paper V included all consecutive patients (*n*=23) operated with H-cranieotomy, between 2012 and 2015, for non-syndromic sagittal synostosis at the Uppsala Craniofacial Center with a preoperative and a postoperative (at 3 years of age) CT scans available. The twenty-three patients (87% males) had completed their follow up at 3 years of age, at the time of the study. The Uppsala patients were matched by gender, preoperative CI, and age with patients from the Gothenburg Craniofacial Registry (operated with craniotomy combined with
springs, between 2006 and 2014, and as well completed a preoperative, a postoperative, at 3 years of age, CT scans and the 3 years of age follow up).

Statistical analyses
Wilcoxon signed ranks tests were used to compare patients operated with craniotomy combined with springs with those undergoing H-craniectomy (IBM SPSS statistics version 26). Bland-Altman plots were used to estimate the inter-rater agreement of preoperative CI measurements of the H-craniectomy patients as well as the inter-rater agreement between the two computer software measuring ICV, i.e. Craniosyn and MATLAB. A $p < 0.05$ was considered significant.

3.3 CALCULATION OF CEPHALIC INDEX AND INTRACRANIAL VOLUME

The CI was measured using CT scans. The width was measured as the widest diameter of the skull, in axial slices. The length was measured as the longest diameter of the skull, parallel to a line between Sella and Nasion, in sagittal slices. The same method was used for patients from the Gothenburg Craniofacial Registry, the Uppsala Craniofacial Center, and control groups of children without sagittal synostosis.

Semi-automatic segmentation of axial CT slices and measurements of ICV, were performed using a computer program previously developed at the Gothenburg unit using MATrix LAboratory (MATLAB) version R2011a (MathWorks, Boston, MA). This method utilizes region growing, watershed, and thresholding to be able to exclude bone tissue and extracranial soft tissue. The Cavalieri principle was applied to calculate the ICV from foramen magnum to vertex by adding each slice area multiplied by slice thickness. The intra-rater coefficient of variation obtained using this MATLAB program for the total ICV at 3 years of age is 5 per mille.\(^{102}\)

The Uppsala Craniofacial Center has also developed an in-house method, Craniosyn, to measure ICV, and relies on the same underlying feature to estimate ICV as the MATLAB program. It uses Hounsfield unit gradients to identify bone and requires manual outlining of the inner boundary of the skull if the bone formation is incomplete.\(^{103}\)

All measurements in Paper II were performed by the first author (S.F) and a co-author (E.W). In Paper III measurements were performed by the first author (S.F) and an assistant, and in Paper IV measurements were performed by the first author (S.F). In Paper V, CI measurements were performed by the first author (S.F) for both Gothenburg and Uppsala patients, whereas ICV measurements were conducted by both first authors (S.F and J.US) for all patients using both MATLAB and CranioSyn.

3.4 ETHICS

All studies were performed in accordance with the Declaration of Helsinki.

The Regional Ethics Review board at Gothenburg University approved all studies (no. 784-11; 26 September 2011, with addendums on 24 November 2011). The Uppsala Ethics Committee approved the study in Paper V (no. 2013/402; 27 January 2016).

All studies were retrospective and the participants had already undergone surgical treatment and CT scans (preoperative for diagnosis and postoperative for surgical follow up). Therefore, the research presented in this thesis did not involve any further interventions for the patients. The results are presented on a group level making identification of individual patients impossible. The participants were un-affected by the outcomes of these studies, and no written consent from patients or parents was required.

The authors declare no conflicts of interest.
4 RESULTS

4.1 PAPER I

The systematic literature search identified a total of 241 abstracts (83 in PubMed, 89 in EMBASE, and 69 in The Cochrane Library), 81 of which were found to be duplicates; therefore, 160 abstracts were unique. Five of the studies met the inclusion criteria according to the pre-defined PICO: patients diagnosed with sagittal synostosis and that had undergone surgery with craniectomy of the sagittal suture combined with springs placed across the osteotomy line. Patients were compared with a control group of patients operated with an alternative surgical method, and the studies reported objective measurements on outcomes. Four of the five studies were generated from the same craniofacial centers: Guimarães et al.\textsuperscript{126} and Wind et al.\textsuperscript{127} from Goteborg, Sweden; and David et al.\textsuperscript{67,128} from Winston-Salem, NC, USA. Because the two later studies from each center presented data from a larger patient cohort from the same population and/or a longer follow-up period, it was decided to consider the two earlier studies as preliminary; therefore, the two former studies were excluded. Thus, three studies were included in the systematic review.\textsuperscript{67,127,129}

The three studies meeting the PICO inclusion criteria are summarized in Table 2.

The validity of each single study was 56% of the maximum score in MINORS and 47% using in the scale for retrospective studies concerning pediatric surgery.

All 3 studies presented CI as an outcome (both preoperative and postoperative) for the patients with sagittal synostosis that underwent strip craniectomy in combination with springs, as well as for the controls. The follow up time ranged from a mean of 6.3 to 46 months. One of the studies showed a statistically significant worse postoperative CI for the springs group, whereas the other two studies could not confirm any difference.

The three studies presented other objective outcomes showing that the control group had a significantly longer operation time, greater blood loss, and longer stay at the ICU and total hospital stay.

The results of Paper I concluded that there was very low quality of evidence that spring-assisted surgery was as efficient a surgical method as more extensive craniofacial surgery: GRADE \(\Box\Box\Box\).

Table 2. PICO inclusion criteria for the three studies used for the systematic review:

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<thead>
<tr>
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<tbody>
<tr>
<td>P. No of patients with SS</td>
<td>20</td>
<td>75</td>
<td>7</td>
</tr>
<tr>
<td>I. Springs (age at surgery in months)</td>
<td>Yes (3.5)</td>
<td>Yes (5.7)</td>
<td>Yes (3.7)</td>
</tr>
<tr>
<td>C. Surgical technique (no. of controls)</td>
<td>Pi-plasty (20)</td>
<td>CVR (18)</td>
<td>Strip craniectomy combined with parietal barrel staving (7)</td>
</tr>
<tr>
<td>O. CI, OR time, ICU stay, hospital stay, blood loss</td>
<td>Data are presented</td>
<td>Data are presented</td>
<td>Data are presented</td>
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</table>

SS, sagittal synostosis. CVR, cranial vault remodeling. CI, cephalic index. OR time, operation time. ICU stay, stay at intensive care unit.
4.2 PAPER II

ICVs (mean ± standard error of the mean) of patients diagnosed with sagittal
synostosis and the corresponding controls (unaffected children) were 866 ± 13
mL and 870 ± 15 mL, respectively (p = 0.745). The mean age for the patient
and the control groups was 173 ± 8 days and 172 ± 8 days, respectively.
Subgroup analyses of gender or age at CT (≤180 days or >180 days) revealed
no statistically significant differences between groups.

The implications of these results are summarized in Table 3. The detailed
findings are provided in the included paper.

4.3 PAPER III

Craniotomy combined with springs increased ICV from 802 ± 127 mL (mean
± standard deviation (SD)) to 1300 ± 158 mL, and CI from 70.1 ± 4.0 to 73.1
± 3.3 as compared with those of the controls (unaffected children; ICV from
796 ± 136 mL to 1334 ± 136 mL and CI from 83.6 ± 7.3 to 80.0 ± 4.5). There
were no statistically significant differences between groups for ICV (p = 0.621
preoperative and p = 0.223 postoperative, respectively), but there were
statistically significant differences in CI (p < 0.001 preoperative and p < 0.001
postoperative, respectively).

Plasty increased ICV from 1014 ± 115 mL (mean ± SD) to 1286 ± 122 mL,
and CI from 69.7 ± 3.3 to 74.1 ± 2.6 as compared with those of the controls
(unaffected children; ICV from 1043 ± 153 mL to 1362 ± 122 mL, and CI from
83.4 ± 7.0 to 79.6 ± 3.9). There was no statistically significant preoperative
difference in ICV, but there was a significant postoperative difference in ICV
(p = 0.004), as well as in preoperative and postoperative CI (p < 0.001 and p <
0.001, respectively).

There were no statistically significant differences between the two surgical
methods regarding increases in ICV or CI (p = 0.293 and p = 0.170,
respectively).

The age matching between patients and controls was very precise.

The implications of these results are summarized in Table 3. The detailed
findings are provided in the included paper.

4.4 PAPER IV

Craniotomy combined with two springs increased ICV from 792 ± 113 mL
(mean ± SD) to 1298 ± 181 mL, whereas craniotomy combined with three
springs increased the ICV from 779 ± 128 mL to 1283 ± 136 mL. The relative
increase in ICV was not statistically significantly different between the two
surgical methods when adjusted for the possible effects of age at surgery (p =
0.281).

The absolute increase in CI was greatest from preoperative measurements to 6
months after spring insertion in both groups:

two springs 5.0 ± 2.5; three springs 6.9 ± 3.1.

For the entire period (from preoperative measurements to at follow up at 3
years of age), the absolute increases in CI were, as follows:

two springs 2.5 ± 2.3; three springs 4.1 ± 3.4.

There was a statistically significant difference (p = 0.003) in CI for the entire
period between the two springs group and the three springs group (adjusted for
possible effects of age at surgery).

The implications of these results are summarized in Table 3. The detailed
findings are provided in the included paper.

4.5 PAPER V

Paper V included meticulous matching of preoperative CI and age between the
Uppsala patients (H-cranietectomy) with Gothenburg patients (craniotomy
combined with springs).

Morphologically, there were no statistically significant differences in pre- or
postoperative ICV between the groups, although the increase in CI was
significantly greater in patients operated with craniotomy combined with
springs as compared with patients undergoing H-cranietectomy. Analyses of the
perioperative data indicated no difference in hospital stay or operation time
between methods, although less blood loss and transfused blood was recorded
for patients undergoing cranietomy combined with springs.
The implications of these results are summarized in Table 3 and detailed findings are provided in the included manuscript.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Research questions/aims</th>
<th>Main results</th>
<th>Meaning of main results</th>
</tr>
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<tr>
<td>II</td>
<td>How does the ICV in untreated patients with non-syndromic sagittal synostosis compare to that in gender- and age-matched healthy children?</td>
<td>The mean ICV for the 143 patients was 866 ± 13 mL, as compared with 876 ± 16 mL for the controls ( (p = 0.745) ).</td>
<td>ICV was normal in infants with sagittal synostosis, according to this large cohort of evaluated patients.</td>
</tr>
<tr>
<td>III</td>
<td>Determine and compare the ICV and CI in patients with sagittal synostosis operated with craniotomy combined with springs or pi-plasty, and relative to the ICV and CI of children without sagittal synostosis.</td>
<td>The mean postoperative ICV for spring patients at 3 years of age was 1300 ± 158 mL and for pi-plasty patients 1286 ± 122 mL. There was no significant difference in ICV between children without SS and spring patients; however, there was a significant difference in ICV between pi-plasty patients and controls. The mean difference (42 mL) between the two surgical techniques was not significant. There was no difference in CI between the two methods.</td>
<td>Improvement in ICV was the same for both methods. Pi-plasty patients might experience postoperative growth retardation. Neither the use of springs nor pi-plasty fully normalized the head shape.</td>
</tr>
<tr>
<td>IV</td>
<td>To determine and compare changes in ICV and CI between the use of two or three springs.</td>
<td>There was a greater increase mean CI in absolute and relative terms in patients operated with three springs as compared with two springs.</td>
<td>Three springs resulted in a greater change in CI, relative to two springs, also in long-term.</td>
</tr>
<tr>
<td>V</td>
<td>To compare ICV, CI, and perioperative outcomes between patients operated with either craniotomy combined with springs or H-cranieotomy.</td>
<td>This study includes patients and controls that were extremely well matched. The results revealed a significantly greater increase in CI for spring patients, as well as less blood loss and need for blood transfusion. The two semi-automatic methods of measuring ICV returned different values.</td>
<td>The spring method increased CI to a greater degree and was less invasive relative to H-cranieotomy.</td>
</tr>
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5 DISCUSSION

5.1 PAPER I

Paper I represented a systematic study to evaluate levels of evidence concerning the effects of spring-assisted surgery. Investigation of the medical literature published up to 2013 yielded 160 abstracts, among which only three studies met the PICO criteria for inclusion in the review. Many of the excluded studies lacked adequate controls and were often limited by evaluation of a low number of patients.

We found no relevant randomized controlled studies. Authors of a systematic review on the management of non-syndromic isolated sagittal synostosis and using the same quality assessment as our review (MINORS) similarly observed that most studies on craniofacial surgery are non-randomized. Moreover, they found many studies describing short-term outcomes of various surgical treatments but a deficit of longitudinal and comparative studies with defined endpoints. Another systematic review investigating endoscopic versus open approaches for correcting craniostenosis found a low quality of evidence for all evaluated outcomes (complications, reoperations, blood-transfusion rates, estimated blood loss, operation time, and length of hospital stay). Outcomes should be clearly defined and measured according to both short- and long-term timelines. Analyzing cost effectiveness and relapse and re-operation rates are necessary to evaluate surgical treatments and elucidate the role of different surgical treatments in sagittal synostosis.

The incidence of craniosynostosis is low; therefore the paucity of evaluations in the field will affect a systematic review. Additionally, the low quality of studies can make it challenging for surgeons to decide on the technique to use. The level of evidence for a particular surgical method can be increased by increasing the size of patient cohorts for such studies and including a well-matched control group that allows evaluation of long-term results and improved definitions of outcomes. This could facilitate comparison of various management strategies to potentially improve craniosynostosis care. These were the aims of Papers II through V.

The lack of definitive and conclusive findings in this field at that time requires continued efforts to seek and perform higher quality research and initiate studies incorporating better methodology.

5.2 PAPER II

Studies of normal ICV values in patients with sagittal synostosis show inconsistent results, as there is evidence of smaller, larger and equivalent ICVs. Methodological considerations are important when obtaining ICV data. Many studies compared patient values using growth curves similar to “Lichtenberg growth curve”, which was mathematically based and derived from measurements using adult skulls as a calibration factor. However, possible shape differences between adult and child skulls could impact these curves. Moreover, comparisons of modern measurements using CT scans with data from 2D roentgenograms can be misleading. A previous Australian study described creation of “Abbott-Netherway normal ICV values”, which have been used by others for reference. These ICV values were based on CT scans using a standardized CT volumetry technique and created data from 157 individuals from birth up to 17.8 years of age (median 3.5 years) Although measuring a large population of individuals, the age span was wide and there were no details offered considering the distribution of the age of the included individuals, resulting in uncertainty as to whether their curve would be suitable as comparison for our patient groups.

The aim was to conduct a study that accurately defined ICV in a large cohort of patients with sagittal synostosis, as well as a well-matched set of children without sagittal synostosis in the control group. To date, Paper II represents the largest investigated cohort published on ICV measurements in young children. Later studies also presented control groups, although often sub-grouped into wider age ranges. Ideally, age ranges should not be wide, given that cranial vault volume increases rapidly in early childhood. The human brain doubles its mass in the first 6 months of life and reaches ~80% of its full size by 2.5 years of age and 100% between ages 6 and 10 years.

5.3 PAPERS III AND IV

Variations in the definitions of normal or abnormal CI-values are accompanied by similar variations in CI-measurement methods. Additionally, “normal” in this context can vary according to human populations due to ethnicity. The traditional measurement of CI involves determining the maximal width (the distance between euryons) and maximal length (the distance between glabella and opisthocranion). Euryon is the widest point of the skull, glabella the most anterior (normally) and opisthocranion the most posterior point of the skull (Figure 1). Traditional CI values have limitations, in that such values do not
address regional variations in scaphocephaly (e.g., frontal bossing or occipital coning), or consider the vertical component. Surgery might improve the biparietal diameter; however, if the bitemporal diameter remains the greatest width, the CI will also not reflect the true improvement in cranial aesthetics.

In a patient with sagittal synostosis the bossing of the frontal bone can lie more anterior than the glabella. Modifications of how traditional CI is determined have been undertaken, including measuring the length as the maximal distance from the most anterior point to opisthocranium. Comparison of that modified CI with those obtained using traditional methods and 3D photography revealed that the traditional method underestimated the degree of scaphocephaly. Another comparison study found that the widest point (euryon) of the skull was close to the middle part of the parietal bone in children without sagittal synostosis, whereas in sagittal synostosis patients (with biparietal narrowing) the widest point is anterocaudal on the temporal bone and close to the squamosal suture. The normative CI value was measured using an ideal euryon location at a 56% fraction of the glabella–opisthocranium distance and a 56% fraction of the Nasion–vertex vertical distance and was significant lower than the CI obtained using a traditional method. Therefore, they meant that the normative CI was more accurate in measuring scaphocephaly than the traditional CI. Still, traditional CI is the standard for comparison.

In these studies, we measured CI as the widest diameter divided by the longest diameter parallel to the Sella-Nasion line and then multiplied by 100 (Figure 8), with the same measurements applied to both patients and controls. We believe that this allowed measurement of the longest possible widths and lengths with high reproducibility, thereby reducing the impact of regional variations associated with scaphocephaly and also lowering possible intra- and inter-rater errors.

All of the patients included in Papers II, III, and IV presented with a mean preoperative CI between 69.7 and 72.1 followed by a postoperative mean CI at 3 years of age between 73.1 and 74.8. The craniofacial center in Philadelphia, PA, USA, reported a postoperative CI of 73.7 during follow up of sagittal synostosis patients operated with springs, concluding that this method effectively corrected the CI. Further, they concluded the technique as safe, and because it could be performed at 4.2 months of age, it showed potential for improving cognitive benefits due to the possibility of early intervention. Previous studies have reported improved neuropsychological outcomes following surgery performed before 6 months of age. Additionally, another report on patients with sagittal synostosis and operated as infants and followed up at age 7 to 16 years showed normal intellectual ability at school age; however, there was no difference observed between patients operated before 6 months of age (craniotomy combined with springs) and after 6 months of age (pi-plasty).

Generally spring-assisted surgery represents a safe and effective treatment, with low morbidity. In 2020, Runyan et al. reported successful corrections of scaphocephaly using spring-assisted surgery, during which the springs were inserted at a mean age of 4.6 months and removed after 5 months. They reported an increase in CI from 70.7 (preoperative) to 74.6.
(postoperative); however, at age 3 years the CI had regressed to 72.6. This suggested that the CI improvement peaks early after surgery and declines over time, which agreed with our findings in Paper IV. Both patient groups (two springs and three springs) in Paper IV had a greater CI when the springs were removed at 6 months after insertion (when the patients were ~1 year of age) as compared with the CI at 3 years of age. Runyan et al.\textsuperscript{139} observed an increase (74.7) at 6-year follow up, although the follow-up sample had experienced a large dropout. We did not evaluate the patients from Papers III and IV beyond age 3, therefore we cannot comment on the applicability of this finding to our patients.

van Veelen et al.\textsuperscript{70} reported similar findings, as 83 cases of sagittal synostosis corrected with spring-assisted surgery showed an increase in mean CI from 69.0 (preoperative) to 75.2 (postoperative), followed by a decrease to 72.4 at ~4.5 years of age. Other studies have also demonstrated a greater change in CI at short-term follow up as compared with medium and long-term follow up.\textsuperscript{140,141}

Furthermore, we are unaware of whether this represents the natural course of cranial shape. The CI measurements obtained from the control group of children without sagittal synostosis in Paper III indicated that CI spontaneously regressed over time (from 83 as infants to ~80 at 3 years of age). Similar findings were reported in other Nordic children,\textsuperscript{142,143} and those from the United Kingdom unaffected by sagittal synostosis.\textsuperscript{144} Cranial shape appears round in young infants and becomes more elliptical as they grow. A possible explanation could be the back-to-sleep campaign that results in shorter skulls in very young children and spontaneous elongation as the child starts to move and relieves pressure to the back of the head with increasing age.

The results of spring assisted surgery presented by van Veelen et al.\textsuperscript{70} were comparable to their cranial vault remodeling outcomes, resulting in their concluding that the spring method is a potent and important tool in the field of minimally-invasive craniotomy. Thwin et al.\textsuperscript{133} conducted a systematic review on morphological outcomes of craniectomy versus cranial vault remodeling, finding that neither procedure showed a long-term advantage relative to the other. Paper III suggested that craniotomy combined with springs is as effective as the more extensive cranial vault remodeling technique pi-plasty, at improving cephalic index and intracranial volume, provided that it is performed early. Notably, we found no significant differences in CI between the two surgical methods at follow up at 3 years of age. A typical shortcoming in comparing surgical techniques was noted in Paper III, as comparison of the two surgical methods (craniotomy combined with springs and pi-plasty) was performed between groups of patients with different ages. Therefore, the stipulation that springs must be used at an early age in order to be equally as efficient as pi-plasty done at an older age is important, and motivated the study presented in Paper V, in which the age and gender matching between the two patient groups was done meticulously.

5.4 PAPER V

Collaboration between the two Swedish National Craniofacial Centers and synchronization of diagnostic and follow up routines enabled the study presented in Paper V, which presents a unique comparison of the two surgical techniques; craniotomy combined with springs and H-cranietomy.

The results indicated that craniotomy combined with springs achieved a significantly greater increase in CI as compared with H-cranietomy along with fewer perioperative co-morbidities. These findings were similar to previously reported results.\textsuperscript{5,5,54,70} Additionally, two software platforms (MATLAB and CranioSyn) were used for volume measurements of all patients, resulting in observation of a systematic difference between the two programs. To address this possible confounder, we presented only the ICV measurements generated by one software (CranioSyn) for statistical analyses, resulting in comparable values. This separate finding highlighted the importance of using the same method of volume measurement in order to allow accurate interpretation and comparison of ICV measurements between studies and institutions.

5.5 STRENGTHS AND LIMITATIONS

The limitations of Paper I included that we did not register the study in PROSPERO prior to the start of the study, to rule out that no similar review already existed. However, the field of spring-assisted surgery in sagittal synostosis is very narrow and we were convinced that such a review had not been conducted before.

Those for Papers II through V were the observational, retrospective nature of the studies, which were based on registry data and thereby subject to a risk of systematic bias. We assumed that the groups being compared were largely
similar, which introduced the possibility that lack of similarity in certain patients would suggest that the results were a consequence of other unmeasured variables. To minimize the risks associated with differences between surgical methods and groups used for comparison, future studies should ensure that the patient and control groups are as similar as possible through rigorous age and gender matching.

A limitation of all the studies was the time period used for the observations. Long-term follow up was conducted at 3 years of age; however, it is possible that this is inadequate, as follow up at ≥5 years might introduce evidence of better long-term outcomes. For the purpose of this thesis and the associated studies, longer follow-up time was not considered.

In Paper IV, the postoperative CI was highly similar between patients operated with two and three springs, respectively; however, the preoperative CI was lower for patients that had undergone surgery with three springs, which resulted in a greater increase in postoperative CI. It is possible that randomization of the number of springs is needed to definitively determine whether three springs are more effective than two.

The strengths in Papers II through V include the comparison of clearly defined objective measurements (cephalic index, intracranial volume and perioperative values, such as blood loss, operation time, and hospital stay). Furthermore, all patients were consecutive and treated using different surgical methods but similarly evaluated using standardized measuring instruments.

A major strength of Papers II and III was the rigid matching of patients with children without sagittal synostosis, which had not been accomplished in previous studies. Head CT scans of children unaffected by craniosynostosis, tumors, hydrocephaly, or major fractures (i.e. children with expected normal head shapes and sizes) are not often undertaken; therefore, these matched controls contributed to the value of the studies.

It is worth noting that Paper V was limited by a small sample size, which was largely due to the need to wait for the operated patients to reach 3 years of age and undergo follow up. However, the comparison of outcomes between two different national craniofacial centers that practice different surgical methods along with the use of well-matched controls (according to age, gender and preoperative cephalic index) remains unique.

6 CONCLUSION

I. The quality of evidence that spring-assisted surgery is as efficient as more extensive cranioplasties is very low. Studies performed with a greater degree of rigor are needed.

II. Children with sagittal synostosis have normal ICV.

III. Craniotomy combined with springs appeared equally as effective as a surgical method as pi-plasty in terms of improving cephalic index and intracranial volume, provided it can be performed before 6 months of age.

IV. Three springs appeared more effective at improving the cephalic index as compared with two springs, according to long-term follow up.

V. Craniotomy combined with springs appeared to better correct cephalic index than H-craniectomy in sagittal synostosis patients.
7 CLINICAL RELEVANCE

The primary goal of this thesis was to enhance the clinical care of patients with sagittal synostosis, through systematic evaluations of surgical outcomes and long-term results. Evaluation of current treatments is an important method for enhancing patient care, which in turn can result in better quality of life and long-term results.

This thesis emphasizes the importance of early discovery and referral of patients with sagittal synostosis, to enable the application of minimally invasive procedures, such as craniotomy combined with springs, rather than more extensive cranial vault remodeling techniques.

8 FUTURE PERSPECTIVES

Standardized follow up regimens would be of great benefit to the field and potentially enable easier comparison of outcomes between different techniques and craniofacial centers. Ideally, the outcomes should be measured using non-invasive techniques that are fast, easily reproducible and of low cost. Development of 3D photogrammetry could be a possible contributor to these improvements, as well as a way to reduce the number of CT scans.

Additional effort is required to appropriately define which outcomes to use when evaluating the effectiveness of surgical techniques. Today minimal uniformity exists in the definition of measures such as CI, ICV, and blood loss.

Research methodology needs to be improved, and randomized controlled trials are needed whenever applicable. Regarding the studies used for this thesis, the number of springs could possibly have been randomized. Randomization could also have been applied for comparison of craniotomy combined with springs with H-craniection (Paper V). Although now it seems as if that possibility has passed due to the convincing differences in outcomes.

Future studies should include neuropsychological developmental skills as outcomes and comparisons with children without sagittal synostosis. The studies used for this thesis focused exclusively on objective standardized measures, such as CI, ICV, and perioperative surgical outcomes (e.g., blood loss, operation time, and hospital stay). Future work should consider the neurocognitive aspects of patients operated with sagittal synostosis, which will likely attract increase interest.
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