Neuropsychological outcomes and health-related quality of life of children operated for nonsyndromic craniosynostosis

Marizela Kljajić

Department of Plastic Surgery

Institute of Clinical Sciences

Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

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marizela.kljajic@vgregion.se

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To all parents of children born with craniosynostosis

Neuropsychological outcomes and health-related quality of life of children operated for nonsyndromic craniosynostosis

Marizela Kljajić

Department of Plastic Surgery, Institute of Clinical Sciences
Sahlgrenska Academy, University of Gothenburg
Gothenburg, Sweden

ABSTRACT

The primary aim of this thesis was to assess the intelligence quotient, attention function, adaptive behavior skills, and health-related quality of life of children operated for nonsyndromic craniosynostosis. The secondary aim was to evaluate whether surgical methods for treating sagittal synostosis were related to the outcomes. The participants were tested using a range of psychological tests, including The Wechsler Intelligence Scale for Children 4th Edition (WISC-IV), The Conners Continuous Performance Test 3rd Edition (CPT-3), Adaptive Behavior Assessment System 2nd Edition (ABAS-II), and Pediatric Quality of Life Inventory (PedsQL) Generic Module. Seventy-three children operated for nonsyndromic craniosynostosis participated in studies I, III, and IV, and 65 children operated for sagittal or metopic synostosis participated in study II. The results revealed average levels of intelligence quotient, attention skills, adaptive behavior skills, and health-related quality of life, and that the surgical methods used to treat sagittal synostosis were unrelated to lower or higher outcomes. Furthermore, the findings of this thesis suggest that children treated for nonsyndromic craniosynostosis exhibit average neuropsychological function and good health-related quality of life.

Keywords: nonsyndromic craniosynostosis, neuropsychological functioning, adaptive behavior skills, health-related quality of life

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SAMMANFATTNING PÅ SVENSKA

Icke-syndromal kraniosynostos är en missbildning som innebär för tidig slutning i någon av sömmarna i kraniet. Detta tillstånd opereras, ofta redan under första halvåret. Syftet med operationen är att skapa mer utrymme för hjärnan samt att minska risken för social stigmatisering senare i livet. Tidigare studier gällande denna grupp av patienter har hävdat att kraniosynostos är relaterad till neuropsykologiska bekymmer.

I denna avhandling har barn som opererats för icke-syndromal kraniosynostos genomgått neuropsykologisk testning med avseende på allmän begåvningsnivå, uppmärksamhet och koncentration, adaptiva förmågor samt livskvalitet. Barnen var i åldrarna 7 till 16 år.

I den första studien undersöktes allmän begåvningsnivå via testad intelligenskvot. Resultatet visade att barnen presterade inom normalvariation och hade en genomsnittlig begåvningsnivå.

I den andra studien undersöktes uppmärksamhets- och koncentrationsförmågan via ett datoriserat test. På gruppnivå var förmågan genomsnittlig. På detaljnivå fanns små skillnader där gruppens prestationer var något lägre i vissa avseenden men fortfarande inom normalvariationen.

I den tredje studien undersöktes adaptiva förmågor, dvs. förmågor gällande aktiviteter i dagliga livet (ADL-funktion). Den adaptiva förmågan var genomsnittlig för hela gruppen.

I den fjärde och sista studien undersöktes livskvalitet. Barn och föräldrar fick skatta barnets livskvalitet. Generellt var den skattade livskvaliteten god bland barn som opererats för icke-syndromal kraniosynostos. Det fanns skillnader mellan hur barn och föräldrar svarade på frågorna, där föräldrarna i vissa avseenden rapporterade sitt barns livskvalitet bättre än vad barnet själv gjorde.

Kirurgisk metod för behandling av sagittal synostos visade inte någon skillnad för någon av de uppmätta funktionerna.

Sammanfattningsvis visar avhandlingen att barn som opererats för icke-syndromal synostos har en genomsnittlig neuropsykologisk funktion och god livskvalitet.

LIST OF PAPERS

This thesis is based on the following studies referred to in the text by their Roman numerals.

I. Kljajić M, Maltese G, Tarnow P, Sand P, Kölby L. The Cognitive Profile of Children with Nonsyndromic Craniosynostosis.

Plastic and Reconstructive Surgery 2019; 143:5, 1037-1052.

II. Kljajić M, Maltese G, Tarnow P, Sand P, Kölby L. Sustained Attention and Vigilance of Children Treated for Sagittal and Metopic Craniosynostosis.

Child Neuropsychology 2020; 26:4, 475-488.

III. Kljajić M, Maltese G, Tarnow P, Sand P, Kölby L. Children Treated for Nonsyndromic Craniosynostosis Exhibit Average Adaptive Behavior Skills with Only Minor Shortcomings.

Plastic and Reconstructive Surgery 2021; 147:2, 453-464

IV. Kljajić M, Maltese G, Tarnow P, Sand P, Kölby L. Health-Related Quality of Life of Children Treated for Nonsyndromic Craniosynostosis.

Submitted.

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CONTENT

ABBREVIATIONS

ABAS	Adaptive Behavior Assessment System
ABS	adaptive behavior skills
ADHD	attention-deficit/hyperactivity disorder
CPT	continuous performance test
CPT-3	Connors Continuous Performance Test 3rd Edition
CS	craniosynostosis
ES	effect size
FSIQ	full-scale intelligence quotient
HRQoL	health-related quality of life
HRT	hit-reaction time
IQ	intelligence quotient
ISI	inter-stimulus interval
LS	lambdoid synostosis
MS	metopic synostosis
PedsQL	Pediatric Quality of Life Inventory
PR	perceptual reasoning
PRIQ	perceptual reasoning intelligence quotient
PROM	patient-reported outcome measures
PS	processing speed
PSIQ	processing speed intelligence quotient

SD	standard deviation
SS	sagittal synostosis
US	unicoronal synostosis
VC	verbal comprehension
VCIQ	verbal comprehension intelligence quotient
WIS	Wechsler Intelligence Scales
WISC-IV	Wechsler Intelligence Scale for Children, 4th Edition
WM	working memory
WMIQ	working memory intelligence quotient

1 INTRODUCTION

Surgical techniques and postoperative care have continuously improved in the field of craniofacial surgery. Craniofacial teams have become multidisciplinary with the aim of providing better health care for craniofacial patients. There has been increasing interest and a need to also consider neuropsychological matters in this group of patients. Surgeons are keen to explore whether surgery does more than just correct skull shape, and perhaps more importantly, answers regarding developmental outcomes need to be provided to the parents of children undergoing these procedures.

Previous studies on neuropsychological outcomes have faced challenges. Craniofacial conditions are rare, which often results in small sample sizes, and the presence of multiple synostoses, ages, and varying methodological approaches further complicate the interpretation of results [6].

Additionally, challenges exist in associating surgical and medical data with psychological outcomes *(i.e.*, neuropsychological function). The interpretation of neuropsychological tests is more complex than transferring results to a norm-referenced score. Neuropsychological function and the tests used for its determination overlap conceptually and are inter-related. Therefore, knowledge about neuropsychology and psychological assessment is required [7, 8].

This introduction offers a brief description of psychological assessments and neuropsychological function. Patient perspectives and other important considerations related to psychological assessments are elaborated for both research and clinical settings. Furthermore, insight is provided into the craniofacial anomaly craniosynostosis (CS) and the associated surgical treatment modalities along with the potential consequences of surgical treatment and neuropsychological outcomes.

1.1 PSYCHOLOGICAL ASSESSMENTS

Psychological assessments are used to evaluate cognitive function and deficits that might influence everyday life. Assessments are often preceded by a suspicion of cognitive impairment.

Accurate evaluation of cognitive impairments in order to reach conclusions concerning cognitive ability requires assessment of intelligence quotient (IQ) or general cognitive function using a standardized test. The IQ is the foundation of general cognitive function and exerts the greatest impact on other specific cognitive abilities, such as attention, executive function, memory, learning, and perception [7].

1.1.1 IQ

The IQ is a measurement of general cognitive function and predominantly determined using Wechsler Intelligence Scales (WIS) [7], which are a battery of tests that assess different domains of cognitive function, including verbal comprehension (VC), perceptual reasoning (PR), working memory (WM), and processing speed (PS). VC is evaluated by testing different aspects of verbal ability (*e.g.*, vocabulary, conceptual understanding, and verbal abstraction); PR comprises tests measuring problem solving, visual abstraction, and logical reasoning; WM is assessed by measuring attention and the ability to simultaneously hold and use memorized information; and PS measures the time required to respond to and/or process information under time constraints [4].

These four domains represent the cognitive profile, and when this profile is evenly distributed over the four domains, it is likely that the full-scale IQ (FSIQ) adequately describes the general cognitive function. An uneven cognitive profile indicates the possible presence of specific cognitive impairments unrelated to the level of general cognitive function. The distribution of the cognitive profile is an important aspect to consider in psychological assessments. Uneven profiles with weaknesses in WM or PS might be related to executive dysfunction, attention impairment, or learning disabilities, whereas a weakness in VC might be associated with specific language disorders. An even cognitive profile with cognitive levels one or two standard deviations (SDs) below the mean might also suggest similar impairments associated with the overall cognitive level rather than specific disabilities.

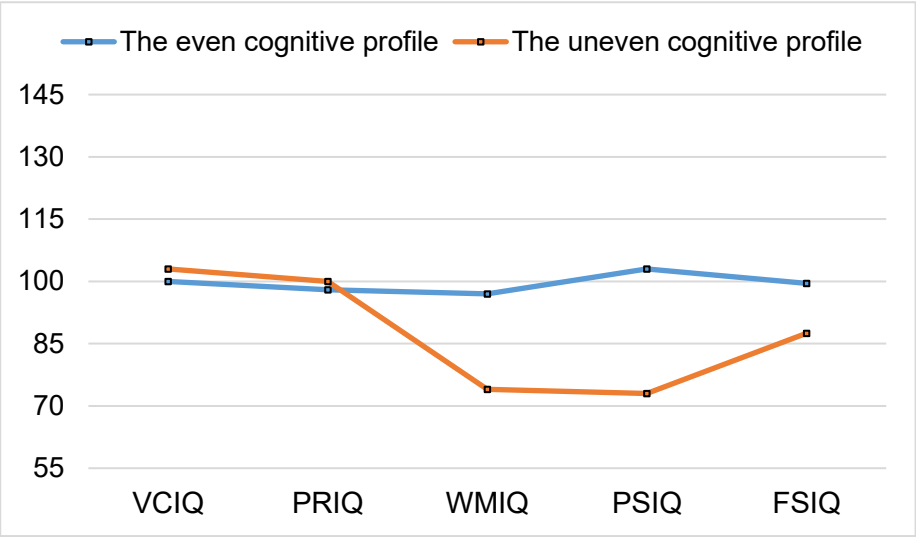


Figure 1. Uneven and even cognitive profiles.

WIS are used worldwide to assess general cognitive function and represent standardized tests that provide norm-referenced standard scores that are calculated from the population and normally distributed. The mean IQ is 100±15 (mean±SD), with two SDs above or below the mean estimated to be within the normal range (Figure 2). Ninety-five percent of the population is estimated to qualify within this range, with 2% of the population estimated to be below two SDs from the mean (an IQ < 70) and corresponding to impairments of general cognitive function that might require assistance in everyday life [4, 7].

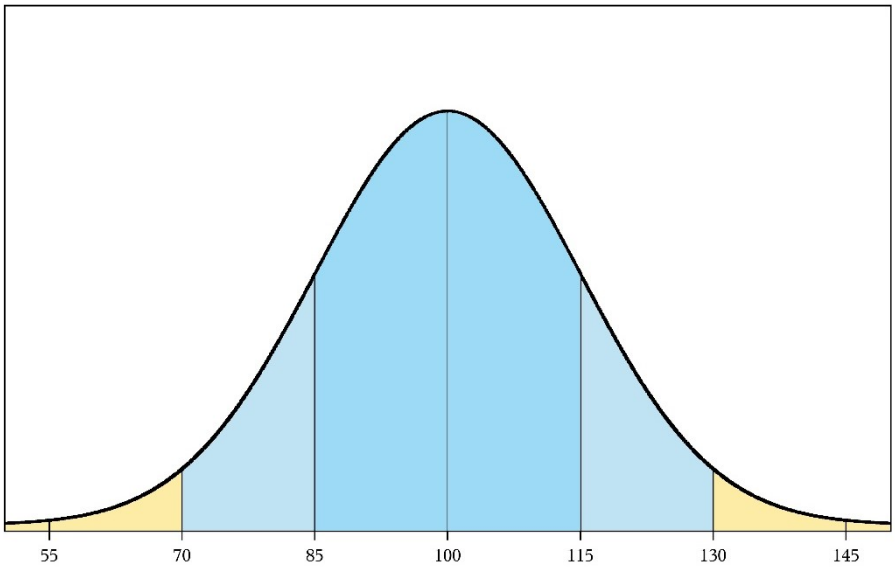


Figure 2. IQ distribution in the general population. The mean±SD value is 100±15, with 95% of the population estimated to within ±2 SDs of the mean [4].

1.1.2 ADAPTIVE BEHAVIOR SKILLS (ABS)

ABS cover abilities important to everyday life and are often measured by questionnaires regarding conceptual, practical, and social skills. Parents, caregivers, or teachers can act as informants for these assessments, which can be performed using several instruments. Two common tests are the Adaptive Behavior Assessment System (ABAS) and Vineland Adaptive Behavior Scale. Both tests are normalized and culturally adapted for the intended population [7, 9].

ABS are a complement to IQ and provide an overall evaluation of general cognitive function in everyday life. ABS generally correlate with intelligence, although there can exist possible discrepancies between the two [10, 11]. An average general cognitive function with impairments in ABS can cause problems in everyday life. This suggests that cognitive capacity as measured by general cognitive function is not fully transferable to how the capacity is used in everyday life. For example, an individual can have problems with independence or the completion of practical tasks while possessing theoretical

knowledge at an average level. Conversely, an individual can possess an average level of ABS but exhibit low theoretical knowledge.

To correctly diagnose intellectual disability, psychological assessments should indicate both an IQ below two SDs from the mean and impaired ABS at the same level [7, 12].

1.1.3 NEUROPSYCHOLOGICAL FUNCTION

Neuropsychological function refers to specific brain functions that can affect behavior and mental processes. For psychological assessments, neuropsychological tests can detect specific cognitive impairments. In addition to the evaluation of general cognitive function, neuropsychological tests provide a detailed assessment of attention, executive function, memory, and perception [7].

1.1.3.1.1 Attention

Attention describes an ability toward focused behavior and is present in most mental activities, which makes it difficult to separate and differentiate from other skills. Attention can be measured by continuous performance tests (CPTs), which evaluate sustained attention, vigilance, and impulsivity. Common CPTs include the Connors CPT 3rd Edition (CPT-3) and the test of variables of attention. Additionally, for performance tested using the WIS, scores for WM and PS can indicate or confirm attention-related problems [7].

1.1.3.1.2 Executive functions

Executive function refers to an ability to plan, organize, and execute tasks that range from modest household tasks, such as preparing a meal, or more complex tasks, such as lecturing in front of students. Executive function includes the abilities of cognitive flexibility, WM, self-monitoring, self-control, and time management. There are several models that describe executive functions. Figure 3 presents Brown's model. In psychological assessments, executive functions are often evaluated by a Trail-making Test, the Wisconsin Card-sorting Test, the Verbal Fluency Test, or Stroop Test [7].

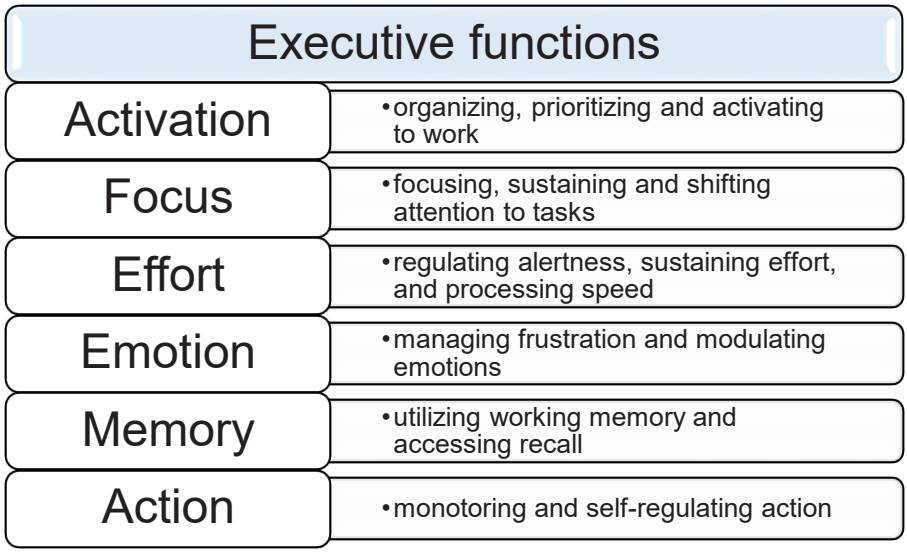


Figure 3. Brown's model of executive functions [5].

1.1.3.1.3 Memory

Memory is a function in constant use and sometimes described in terms of short-term, long-term, semantic, or episodic. Short-term memory is used to hold and process information at the same time, whereas long-term memory is used to store information over time. Long-term memory can be either semantic or episodic, with semantic memory comprising factual knowledge, and episodic describing experienced knowledge, such as specific events or situations. Memory is often influenced by other cognitive functions (*e.g.*, WM, PS, attention, executive functions, and learning ability). Memory tests commonly used in psychological assessments are the Rey Complex Figure Test, Rey Auditory Verbal Learning Test, Boston Naming Test, or digit span and letter–number sequencing from the WIS [7, 13].

1.1.3.1.4 Perception

Perception functions through the senses to organize and identify information in order to clarify its meaning. Perceptual functions are often used to solve problems and require abstract thinking. An ability to orientate in new environments and exhibit local sense is one aspect of perceptual ability, whereas another might be an ability to assemble a piece of furniture. Perceptual impairments are mostly related to acquired brain damage. Block design,

picture concepts, matrix reasoning, and symbol search from the WIS are used to measure aspects of visual perception. Other common tests include the Rey Complex Figure Test, Benton Line Orientation Test, and Brief Visuospatial Memory Test [7, 13].

1.1.4 PATIENTS' PERSPECTIVES

Patients' perspectives are important in both clinical and research settings. In a clinical setting and during psychological assessments, patients' perspectives can be captured by anamnestic interviews or self-reporting. The anamnestic interview represents the core measurement and is often important in determining a diagnostic conclusion. Psychological test results with indications of problems or difficulties must be assessed in a context of what impact they might have. Both patient reports and anamnestic background are key to a valid psychological assessment [7].

In clinical research, patients' perspectives have gained increasing importance over the preceding 10 to 20 years, as there has been an increased interest in using patient-reported outcome measures (PROM) or patient-reported experience measures in clinical care and research. Patient-centered care requires inclusion of patients' perceptions of their health status and experiences. Measuring health-related quality of life (HRQoL) is one alternative to PROM [14] and can be measured using generic or specific questionnaires. In pediatric populations, both self- and proxy reports are sometimes provided [15-17]. Additionally, psychometric quality can vary between different HRQoL measurements. A reliable and validated questionnaire is the Pediatric Quality of Life Inventory (PedsQL) Generic Module [18]. This instrument was evaluated in a large group of Swedish school children [19], and a previous study of children with congenital heart disease found associations between cognitive functions and HRQoL [20]. Moreover, the instrument was used as a disease-specific version for cardiac patients [21], with correlations revealing a strong association between subscale cognitive problems and results from the WIS [20].

1.2 CRANIOSYNOSTOSIS (CS)

The human brain grows rapidly during the first year of life, and cranial sutures allow the skull to grow at the same pace. CS describes a prematurely fused suture in the cranium that results in an atypical head shape. CS can vary from one isolated single-fused suture to more complicated conditions with several fused sutures and other malformations associated with craniofacial syndromes. Approximately 100 new cases of CS are diagnosed annually in Sweden, with an estimated incidence of 1 in 2500 newborns. Additionally, CS is more common in males, with a ratio of 4:1 [2, 3, 22].

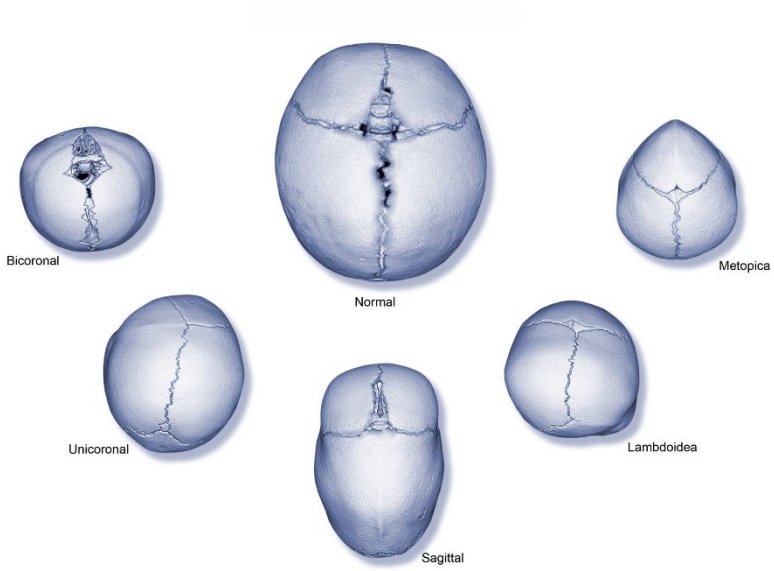


Figure 4. Atypical head shapes due to different CS types. The normally-shaped head presents open sutures [1].

1.2.1 CS TREATMENT

CS is treated with surgery usually within the first year of life and with the aim of restoring a normal shape and minimizing the risk of increased intracranial pressure in adulthood [6, 23].

At Sahlgrenska University Hospital in Gothenburg, Sweden, sagittal synostosis (SS) is treated by spring-assisted surgery if operated before 6 months of age and by pi-plasty after 6 months of age [3]. The recovery time is ~3 to ~4 days after spring-assisted surgery and ~5 to ~6 days after pi-plasty [24].

Metopic synostosis (MS) is treated by fronto-orbital reshaping combined with either a spring or a bone graft [2], with recovery time after surgery at ~5 to ~6 days [24]. Unicoronal, bicoronal, and lambdoid synostoses (US, BS, and LS, respectively) can be treated by distraction, springs, or cranioplasty [25, 26].

Figure 5. Surgical methods for treating SS at Sahlgrenska University Hospital: spring-assisted surgery (left) and pi-plasty (right) [3].

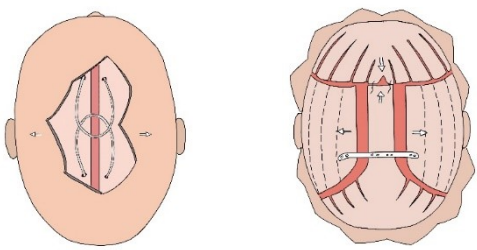
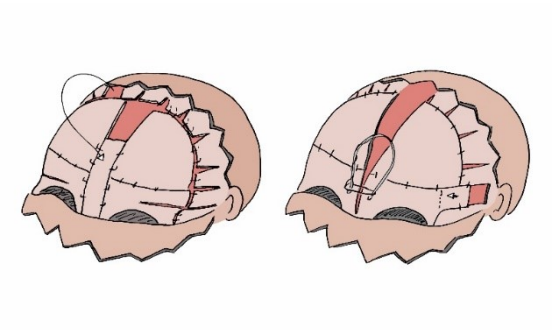


Figure 6. MS is treated by fronto-orbital reshaping combined with either a spring or bone graft [1, 2].



1.2.2 TREATMENT OUTCOMES

Surgical treatment is recommended for CS in Sweden, and untreated patients are very rare. This makes measuring outcomes of surgical treatment as compared with non-treatment challenging.

Treatment outcomes have been measured by medical variables, such as intracranial volume, blood loss, and recovery time after surgery; however, over the previous 20 years, interest in developmental aspects related to surgery has risen. Many studies have been conducted with the aim of gaining additional knowledge about the impact of surgery on cognitive functions, such as attention, speech/language, and learning, as well as emotional and behavioral functions, in treated/untreated CS patients [6].

1.2.2.1.1 Neuropsychological outcomes associated with SS

The impact of surgery on neuropsychological development in SS has been studied. One study comparing operated SS with unoperated controls indicated that SS results in preoperative impairment of gross motor skills that can be reversed by surgery. Moreover, that study, which was initiated before surgery at ~7 months of age with follow-up at 3 years of age, suggested that surgery for CS might be more than a cosmetic procedure [27]. Additionally, the same cohort of patients assessed at age 5 resulted in similar conclusions, specifically that unoperated patients showed delayed improvement of motor skills accompanied by deterioration of fine locomotor control [28].

Furthermore, long-term neuropsychological outcomes in school-age patients have been evaluated, with most studies agreeing that SS patients exhibit average cognitive function [29-32]. Chieffo et al. [33] identified an indication of impaired visuospatial function related to visual memory recall and sustained attention in 35 SS patients. Similar results were reported in another study showing a discrepancy between verbal function and performance, with the authors suggesting that the results might be indicative of more subtle difficulties in achievement [31]. In a small-sample study of 16 patients with SS, 50% were found to have reading or spelling impairments [30]. Another assessment of speech and language found a high prevalence of problems, with issues concerning expressive language the most common [29].

The effects of surgery timing and techniques have also been assessed. Early surgery performed before 6 months of age reportedly shows better neuropsychological outcomes than surgery after 6 months of age [31, 34]. Additionally, a study suggested that the most favorable cognitive outcomes are

achieved when surgery is performed before 6 months of age and using whole-vault craniotomy [35]. However, a recent literature review found it difficult to draw strong conclusions regarding the impact of surgery timing due to multiple confounding factors [36].

1.2.2.1.2 Neuropsychological outcomes associated with MS

Long-term neuropsychological outcomes in MS patients have also been studied. Sidoti et al. [37] identified cognitive and behavioral abnormalities in ~30% of 36 MS patients, although 20 patients in the same study were found to exhibit normal development without any noticeable impairment. Another study reported that among 82 patients with MS, 9% had an IQ qualifying for mental retardation, that IQ impacted the prevalence of psychopathology, and that cognitive impairments were related to a higher prevalence of behavioral problems [38]; however, in that study, adjusting for IQ revealed no relationship between behavioral problems and MS.

In a study of 63 patients with MS, parents were asked to complete a follow-up questionnaire about their child's education. Thirty-three percent of the children had been assessed by a school psychologist and needed extra resources at school, with 34% showing reported speech/language delays, although no differences were observed in behavioral, developmental or educational problems between surgically-treated and untreated patients [39]. Additionally, Speltz et al. [32] evaluated intellectual and academic function in a group of 48 school-age children, finding lower scores in cases relative to controls, although the scores were within a normal range.

Another study assessing relationships between MS severity and the prevalence of speech and language impairments found no correlation [40]. Additionally, a report showed that 31.6% of 76 patients showed developmental difficulties at some level related to synostosis severity, later surgery (performed after 1 year of age), and extracranial malformations [41]. Moreover, a meta-analysis of the impact of surgery regarding cognitive, behavioral, and psychological functions in MS patients revealed that children with MS had generally worse outcomes than their healthy peers, regardless of whether they had been operated [42]. Furthermore, 36 untreated patients assessed with cognitive, behavioral, and psychological measures indicated worse outcomes for MS patients relative to their healthy peers; however, after adjusting for socio-economic status, no major differences were identified [43].

1.2.2.1.3 Neuropsychological outcomes associated with rare synostoses

There have been limited studies of US, BS, and LS due to their rarity, with studies with small cohorts published on patients with US and LS [32, 44-46]; however, there are no studies assessing the psychological outcomes in nonsyndromic BS patients (BS is often related to syndromic CS) [47].

Intellectual and academic function assessed in 46 US and 12 LS patients found lower IQ, mathematical computation, reading/spelling, and phonological-awareness scores relative to those in patients with other fused sutures; however, the lower scores remained within an average range [32]. In a larger group of single-suture synostosis patients, including those with US or LS, attention and executive functions were compared between a clinical group and unaffected controls, with the results showing no clinically relevant differences or associations between functional outcomes and suture type [48]. In another case-control study, US patients exhibited lower scores for language, learning, and memory assessments than controls, although the scores were within an average range [49].

Behavioral adjustment assessed in 44 US and 12 LS school-age patients found no associations between behavioral problems and a specific suture fusion [46]. Additionally, that study reported that patients displayed an average frequency of behavioral problems, although LS patients showed significantly higher scores concerning problem internalization as estimated by mothers, whereas no differences were found regarding behavioral problems in either US or LS patients assessed by fathers or teachers. An earlier study of the same patient cohort found no associations between behavioral adjustment and suture type [45].

1.2.2.1.4 Challenges of assessing neuropsychological outcomes

A majority of previous studies reported methodological challenges that complicate interpretation of the results [44, 50]. Because CS is a rare condition and many studies reported limited sample sizes [30, 40, 51-55], there were other obstacles, including mixed patient cohorts with both nonsyndromic and syndromic CS patients or cohorts that included patients with other craniofacial anomalies [37, 52, 56-58].

Additionally, the ages of patients have also varied, with children and adults included in the same cohort used for some studies [34, 35, 43, 51]. Moreover,

studies have investigated surgery timing without considered the timing of psychological assessments, whereas other studies assessed the cognitive functions of infants or very young children [27-29, 37, 41, 45, 53, 55, 59-65]. Therefore, it is difficult to draw conclusions from these studies, given that many of the children assessed were <6 years of age and exhibited variable rates of development, given that intellectual development reportedly stabilizes at the earliest at school age [66-68].

Importantly, management of the psychological measures and tests has varied across studies, with only specific parts of a test battery or abbreviated versions used while still calculating full-scale scores [31, 34, 35, 38, 43, 54, 58]. Furthermore, some studies used only parental reports to assess neuropsychological outcomes [37, 39, 45, 46, 51, 52, 56, 57]. Although parental reports are commonly used in clinical settings, a detailed assessment of specific cognitive function and development is preferable, given the possible lack of objectivity on the part of parents. Parents exhibit diverse levels of knowledge regarding child development, which suggests the possibility of this affecting their estimations [69].

There has also been a lack of sociodemographic information of patients in studies assessing cognitive function [27, 28, 30, 31, 33, 37-39, 56, 57, 59, 70], and in those studies including sociodemographic variables, differences have been found regarding socioeconomic status [32, 41, 43, 45, 46, 48, 49, 52, 61-64]. Given that sociodemographic variables effect intellectual development, inappropriate assessment can increase the risk of biased samples [71, 72].

Although significant attention has been focused on cognitive functions, little is known about adaptive behavior, which plays an important role in assessments of cognitive function. Information concerning adaptive skills is crucial for evaluating intellectual impairment; however, HRQoL remains almost unexplored in treated nonsyndromic CS patients.

2 AIMS

The aims of this thesis are as follows:

1. To assess the FSIQ of children operated for nonsyndromic CS and compare these outcomes with norms;

2. To assess the sustained attention and vigilance of children operated for SS and MS and compare these outcomes with norms;

3. To assess the ABS of children operated for nonsyndromic CS and compare these outcomes with norms;

4. To assess the HRQoL of children operated for nonsyndromic CS and compare these outcomes with norms; and

5. To evaluate whether CS type or the surgical method used to address SS affect outcomes related to IQ, sustained attention and vigilance, ABS, and/or HRQoL.

3 PARTICIPANTS AND METHODS

The participants included were children previously treated for nonsyndromic CS at the Gothenburg Craniofacial Unit. The children were 7- to 16-years old and resided in the regions of Västra Götaland and Halland in Sweden during the time of data collection (October 2015 to June 2016).

Exclusion criteria were untreated CS, secondary CS due to other health conditions, language barriers, and protected identity.

Data were collected during a 3-hour visit to the hospital, during which the families met a psychologist for testing. The parents and children that agreed to participate in the study were asked to fill out separate informed consent forms. Age-adapted written consent forms were developed and included for older children and adolescents. Children completed a battery of psychological tests and a questionnaire during the visit, and parents completed proxy reports and questionnaires regarding their child. Data regarding surgical variables were extracted from the Gothenburg Craniofacial Registry.

Table 1. Measurements, participants, and CS type for each study.

Studies	Age (y)	CS type	Measured outcome
Study 1	7–16	Nonsyndromic	Intelligence Quotient
Study 2	7–16	SS/MS	Sustained attention and vigilance
Study 3	7–16	Nonsyndromic	Adaptive behavior skills
Study 4	7–16	Nonsyndromic	Health-related quality of life

3.1 PROCEDURES AND MEASURES

3.1.1 STUDY I

3.1.1.1.1 Procedure

The participants underwent testing (administered using a pen and paper) by a psychologist over the course of 60 to 80 minutes with a break included. During the test, the parents separately completed a questionnaire regarding background information.

Children that had undergone clinical testing within the previous 2 years participated by providing their records from the psychological assessments along with the completed test protocols. In those cases, children and parents were requested to answer additional questions regarding their background from home.

3.1.1.1.2 Measures

The WIS for Children 4th Edition (WISC-IV) was used to assess general cognitive function. The WISC-IV battery includes subtests for block design, similarities, digit span, picture concepts, coding, vocabulary, letter–number sequencing, matrix reasoning, comprehension, and symbol search (Table 2). The cognitive profile, including FSIQ, VCIQ, PRIQ, WMIQ, and PSIQ, was calculated for each patient according to the manual and using Swedish norms [4].

Table 2. Overview of the WISC-IV measures.

Indexes and WISC-IV subtests			
VC	**PR**	**WM**	**PS**
Similarities	Block design	Digit span	Coding
Vocabulary	Picture concepts	Letter–number sequencing	Symbol search
Comprehension	Matrix reasoning		

3.1.2 STUDY II

3.1.2.1.1 Procedure

All participants were given a computer-administered test with a psychologist present. The children received verbal instructions prior to testing, and the duration of the test was ~15 minutes. Information regarding IQ from Study I was added to background data.

3.1.2.1.2 Measures

The CPT-3 was used to assess sustained attention and vigilance. The test measures different aspects of attention (Table 3), with high scores indicating problems with attention, and low scores indicating good performance. American norms were used for the tests [73].

Table 3. Description of CPT-3 variables [73].

DIMENSION	SCORE	DESCRIPTION
Inattentiveness	Detectability (d')	Ability to discriminate targets from non-targets
	Omissions	Rate of missed targets
	Commissions	Rate of incorrect responses to non-targets
	HRT	Response speed
	HRT standard deviation	Response-speed consistency
	Variability	Variability of response-speed consistency
Impulsivity	HRT	Response speed
	Commissions	Rate of incorrect responses to non-targets
	Perseverations	Rate of anticipatory, repetitive, or random responses
Sustained attention	HRT block change	Change in response speed across blocks of trials
	Omissions by block	Missed targets by block
	Commissions by block	Incorrect responses to non-targets by block
Vigilance	HRT ISI change	Change in response speed at various ISI
	Omissions by ISI	Missed targets by ISI
	Commissions by ISI	Incorrect responses to non-targets by ISI

ISI, inter-stimulus interval. HRT, hit-reaction time.

3.1.3 STUDY III

3.1.3.1.1 Procedure

Parents were asked to complete a report regarding their child. Verbal instructions were provided by a psychologist, and the parents were able to ask for assistance if needed. The time required to complete the report was 15 to 30 minutes. Information regarding IQ from Study I was added to background data.

3.1.3.1.2 Measures

ABAS 2nd Edition (ABAS-II) was used to assess ABS. The report comprises nine subscales (communication, community use, functional academics, home/school living, health and safety, leisure, self-care, self-direction, and social) that measure conceptual, practical, and social aspects of ABS (Table 4). Swedish norms were used for the tests [9].

Table 4. Overview of ABAS-II measures.

Indexes and ABAS-II subscales		
Conceptual composite	**Social Composite**	**Practical composite**
Communication	Leisure	Community use
Functional academics	Social	Home/school living
Self-direction		Health and safety
		Self-care

3.1.4 STUDY IV

3.1.4.1.1 Procedure

Children and parents were asked to complete separate questionnaires, with the children assisted by a psychologist present throughout the administration. Parents received verbal instructions before completing the questionnaire. The time required to complete the questions was 7 to 10 minutes. Information regarding IQ from Study I and ABS in Study III were added to background data.

3.1.4.1.2 Measures

PedsQL 4.0 Generic Core Scales was used to assess HRQoL. The questionnaire comprises 23 questions that measure physical, emotional, social, and school functioning, with a psychosocial scale also capable of being calculated by summarizing the results of each of these functional outcomes (Table 5). Self- and proxy reports together with age-adapted versions are provided by the test. Swedish norms were used [18].

Table 5. Overview of Pediatric Quality of Life Inventory measures (PedsQL).

PedsQL subscales				
Physical	**Emotional**	**Social**	**School**	**Psychosocial**
8 items	5 items	5 items	5 items	Emotional+Social+School (15 items)

3.2 STATISTICAL ANALYSES

Table 6. Statistical analyses.

Overview of Statistical methods	Study I	Study II	Study III	Study IV
Descriptive analyses. Mean, SD, median, minimum; maximum or Q1; Q2 for continuous variables and numbers and % for categorical variables.	X	X	X	X
Statistical analyses between two groups				
Fisher's Exact test for analyses of dichotomous variables	X	X	X	X
Fisher's non-parametric permutation test for analyses of continuous variables	X	X	X	X
Mann–Whitney *U* test for analyses of non-normally distributed continuous variables			X	X
Mantel–Haenszel chi-squared test for analyses of ordered categorical variables	X	X	X	
Pearson's chi-squared test for analyses of non-ordered categorical variables	X	X	X	X
Analyses of covariance for adjustment of baseline covariates in comparisons of two groups	X	X	X	X
Mean difference with 95% confidence interval for all main results in comparisons of two groups	X	X	X	X
Effect size = mean difference / pooled SD in comparisons of two groups		X	X	X
Attrition analysis	X	X	X	X
Statistical analyses against norms				
Calculation of Z-scores for each value and analyze their significant difference from zero using Fisher's one-sample non-parametric permutation test. If significant, the population differs from the norm. Z-score = (measured value − mean norm / SD norm)	X	WSR	X	X
ES as compared with the norm group	X	X	X	X
Correlation analyses				
Pearson's correlation coefficient for correlation analyses		X		
Spearman's correlation coefficient for correlation analysis			X	X
Agreement between child and parent raters				
Distribution of differences between child and parent according to ES and standardized response mean				X
Fisher's non-parametric permutation test for paired observations for tests of systematic differences				X
P-values < 0.05 were considered significant. *Fisher's one-sample non-parametric permutation test is identical to Fisher's non-parametric permutation test for paired observations. WSR, Wilcoxon signed-rank test.				

3.3 ETHICAL CONSIDERATIONS

All of the studies were performed in accordance with the Declaration of Helsinki and reviewed and approved by the Regional Ethics Review Board of Western Sweden (no. 856-13).

Research involving patients requires the consideration of several ethical questions. One consideration concerned patient selection. The patients included in the studies had already undergone surgery several years prior and were not planned for further clinical follow-up. This might have facilitated agreement by patients and their parents to participate in the research.

Another concern involves the opportunity to participate. Patients living in Västra Götaland and Halland regions were included with the intention of reducing travel time to the hospital for the families and thereby increasing the opportunity to participate.

Patient age was also considered. School-age patients are able to understand information regarding the project and decide for themselves whether they wanted to participate along with their parents. Information about the project was provided in several steps, initially through a letter, followed by a phone call and finally at a hospital visit. The letter and verbal information were adapted to patient age. Written consent was also adapted according to age and obtained from both patients and parents.

Additionally, ethical issues regarding the use of psychological tests that might interfere with patient integrity were considered. Patients were able to access their results upon request, and parents were able to access their child's test results if the child gave permission. In some cases, patients and parents wanted to use the test results for a clinical psychological assessment. Although it is possible that patients/parents with this motive could have felt indirectly forced to participate, there also existed a direct benefit to the patient.

In general, parents were very positive concerning the information received about the project and willing to help through their participation. Parents expressed gratitude to the craniofacial team, and each family had their own story about their child's surgery that they wanted to share.

4 RESULTS

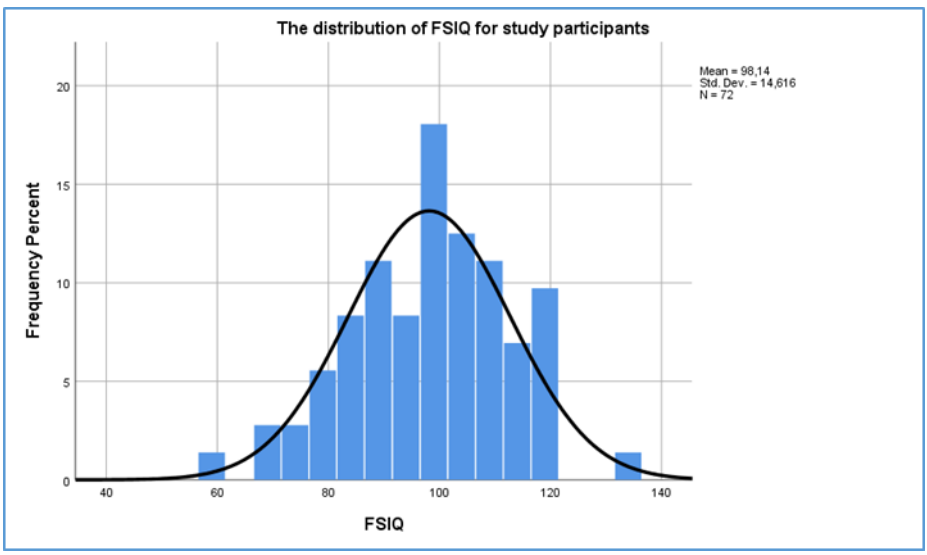
4.1 STUDY I: THE COGNITIVE PROFILE

4.1.1 PARTICIPANTS

Study I included 73 children treated for nonsyndromic CS, with SS (n = 41) and MS (n = 24) the most common CS types, although the cohort included patients with rare nonsyndromic synostoses (n = 8). The response rate was 80.2%, and no significant differences were found between responding and non-responding groups regarding sex, age at study, CS type, age at surgery, surgical method, or premature birth. Of the SS participants, 17 were operated with pi-plasty and 23 with spring-assisted surgery. One participant was treated by barrel-stave osteotomy.

Fourteen children had undergone psychological assessments prior to the study, and five participated by retrieved records from previous psychological assessment. Eight children with SS had a neuropsychological diagnosis (four with autism and four with attention-related problems). In the MS group, three children had diagnoses [two with combined autism and attention-deficit/hyperactivity disorder (ADHD) and one with an intellectual disability]. Age at study was significantly lower in the MS group and adjusted for prior to the between-group comparisons ($p \leq 0.0001$).

Figure 7. The distribution of FSIQ data from the study participants.

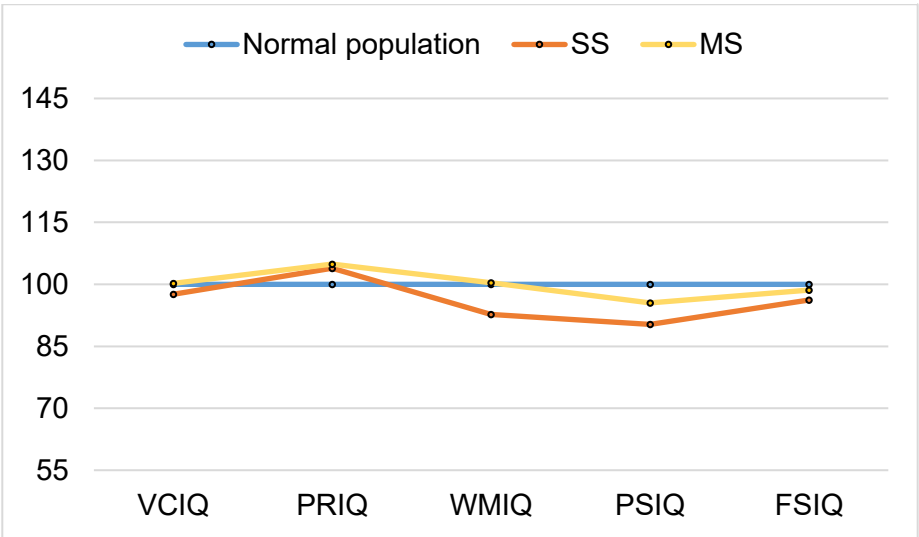


4.1.2 COGNITIVE PROFILES

FSIQ was average for both SS (96±13.1) and MS (100.6±16.5) groups, respectively. WMIQ (92.7±11.8) and PSIQ (90.3±12.9) were significantly lower [$p \leq 0.0001$, effect size (ES)=0.49; and $p \leq 0.0001$, ES=0.65], respectively] in the SS group relative to norms but with mean values within one standard deviation. Additionally, PRIQ (103.9±11.1) was significantly higher ($p = 0.032$, ES=0.26) in the SS group relative to the norms.

There were no statistical differences between the MS group and norms, and the MS group showed an even cognitive profile. Group comparison revealed that MS members exhibited a significantly higher WMIQ than SS members ($p = 0.043$) (Figure 8).

Figure 8. Cognitive profiles with mean values for the SS and MS groups relative to estimated mean values in the normal population.



4.1.3 THE IMPACT OF THE SURGICAL METHOD

The results showed that the surgical method (spring-assisted surgery or pi-plasty) employed for SS was unrelated to lower or higher cognitive outcomes.

4.2 STUDY II: SUSTAINED ATTENTION AND VIGILANCE

4.2.1 PARTICIPANTS

Study II included 61 children treated for SS (n = 38) or MS (n = 23). The response rate was 76.3%, and no differences were found between responding and non-responding groups regarding sex, age at study, CS type, age at surgery, surgical method, or premature birth.

All participants were tested within the context of this thesis. Five children had a known attention-related diagnosis, and one received medical treatment for the condition. The majority of the participants demonstrated general cognitive function within an average range, with this information extracted from Study I and used this study. The mean FSIQ for the SS and MS groups was 97.3±12.4 (range: 59–121) and 102.1±15.2 (range: 77–135), respectively.

The mean age at the time of the study was significantly lower (p = 0.019) in the MS group relative to the SS group and significantly correlated with the outcomes. This was adjusted for in between-group comparisons.

4.2.2 SUSTAINED ATTENTION AND VIGILANCE

The SS group exhibited significantly higher scores (lower performance) in most of the measured variables relative to the norms (p = 0.018). Additionally, five of the six variables measuring inattentiveness and two of the three variables measuring impulsivity and sustained attention were higher in the SS group relative to the norms. All variables measuring vigilance were higher, indicating poor performance as compared with the norms (Table 7).

Additionally, the MS group displayed significantly higher scores in several variables relative to the norms (p = 0.045). Specifically, there were indications of inattentiveness in four of the six variables, impulsivity in two of the three variables, deficient sustained attention in two of the three variables, and poor vigilance in two of the three variables (Table 7).

Between-group comparisons revealed one significant difference in hit-reaction time (HRT) as a measurement of the mean response speed of correct responses

throughout the test. Moreover, the MS group showed higher scores than the SS group (p = 0.049, ES=0.56) (Table 7).

Table 7. Overview of score comparisons regarding CPT-3 variables.

CPT-3 variables	SS group vs. norms	MS group vs. norms	SS vs. MS
Response style	p=0.0086 ES=0.25	*NS*	*NS*
Detectability	p≤0.001 ES=0.68	p=0.0047 ES=0.56	*NS*
Omissions	p=0.0004 ES=0.65	*NS*	*NS*
Commissions	p=0.0013 ES=0.43	p=0.014 ES=0.44	*NS*
Perseverations	p=0.0007 ES=0.89	p=0.012 ES=0.62	*NS*
HRT	*NS*	*NS*	p=0.049 ES=0.56
Hit reaction time SD	p=0.0077 ES=0.66	p=<0.001 ES=0.70	*NS*
Variability	p=0.018 ES=0.61	p=0.0038 ES=0.50	*NS*
HRT block change	*NS*	*NS*	*NS*
HRT ISI change	p=0.0012 ES=0.52	p=0.045 ES=0.38	*NS*

ISI, inter-stimulus interval; NS, not significant.

4.2.3 THE IMPACT OF THE SURGICAL METHOD

The results showed that the surgical method (spring-assisted surgery or pi-plasty) employed for SS was unrelated to lower or higher cognitive outcomes of sustained attention and vigilance.

4.2.4 CPT-3 AS A MEASURE

The results showed that perseveration (r = −0.26), HRT SD (r = −0.30), and variability (r = −0.30) were significantly correlated with FSIQ and VCIQ (p =

0.04), suggesting that higher scores for CPT-3 variables were associated with lower scores for the WISC-IV variables.

4.3 STUDY III: ABS

4.3.1 PARTICIPANTS

Study III included 73 children, 41 of whom had been treated for SS, 24 for MS, and eight for rare synostoses.

The response rate was 80.2%, and no significant differences were found between responding and non-responding groups regarding sex, age at study, CS type, age at surgery, surgical method, or premature birth.

Following extraction of information regarding IQ from Study I, the mean FSIQ was determined at 98.1±14.6 (range: 59–135). Additionally, there was a significant difference between the SS and MS groups regarding age at study and WMIQ ($p = 0.0088$ and $p = 0.010$, respectively), which was adjusted for in between-group comparisons.

4.3.2 ABS

The CS group showed significantly lower ABS ($p = 0.020$, ES=0.38) as measured by the full-scale scores (94.4±20.2) and relative to the norms. Additionally, the conceptual (93.9±20.1), social (93.4±19.6), and practical (94.6±19.8) composites were significantly lower as compared with the norms ($p = 0.011$, ES=0.41; $p = 0.0062$, ES=0.44; and $p = 0.024$, ES=0.36, respectively). All mean values were within one SD.

SS participants showed average ABS as measured by the full-scale scores (94.4±21.8) and relative to the norms. Only social composite was significantly lower ($p = 0.039$, ES=0.48) for this group (Figure 9).

MS participants showed significantly lower ABS ($p = 0.031$, ES=0.53) according to full-scale scores (92.0±16.7) and relative to the norms, with the conceptual (90.8±18.8) and social (91.7±17.4) composites the main contributors to the lower scores ($p = 0.021$, ES=0.61; and $p = 0.029$, ES=0.55). The mean values were within one SD (Figure 9).

No differences were found between the SS and MS groups in ABS outcomes (Figure 9). Moreover, the full-scale ABS scores significantly correlated with FSIQ ($r = 0.27$, $p = 0.022$), as higher scores for ABS were associated with higher IQ scores.

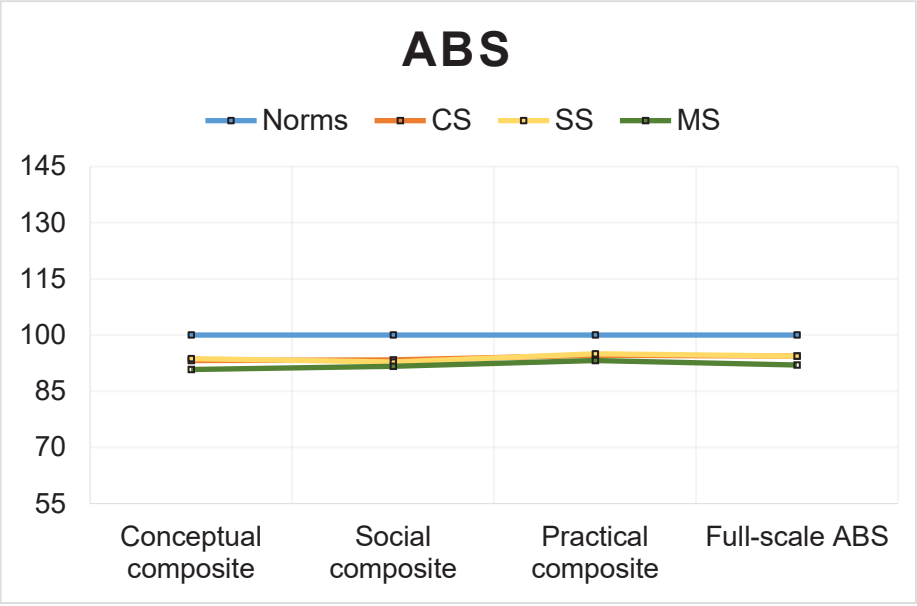


Figure 9. Profiles of ABS for norms, SS, and MS patients.

4.3.3 THE IMPACT OF THE SURGICAL METHOD

The results showed that the surgical method (spring-assisted surgery or piplasty) employed for SS was unrelated to lower or higher cognitive outcomes of ABS.

4.4 STUDY IV: HRQoL

4.4.1 PARTICIPANTS

Study IV included 73 children with SS (n = 41), MS (n = 24), or rare (n = 8) synostoses along with their parents. The response rate was 80.2%, and no significant differences were found between responding and nonresponding groups regarding sex, age at study, CS type, age at surgery, surgical method, or premature birth.

Following addition of IQ information from Study I and ABS from Study III to the background data, the means of FSIQ (98.1±14.6; range: 59–135) and full-scale ABS scores (94.4±20.2; range: 47–120) were average.

Age at study (p = 0.0088) and WMIQ (p = 0.010) differed significantly between the SS and MS groups and were, therefore, adjusted for in between-group comparisons.

4.4.2 HRQoL

No difference in estimated HRQoL scores according to full-scale measurements was found in the CS group relative to the norms; however, there were significant differences regarding school functioning (p = 0.0014, ES=0.51) and psychosocial function (p = 0.035, ES=0.33), for which the estimations were lower relative to the norms.

SS patients showed average overall HRQoL scores as compared with the norms, although school functioning (p = 0.0018, ES=0.68) and psychosocial function (p = 0.031, ES=0.45) were estimated as significantly lower.

MS patients showed average overall HRQoL scores according to full-scale measurements and detailed measurements using the subscales. No differences were observed in HRQoL outcomes between the SS and the MS groups (Table 8).

Table 8. Overview of comparisons of HRQoL scores.

PedsQL variables	CS vs. norms	SS group vs. norms	MS group vs. norms	SS vs. MS
Full-scale PedsQL	*NS*	*NS*	*NS*	*NS*
Physical function	*NS*	*NS*	*NS*	*NS*
Emotional function	*NS*	*NS*	*NS*	*NS*
Social function	*NS*	*NS*	*NS*	*NS*
School functioning	*p*=0.0014 ES=0.51	*p*=0.0018 ES=0.68	*NS*	*NS*
Psychosocial function	*p*=0.035 ES=0.33	*p*=0.031 ES=0.45	*NS*	*NS*

NS, not significant.

4.4.3 THE IMPACT OF THE SURGICAL METHOD

The results showed that the surgical method (spring-assisted surgery or pi-plasty) employed for SS was unrelated to lower or higher cognitive outcomes of HRQoL.

4.4.4 SELF- AND PROXY REPORTS

There were inconsistencies in the conformity of self- and proxy reports. Proxy reports by parents were significantly higher according to full-scale measurements ($p = 0.031$, ES=0.29), physical function ($p = 0.0022$, ES=0.43), and school functioning ($p = 0.012$, ES=0.33) as compared with self-reports by children. However, assessment of emotional function was consistent between estimations by parents and children.

4.4.5 ASSOCIATIONS BETWEEN COGNITIVE FUNCTION AND ABS

HRQoL as measured by the PedsQL (full-scale and subscales) significantly correlated with all ABS variables ($p = 0.022$, r = 0.28). Additionally, full-scale HRQoL measurements significantly correlated with FSIQ ($p = 0.0004$, r = 0.42).

5 DISCUSSION

5.1 STUDY I

Study I reported average cognitive function as measured by the WISC-IV. Specifically, the SS group showed significantly higher PR and lower WM and PS relative to the norms. Although some of the results differed significantly from norms, all scores were within one SD and could be interpreted as average within the frame of the test. This result agreed with those from previous studies reporting small differences and average cognitive levels [31, 32, 49, 64]. Additionally, previous studies reported that surgical method and timing affected cognitive outcomes in treated SS patients [34, 35, 74]. This difference was not confirmed by the present study, given that no difference was observed between spring-assisted surgery and pi-plasty relative to cognitive results.

MS is reportedly related to worse neuropsychological outcomes [37-39, 75]. We found average cognitive function throughout the four measured domains (VCIQ, PRIQ, WMIQ, and PSIQ); therefore, worse outcomes for MS patients could not be confirmed, which agreed with a review of single-suture CS that found no correlation between a specific suture synostosis and neuropsychological outcome [44].

Study I included patients that had been previously assessed for neuropsychological function. In the SS group, eight participants had been diagnosed with autism (n = 4) or attention-related problems (n = 4). Additionally, two patients in the MS group had been diagnosed with both autism and ADHD and one with intellectual disability. A recent study identified nonsyndromic CS as associated with an increased risk for psychiatric disorders [76]; however, the risk of a disorder might describe the frequency but not the level of impairment. The prevalence of autism is estimated at ~1%, and that for ADHD is ~7% [77-79]. In the study cohort, the frequency of autism and attention-related problems exceeded the estimate across the normal population; however, given the small sample size, it is difficult to draw conclusions.

The data in this study was not skewed and showed mean values of ~100±15, which is in line with the normal population. Previous studies have reported high mean values that occasionally exceeded +1 SD [34, 35, 54]. Additionally, in study I, 10 subtests were used to calculate the FSIQ. Abbreviated versions with fewer tests have commonly been reported in previous studies [31, 34, 35, 38, 43, 54, 58]. The risk of calculating an unreliable FSIQ by relying on only

a few tests was confirmed by the results presented here. This cohort returned lower scores for WMIQ and PSIQ, which are often omitted in abbreviated versions. Furthermore, our sample was equally distributed regarding sociodemographic variables, which contributed to minimizing the risk of a biased sample.

5.2 STUDY II

Study II assessed sustained attention, vigilance, inattentiveness, and impulsivity. The results revealed significantly lower performance in all measured areas of attention for both the SS and MS groups and relative to the norms. However, all scores were within one SD. Additionally, a difference was identified between groups regarding response speed, for which the MS group showed a lower performance. Previous studies assessing attention in CS patients reported that 17% of SS patients demonstrated selective and sustained attention deficits (33), although attention was assessed by tests mainly measuring WM and PS, and the frequency of attention-related problems was calculated in a very limited sample of 35 patients. Another study with a larger sample size assessed attention using a specific test and reported similar results as our study (*i.e.*, indications of impairments but with small differences and limited evidence of severe attention-related problems) [48].

Comparisons of the effect of surgery between spring-assisted and pi-plasty techniques in the SS group revealed no differences in attention-related outcomes. To the best of our knowledge, this is the first comparison of surgical methods according to the outcomes of attention-related function.

Furthermore, we compared patients with previously diagnosed attention-related problems with those that were no diagnosed. Although the groups had different sample sizes, the results revealed a tendency toward weaker performance regarding perseveration in the group of patients diagnosed with attention-related problems. These results indicated that this test could be helpful in discriminating impairments in patients with diagnosed attention-related problems.

This study included extensive background variables that likely minimized the risk of confounders and selection bias. The background data regarding IQ ensured that attention-related function was the primary measured outcome. Perseveration, response-speed consistency (HRT SD), and response-speed variability (variability) were significantly associated with FSIQ and verbal

comprehension, which confirmed the importance of controlling for IQ when assessing specific cognitive functions, such as attention.

5.3 STUDY III

Study III assessed ABS. Overall, the CS group showed lower scores (full-scale and conceptual, social, and practical composites) as compared with the norms. However, shortcomings were identified in both the SS and MS groups relative to the norms. Specifically, the SS group showed a lower social composite, and the MS group showed lower full-scale scores and conceptual and social composite results, although the lower scores were within the average range in all group comparisons.

Previous studies of psychological outcomes in CS populations mainly included cognitive tests or behavioral questionnaires; however, few studies used tests measuring ABS, and this is the first inclusion of both ABS and IQ in an assessment. In a thesis from 1998, the author included 31 participants and assessed ABS and IQ, finding results similar to those reported here and with small differences and scores within an average range [80].

Comparisons of surgical techniques used to treat SS (spring-assisted surgery vs. pi-plasty) revealed no associations with outcomes of ABS. Adaptive behavior has rarely been unexplored in nonsyndromic CS, and no study has evaluated its association with surgical methods. Adaptive behavior needs to be included in evaluations performed in future studies, given the important role it plays in assessing intellectual function [7, 12].

ABS were significantly correlated with IQ as measured by full-scale scores. This positive correlation indicates that higher ABS scores are related to higher IQ scores. Although the correlation was weak, this confirmed the necessity to assess both aspects in order to draw conclusions regarding cognitive function.

5.4 STUDY IV

Study IV evaluated the HRQoL of children treated for nonsyndromic CS. The results revealed that children estimated their HRQoL as generally high, with no differences found relative to norms. However, there were differences in estimated school functioning and psychosocial function, for which the CS and

SS groups showed significantly lower estimates as compared with the norms. Patients in the MS group estimated their HRQoL as good, with no differences from norms. Furthermore, no difference was found between the SS and MS groups regarding HRQoL.

Few studies have investigated HRQoL in CS patients. One study found that untreated SS patients scored low in regard to positive emotions, although the rest of the scores were within a normal range [51]. Another study found an increased risk of low HRQoL, with comparisons between cases and controls finding lower estimations regarding school functioning and social function [52]. The present results mostly agree with the findings of these studies; however, further investigation of the use of HRQoL is warranted in order to draw definitive conclusions.

Lower or higher outcomes of HRQoL could not be related to surgical method, given that comparison of SS participants treated with spring-assisted surgery or pi-plasty revealed no differences. Because this is the first study investigating associations between surgical method and HRQoL, comparisons with previous findings could not be performed. One difference between surgical methods is the scarring, which varies in size and location according to the surgery. Although this could represent a variable related to perceived HRQoL, this has not been measured or evaluated.

There was some consistency between self- and proxy reports, but there existed significant differences in the full-scale scores, physical function, and school functioning reported between children and parents, with children estimating lower HRQoL in these matters relative to the parents. These results confirmed the value of using both self- and proxy reports when assessing HRQoL.

HRQoL is commonly studied in pediatric research; however, it is rarely assessed in craniofacial patients. HRQoL measurements vary in the composition and number of questions, their reporting style, and the psychometric properties. The HRQoL measurement offered by PedsQL was translated and validated for use in Sweden following evaluation in a large group of Swedish school-age children [18, 19].

The results demonstrated that HRQoL was significantly related to IQ and ABS, which suggests the following two conclusions: 1) IQ and ABS affect HRQoL, which suggests the importance of determining what needs to be measured; and 2) PedsQL can be a useful screening tool for identifying patients in need of further psychological assessment.

5.5 STRENGTHS AND LIMITATIONS

Although previous studies addressed the neuropsychological function and HRQoL of treated nonsyndromic CS patients, the findings of this thesis contribute to the field through its methodological rigor. Attrition analysis was performed in each of the studies. Additionally, complex associations between neuropsychological function and confounders were determined through the use of extensive background data (*e.g.*, sociodemographic variables and medical and psychological histories). Moreover, evaluating the neuropsychological function of school-age children rather than infants and preschool-age children might have increased the quality and stability of the results. Assessments performed in children <6 years of age are less predictive of neuropsychological function in later life.

CS types are distinct, especially in terms of nonsyndromic versus syndromic patients. The rarity of CS has contributed to the use of mixed samples of patients (both nonsyndromic and syndromic) in previous studies. All studies in the present work included only nonsyndromic patients, which allowed comparisons according to CS type. Additionally, there was a high level of interest from families to contribute to this research, resulting in high response rates for all studies, which contributed to low selection bias.

The validity and psychometric quality of psychological tests used in craniofacial research have varied, and the interpretation of lower scores has often been considered a limitation of these studies. In the present work, the tests used in all of the studies had good psychometric properties and provided norm-referenced scores, the majority of which were based on Swedish norms. Lower scores were interpreted with regard to SDs and the extent of the difference. Given that many of the tests reported significant correlations, this suggests internal reliability and criterion validity, which supports the overall methodological quality.

The main limitations were the small sample sizes and lack of control groups, which make it difficult to draw reliable conclusions and generalize the results. Previous studies have reported similar challenges due to the rarity of CS. However, compared with previous studies, the use of attrition analyses and adjustment of confounding background variables strengthened the methodological quality of the present work.

6 CONCLUSION

1. Children operated for nonsyndromic CS exhibit average intellectual ability.

2. Children operated for nonsyndromic CS have average sustained attention and vigilance. Observed weaknesses in the SS and MS groups are likely of no clinical importance.

3. Children operated for nonsyndromic CS display average ABS with minor shortcomings and medium-to-large effect sizes.

4. Children operated for nonsyndromic CS report a generally high HRQoL, which correlated with IQ and ABS. This suggested that HRQoL measurement can be used to detect and identify craniofacial patients in need of extended psychological assessment.

5. Spring-assisted surgery and pi-plasty for correction of SS resulted in no variation in outcomes associated with IQ, attention, ABS, or HRQoL.

7 FUTURE PERSPECTIVES

During the first visit at our craniofacial clinic, many parents have questions regarding developmental issues, such as, “Is this going to affect my child later in life?” Hopefully, the findings from this thesis provide answers to some of these parental questions and worries.

Moreover, these findings emphasize the importance of long-term follow-up and screening for patients in need of further neuropsychological assessment. A common experience by parents is a lack of knowledge of craniofacial conditions in general healthcare. CS is a rare condition that is often previously unknown to the general population. Developmental screening performed under general healthcare conditions might be inadequate to address the needs of such patients, even in the event that such screening might detect patients with developmental delays. Offering follow-up and screening opportunities at the craniofacial clinic could improve the recognition of patients in need of not only of developmental evaluations but also those with other issues (*e.g.*, appearance-related questions).

Potentially persistent weaknesses in working memory and processing speed in CS patients might impact academic achievements. Further research in neighboring areas could evaluate specific functions, such as reading and writing skills, which could be assessed by clinical tests or through grades from school.

Another interesting area involves the genetics associated with CS. There are several known genetic variants related to CS, and genetic variants associated with neuropsychological impairment have recently been identified. Linking genetic variations between CS and neuropsychological function would increase the understanding of possible neurodevelopmental risks in CS patients.

ACKNOWLEDGMENTS

Fifteen years ago, I told myself to never write a thesis. I should have learned never to say never. There are a few random occurrences and several people that helped make this happen.

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