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Complete List of Authors:	Tio, Pauline; Erasmus MC University Medical Center Rotterdam, Department of Plastic and Reconstructive Surgery van Staalduinen, Merel; Erasmus MC Sophia, Department of Child and Adolescent Psychiatry/Psychology Okkerse, Jolanda; Erasmus MC Sophia, Department of Child and Adolescent Psychiatry/Psychology Dulfer, K.; Erasmus MC Sophia, Department of Neonatal & Pediatric Intensive Care; Erasmus MC Sophia, Department of Child and Adolescent Psychiatry/Psychology Erler, Nicole; Erasmus MC University Medical Center Rotterdam, Department of Biostatistics; Erasmus MC University Medical Center Rotterdam, Department of Epidemiology Loudon, Sjoukje; Erasmus MC University Medical Center Rotterdam, Department of Ophthalmology Telleman, Marieke; Erasmus MC University Medical Center Rotterdam, Department of Ophthalmology Abdel-Alim, Tareq; Erasmus MC University Medical Center Rotterdam, Department of Neurosurgery; Erasmus MC University Medical Center Rotterdam, Department of Radiology and Nuclear Medicine Roshchupkin, Gennady; Erasmus MC University Medical Center Rotterdam, Department of Radiology and Nuclear Medicine; Erasmus MC University Medical Center Rotterdam, Department of Epidemiology Heemskerk, Stella; Erasmus MC University Medical Center Rotterdam, Department of Public Health Polinder, Suzanne; Erasmus MC University Medical Center Rotterdam, Department of Public Health van Veelen, Marie-Lise; Erasmus MC University Medical Center Rotterdam, Department of Neurosurgery; Erasmus MC Sophia, Child Brain Center Bannink, Natalja; Franciscus Gasthuis en Vlietland, Department of Pediatrics van Driel, Arianne; IJsselland Ziekenhuis, Department of Pediatrics Faasse, Mariët; Dutch Patient and Parent Society for Craniofacial Conditions Ista, Erwin; Erasmus MC Sophia, Department of Neonatal and Pediatric Intensive Care Joosten, K; Erasmus MC Sophia, Department of Neonatal and Pediatric Intensive Care

	Spoor, Jochem; Erasmus MC University Medical Center Rotterdam, Department of Neurosurgery Weissbach, Elin; Erasmus MC University Medical Center Rotterdam, Department of Plastic and Reconstructive Surgery Kats, Jacoba; Erasmus MC University Medical Center Rotterdam, Department of Plastic and Reconstructive Surgery Versnel, Sarah; Erasmus MC University Medical Center Rotterdam, Department of Plastic and Reconstructive Surgery Pleumeekers, Mieke; Erasmus MC University Medical Center Rotterdam, Department of Plastic and Reconstructive Surgery Mathijssen, Irene; Erasmus MC University Medical Center Rotterdam, Department of Plastic and Reconstructive Surgery
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Comparing (Cost-)Effectiveness of Conservative Policy to Craniofacial Surgery in Children with Metopic Synostosis: Protocol for an Observational Cohort Study on Clinical Outcomes, Psychosocial Wellbeing, and Costs

AUTHORS

P.A.E. Tio[1], M.J.A. van Staalduinen[2], J.M.E. Okkerse[2], K. Dulfer[2,13], N.S. Erler[3,7], S.E. Loudon[4], M.A.J. Telleman[4], T. Abdel-Alim[5, 6], G. Roshchupkin[6, 7], S.C.M. Heemskerk[8], S. Polinder[8], M.L.C. van Veelen[5,9], N. Bannink[10], A.H.M. van Driel[11], M. Faasse[12], E. Ista[13], K.F.M. Joosten[13], J. Spoor[5], E. Weissbach[1], J. Kats[1], S.L. Versnel[1], M.M. Pleumeekers[1], I.M.J. Mathijssen[1]

INSTITUTIONAL AFFILIATIONS

1. Department of Plastic and Reconstructive Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands.
2. Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands.
3. Department of Biostatistics, Erasmus University Medical Center, Rotterdam, The Netherlands.
4. Department of Ophthalmology, Erasmus University Medical Center, Rotterdam, The Netherlands.
5. Department of Neurosurgery, Erasmus University Medical Center, Rotterdam, The Netherlands.
6. Department of Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands.
7. Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands
8. Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands.
9. Child Brain Center, Erasmus University Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands.
10. Department of Pediatrics, Franciscus Gasthuis and Vlietland, Rotterdam and Schiedam, The Netherlands
11. Department of Pediatrics, IJsselland Ziekenhuis, Capelle aan den IJssel, The Netherlands
12. Dutch Patient and Parent Society for Craniofacial Conditions (LAPOSA), The Netherlands
13. Department of Neonatal and Pediatric Intensive Care, Division of Pediatric intensive Care, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands.

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CORRESPONDING AUTHOR

P.A.E. Tio, Department of Plastic and Reconstructive Surgery, Erasmus University Medical Center, Sophia's Children's Hospital Rotterdam, Doctor Molewaterplein 40, 3015 GD Rotterdam, The Netherlands; email: p.tio@erasmusmc.nl

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ABSTRACT

Introduction

Traditionally, surgical intervention has been the standard treatment for children with metopic synostosis, assuming that it reduces the risk of raised intracranial pressure, thereby preventing vision and cognitive impairment, and also restores the abnormal head shape. However, recent research suggests a sporadic occurrence of raised intracranial pressure in patients with metopic synostosis. In addition, following surgery, an overall tendency to have worse cognitive and behavioral outcomes, and more refractive errors compared to healthy peers is observed. Research on conservative (nonsurgical) treatment in metopic synostosis is limited and lacks a comparative design. The purpose of this study is to compare the (cost-)effectiveness of conservative and surgical treatment in patients with metopic synostosis.

Methods and analysis

This is the protocol for an observational cohort study with a duration of 8 years. A total of 450 patients with metopic synostosis will be included. The primary outcome is head growth as predictor for increased intracranial pressure. Non-inferiority with regard to head growth from 0-8 years (yearly difference in standard deviation) is determined using a linear mixed model adjusted for potential confounders. Secondary outcomes include papilledema, orthoptic outcomes, forehead shape, cognitive, behavioral, and psychological outcomes, and societal costs. A cost-effectiveness analysis will be performed.

Ethics and dissemination

The study has been reviewed and approved by the Medical Research Ethics Committee of the Erasmus MC, University Medical Centre Rotterdam (MEC-2022-0142). Written informed consent will be obtained from both parents of each participant. The results will be disseminated by publication in international peer-reviewed journals.

Trial registration

ClinicalTrials.gov NCT06069479

Keywords

Trigonocephaly, craniosynostosis, cohort studies, cost-benefit analysis, intracranial pressure, cognition

ARTICLE SUMMARY

Strengths and limitations of this study

1. This study will be the largest prospective cohort of patients with metopic synostosis.
2. This is the first study that compares the (cost-)effectiveness of different treatment policies in patients with metopic synostosis.
3. This large cohort will provide information on clinical outcomes, psychosocial wellbeing, and costs.
4. Because randomization of the type of treatment is not accepted by parents, an observational cohort study was chosen instead of a randomized trial.

INTRODUCTION

Premature closure of the metopic suture, also known as trigonocephaly or metopic synostosis, is the second most common type of craniosynostosis (1, 2). The head shape in these patients is characterized by a wedge-shaped forehead, hypotelorism, temporal retrusion, and biparietal widening (2, 3). In contrast to other sutures of the calvaria, the fusion of the metopic suture early in life is a normal developmental process, with physiological closure occurring before 9 months of age (4-6).

Traditionally, craniofacial surgery has been the standard treatment for these children, assuming that it reduces the risk of raised intracranial pressure, thereby preventing vision and cognitive impairment, and also restoring the abnormal head shape. There are two main options for surgical interventions, namely fronto-orbital advancement and endoscopic-strip craniectomy followed by helmet therapy. Recent research suggests that raised intracranial pressure occurs sporadically in these patients (7, 8). Predictors for raised intracranial pressure include a decline in head growth and the presence of papilledema at fundoscopy, which are described in 9% and 1.8% of surgically treated non-syndromic metopic synostosis patients, respectively (7). Although the second aim of surgery is to correct the abnormal head shape, a common long-term outcome observed after surgery is the recurrence of forehead deformities, occasionally resulting in a second surgical procedure (8-10).

Patients with metopic synostosis have a higher risk of ophthalmologic, cognitive, and behavioral problems. A higher prevalence of refractive errors is seen in patients with metopic synostosis compared to healthy controls (11-13). Patients with metopic synostosis experience hyperopia and astigmatism at rates of 22% and 23%, respectively, versus 8% and 4% in the age-matched norm population, which can contribute to headaches in these patients (13). Following surgery, patients with metopic synostosis score worse compared to healthy peers on several domains of cognitive and behavioral functioning (14-19).

There are certain risks accompanying craniofacial surgery in these young patients. Complications occur sporadically but they do occur, and include dural tears and wound infections (8-10). In addition, a blood transfusion is imperative in these patients when performing a fronto-orbital advancement. The coronal incision necessary with a fronto-orbital advancement results in a large scar for the child. Surgery is a stressful event not only for the child but also for the family and projects a significant amount of stress on the whole family (20). Caregivers of whom the child is planned for a surgical procedure can experience emotional distress and anxiety, which influences the child's development (21-24).

In recent years, the indication for craniofacial surgery in patients with metopic synostosis, particularly those with mild to moderate severity, has become a subject of debate (25). Conservative (nonsurgical) management, involving regular follow-up appointments without surgical intervention, has gained interest due to the sporadic occurrence of signs indicating raised intracranial pressure. In a small group of patients that did not undergo surgery (n=40), none of these patients required surgical intervention for increased intracranial pressure during their follow-up (8). None of the existing literature has investigated the development of head shape overtime in conservatively treated patients with metopic synostosis. It is hypothesized that a conservative policy allows for natural improvement of the abnormal head shape over time, however the extent of the self-correction remains unknown (26). Conservative treatment could probably also remove the additional stress on the child and the family and the risk of complications associated with craniofacial surgery. While literature concerning cognitive outcomes in conservatively treated patients with metopic synostosis is limited and heterogeneous, there is a

tendency for patients without surgical intervention to score slightly below average or exhibit a higher prevalence of concerns when compared to healthy controls (14, 17, 27, 28). No research has been conducted in a large sample that directly compares cognitive and behavioral functioning between patients with metopic synostosis treated conservatively and those treated surgically.

Over the course of the past six years at Erasmus Sophia Children's Hospital (Rotterdam, The Netherlands), approximately two-thirds (142/216) of parents of patients with metopic synostosis chose conservative treatment, while the remaining one-third opted for surgical treatment. None of the conservatively treated patients developed signs of increased intracranial pressure nor required craniofacial surgery. The choice of conservative treatment extends beyond its clinical consequences, influencing financial expenses associated with the management of patients with craniosynostosis. Although studies in the field of craniosynostosis have compared costs and established the cost-effectiveness of various surgical techniques (29-31), an evident gap exists in the literature concerning cost-effectiveness analyses comparing conservative and surgical treatments, particularly in patients with metopic synostosis.

Taking into account the sporadic occurrence of increased intracranial pressure and the overall tendency to have worse cognitive, behavioral, and ophthalmologic outcomes even after surgery, the functional indication for surgical intervention for patients with metopic synostosis seems uncertain. In the existing literature, all outcomes following conservative treatment for patients with metopic synostosis are hard to determine due to small sample sizes, relatively short duration of follow-up, and mild characteristics in the majority of the conservatively treated patients (14, 26-28, 32). Therefore, a prospective cohort study with adequate follow-up is needed to determine if a conservative policy is as effective as surgical intervention. We present the study protocol for an observational cohort study on the (cost-)effectiveness of a conservative policy compared to craniofacial surgery in metopic synostosis. This study presents a unique opportunity to assess differences in outcomes between conservatively and surgically treated patients with metopic synostosis in domains including intracranial pressure, vision, cognitive and behavioral functioning, impact on family and child, aesthetic outcomes, and societal costs.

METHODS

Patient involvement

The Dutch Patient and Parent Society for Craniofacial Conditions (LAPOSA) is a partner in the proposal and was involved in the design of the study. LAPOSA will also be involved in the dissemination of the results.

Study design

Based on discussions with the patient society LAPOSA, an observational cohort design was chosen as study design instead of a randomized trial, because randomization of the type of treatment is not accepted by parents.

Setting

In the Netherlands, treatment for craniosynostosis is fully reimbursed by the National Health Insurance program. The care for patients with craniosynostosis is centralized in the Netherlands in two centers,

with Erasmus Sophia Children's Hospital treating over 80% of the Dutch population. This study is taking place at Erasmus Sophia Children's Hospital. To evaluate the feasibility of transitioning a portion of follow-up care to non-specialized centers, follow-up appointments at the ages of 5 and 7 years are conducted in non-specialized hospitals (Franciscus Gasthuis and Vlietland, Rotterdam and Schiedam, The Netherlands and IJsselland Ziekenhuis, Capelle aan den IJssel, The Netherlands).

Eligibility criteria

Patients diagnosed with metopic synostosis at Erasmus Sophia Children's Hospital will be recruited in the clinic. Eligible patients are up to 3 years of age and are diagnosed with either non-syndromic or syndromic metopic synostosis. These patients will be offered the opportunity to participate in the study by their clinician. Patients are excluded if they present with a metopic ridge only.

Interventions

The study protocol aligns with our current clinical protocol up until the age of 8 years, except for additional questionnaires. At our center, as of 2017, treatment decisions are made through a shared decision-making process in which parents can choose between two treatment options: conservative treatment or surgical treatment. Conservative treatment involves a nonsurgical approach with yearly routine follow-up appointments. The choice of the type of surgical treatment depends on the age at presentation and parental preferences, with two options available: fronto-orbital advancement and endoscopic-strip craniectomy with helmet therapy. If parents opt for a conservative policy, surgery is only performed if raised intracranial pressure occurs.

All patients with metopic synostosis receive identical follow-up care, irrespective of whether they undergo surgical or conservative treatment. This entails yearly hospital visits until the age of 8 years, followed by subsequent visits every 3 years until the age of 18 when craniofacial growth is considered to have reached its final stage. Head growth is measured every visit and fundoscopy is performed annually up to the age of 4 years. Assessment of refractive errors occurs at 1, 4, and 8 years of age. Psychological screening is routinely offered between the ages of 2 to 8 years. 2D- and 3D-imaging is performed every other year at the ages of 0, 2, 4, 6, and 8 years.

Outcomes

Clinical outcomes

Table 1 provides a visual overview of the clinical outcomes. When available, supplementary retrospective patient data will be collected in addition to prospective data.

Table 1. Clinical outcomes

CLINICAL OUTCOMES	0 Y	1Y	2 Y	3 Y	4 Y	5 Y	6 Y	7Y	8 Y
HEAD CIRCUMFERENCE	X	X	X	X	X	X	X	X	X
PAPILLEDEMA		X	X	X	X	*	*	*	*
ORTHOPTIC OUTCOMES		X			X				X
FOREHEAD SHAPE	X		X		X		X		X

*only if a decline in head circumference occurs or the child experiences headaches.

Head circumference

The primary outcome is the change in head circumference, as head growth decline is an indicator for raised intracranial pressure. Head circumference is repeatedly measured every year from age 0-8 years. Measurements are performed manually with a measuring tape by skilled clinicians. Head circumference is defined in cm and corresponding standard deviation based on national normative values. A decline in head circumference of more than 0.5 SD is considered clinically relevant.

Papilledema

Fundoscopies are performed annually by a pediatric ophthalmologist in children up to the age of 4 years to detect the presence (or absence) of papilledema, as an indicator for raised intracranial pressure.

Orthoptic outcomes

A full orthoptic examination is performed at the age of 1, 4 and 8 years by a pediatric orthoptist. The examination provides data on the refractive error (myopia, hyperopia, astigmatism), visual acuity, strabismus and amblyopia. Visual acuity scores are converted to logMAR; hyperopia, myopia, and astigmatism are measured in diopters; presence of strabismus is measured in degrees; amblyopia is assessed as present or absent.

Forehead shape

Forehead shape is assessed at the ages of 0, 2, 4, 6, and 8 years using 2D and 3D photogrammetry and a visual analogue scale (VAS) score determined by the parents. Within the ERN CRANIO, a core outcome set for metopic synostosis has been developed, based on 2D photos (33). Serial 2D and 3D photos during follow-up will illustrate and quantify the growth pattern of the forehead over time. Comparison of the objective data (2D and 3D photos) with the subjective data (VAS score) will show how realistic parents experience their child's forehead shape.

Cognitive, behavioral and psychological instruments

Table 2 offers an overview of the cognitive, behavioral and psychological instruments. For a more detailed description of all psychometric properties, see Supplement A. Questionnaires will be sent through email at pre-specified times and completed online using GemsTracker.

Table 2. Cognitive, behavioral and psychological instruments

ASSESSMENT/QUESTIONNAIRE	0 Y	2 Y	4 Y	8 Y
DEVELOPMENT & COGNITION				
ASQ-4	x			
BSID-III-NL		x[a]		
WPPSI-IV-NL			x[a]	
WISC-V-NL				x[a]
SCHOOL PERFORMANCE (CITO)			x[b]	x[b]
EMOTION, BEHAVIOR & PSYCHOSOCIAL				
SDQ		x	x	x
POSTTRAUMATIC STRESS				

KJTS	x	x	x	x
PCL-5	x	x	x	x
IMPACT ON FAMILY & CHILD				
INTERVIEW	x	x	x	x
OBVL	x	x	x	x
CBSK				x[c]
DECISIONAL CONFLICT SCALE	x			
DECISIONAL REGRET SCALE				x
PEDSQL		x	x	x[d]
EQ-5D-Y-5L	x	x	x	x

[a] assessments by psychologist; [b] school reports provided by parents; [c] child-reported questionnaire; [d] both parent- and child-reported questionnaire

ASQ: Ages and Stages Questionnaire; BSID: Bayley Scales of Infant and Toddler Development; WPPSI: Wechsler Preschool and Primary Scale of Intelligence; WISC: Wechsler Intelligence Scale for Children; SDQ: Strength and Difficulties Questionnaire; KJTS: Kinder- en Jeugd Trauma Screener; PCL-5: posttraumatic stress disorder checklist for DSM-5; OBVL: Opvoedingsbelasting vragenlijst; CBSK: Competentiebelevingsschaal voor kinderen; PedsQL: Pediatric Quality of Life Inventory; EQ-5D-5L-Y: EuroQol five dimensions health questionnaire youth

Development & cognition

The cognitive and behavioral development of the children is evaluated at different ages using the following modalities:

At the age of 0 years old, the Ages and Stages Questionnaire-4 (ASQ-4), a parent-reported computerized adaptive testing questionnaire for children aged 0-6 years which is adapted from the ASQ-3, is used to screen the child's development (34). At the age of 2, 4 and 8-years, respectively the Bayley Scales of Infant and Toddler Development (BSID-III-NL), Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV-NL) and Wechsler Intelligence Scale for Children (WISC-V-NL) are assessed by a psychologist. The BSID-III-NL is validated for children between the age of 2 weeks to 3.5 years and is widely used to assess neurodevelopment (35). The WPPSI-IV-NL is an intelligence test that is validated for children between the ages of 2 years and 6 months and 6 years and 11 months (36). The WISC-V-NL is an intelligence test that is validated for children between the ages of 6 years and 16 years and 11 months (37). At the age of 4- and 8-years old, school performance is assessed with the nationwide Centraal Instituut voor Toetsontwikkeling (CITO) score to determine performance in elementary school (38). The CITO scores are provided by parents.

Emotional, behavioral and psychosocial functioning

The Strength and Difficulties Questionnaire (SDQ) is a brief behavioral screening questionnaire (39). The parent-reported version of the SDQ will be sent to parents when their child is 2, 4, and 8 years. The Self-perception Profile for Children (*Dutch*: Competentiebelevingsschaal voor kinderen (CBSK)) is a child-reported questionnaire validated for children between the age of 8 and 12 years, which is focused on how children perceive their own capabilities (40). The questionnaire is filled in by the child at the age of 8 years old.

Posttraumatic stress

The Kinder- en Jeugd Trauma Screener (KJTS) is used to screen for posttraumatic stress disorder (PTSD) in the child (41). KJTS is the Dutch validated version of the Child and Adolescent Trauma Screen (CATS). The parent-report version is completed by the parents when their child is 0, 2, 4, and 8 years old. The Dutch PTSD Checklist for DSM-5 (PCL-5) is a self-reported questionnaire used to screen for posttraumatic stress disorder in adults (42). The PCL-5 is sent to the parents when their child is 0, 2, 4, and 8 years old.

Impact on family and child

Multiple questionnaires are used to measure the impact on the family and the child. The Parenting Stress Questionnaire (*Dutch*: Opvoedingsbelasting vragenlijst (OBVL)) is a questionnaire focused on child-parent relationship and parenting stress (43). The OBVL is sent to parents when their child is 0, 2, 4, and 8 years old. The Dutch Decisional conflict scale (DCS) measures parental perceptions of uncertainty in choosing options and effective decision making (44, 45). The DCS is sent to parents after the treatment decision with a window of 8 weeks. The Decisional Regret Scale (DRS) is distributed to parents when the child is 8 years old to measure distress or remorse after the treatment decision (46, 47). The Pediatric Quality of Life Inventory (PedsQL) is a questionnaire measuring the health-related quality of life in children (48). The parent proxy-report form is sent to parents at the age of 2, 4, and 8 years old and the child proxy-report to the child at the age of 8 years old. The EuroQol Five Dimensions Health Questionnaire Youth (EQ-5D-Y-5L) measure the quality of life of children validated from 4 to 15 years (49). The parent-reported version is sent to parents when the child is 0, 2, 4, and 8 years old. Semi-structured interviews with both parents separate are performed when their child is 0, 2, 4 and 8 years old, discussing the following aspects: parental concerns, parental stress indicators, traumatic experiences, hospital experience, relevant family factors, relation between parents and child, impact of disease on the child and family, and decision making process.

Resource use and costs

All related societal costs will be taken into account, including costs related to healthcare resource use and loss of productivity for the parents for sick leave. This will allow for a comparison of the costs for both types of treatment. Healthcare resource use is extracted from the medical system and in addition the validated parent-reported iMTA Medical Consumption Questionnaire (iMCQ) will be used to measure healthcare consumption (i.e. medical specialist care, hospitalization, and extramural healthcare consumption) and other costs directly associated with the treatment. Productivity losses are assessed by the iMTA Productivity Costs Questionnaire (iPCQ). Costs will be calculated by multiplication of healthcare consumption volumes by the cost prices per resource unit. Cost prices for healthcare resources use will be primarily derived from the Dutch manual on costing research (50). Cost prices of surgery will be determined by bottom-up micro-costing method. Productivity costs will be assessed using the friction cost method (51).

Power & sample size considerations

Due to the minimal extra time required from participants and parents, the inclusion rate is expected to be high and the loss to follow-up is expected to be low. Annually, around 50 new patients with metopic synostosis are referred to our center, with an anticipated consent rate of 90% among parents, demonstrating their recognition of this observational study's significance and their willingness to participate. In addition, within the first study year children aged 1-3 years old will be included for follow-

up with sufficient available retrospective data. Because at Erasmus Sophia Children's Hospital, standard care for patients with metopic synostosis includes follow-up until the age of 18 years, drop-out rates are expected to be low. Inclusion will add up to 450 patients total.

A power calculation for the primary endpoint was performed using simulation. To obtain parameters for the simulation, a linear mixed model for age-adjusted standard deviation scores (SD) of head circumference was fitted on existing data of children who underwent surgery. The model included a random intercept and (linear) slope for the child's age at the time of the measurement to account for correlation between repeated measurements of the same child and to allow for child-specific trajectories. To take into account the non-linear shape of the children's SD over time, a natural cubic spline with four degrees of freedom for age at the time of measurement was used in the fixed effects. The parameters from this model formed the assumption for the surgery arm in the power analysis simulation. For the conservative treatment arm, we assumed the SD at baseline follows the same distribution as in the surgery arm, but assumed linearly decreasing SD values over time. The rate of SD decrease in the conservative arm was increased over different simulation scenarios to find the most extreme scenario for which non-inferiority of the conservative arm could be shown with sufficient power.

Each simulated data set contained 245 and 195 children in the conservative and surgery arm, respectively. The number of available observations at each measurement time decreased with increasing age, taking into account the sequential inclusion of children throughout the study period (and resulting differences in length of follow-up). The differences in SD scores between subsequent measurements were calculated and modelled using a random-intercept linear mixed model that had the treatment arm as only fixed effect. The resulting parameter estimate for the treatment arm describes the difference in the yearly decline of SD score in the conservative arm compared to the surgery arm. Non-inferiority was defined as the lower bound of the 95% confidence interval of the treatment effect estimate being larger than -0.5 SD.

Assuming an average yearly decline in head-circumference SD score of -0.25 in the conservative arm resulted in 90% power to demonstrate non-inferiority of the conservative arm at a 2.5% one-sided significance, with a non-inferiority margin of -0.5 yearly SD difference.

Patient recruitment and timeline

Patients are informed by their clinician about the ongoing research and are offered the opportunity to participate in the study. Upon expressing interest, parents will be approached by an independent researcher who will provide them with detailed information about the study. Interested parents will be asked to sign the consent form indicating their willingness to participate with their child. For all parents who decline participations or withdraw from the study, their reasoning for making this decision will be documented.

Enrollment of participants and their parents has started in September 2022. The study follow-up period will extend until either participants reach the age of 8 years or until the end of the inclusion period (September 2030), whichever comes first. Currently, there are 90 participants included in this study (September 2024).

Data collection & management

Data will be handled confidentially and anonymously. After receiving the signed consent form from the parents, every participant receives a unique study number that is used to link the data to the child. The coordinating researcher safeguards the key to the code.

All data from the questionnaires will be collected with GemsTracker, a software package for the distribution of digital questionnaires. Parents of patients receive emails at appropriate times with a secured link to GemsTracker's website to answer questionnaires digitally. Both the emails as well as reminders, if questionnaires remain incomplete, are sent automatically with a maximum of 2 reminders. All data from clinical follow-up will be collected from the medical records. The coordinating researcher will regularly monitor whether all data are registered timely and properly. The combined data from both GemsTracker and the medical records are collected in Castor, a secured database. Daily back-ups are made automatically. Storage of personal data will be in line with the Dutch General Data Protection Regulation. Data access control will be in the hands of the principal investigator. Research data will be preserved for 10 years, according to national law.

Statistical methods

Primary outcome

The primary outcome measurement of the head circumference is transformed to an age- and sex-specific standard deviation score, according to national norms. The yearly decline in head growth is chosen as the primary outcome since this continuous measure has more power, allowing us to adjust for possible confounders. This would not be possible when using binary outcomes with low prevalence (e.g. presence/absence of papilledema at fundoscopy). Non-inferiority with regard to head growth from 0-8 years (yearly difference in SD score) is determined using a linear mixed model adjusted for potential confounders (including severity of phenotype, sex, syndrome, and parental factors) and comparing the lower bound of the 95% confidence interval of the treatment effect estimate (conservative vs surgery) to the non-inferiority margin of -0.5 SD.

Secondary outcomes

The presence or absence of papilledema on fundoscopy is analyzed with a repeated measures logistic regression to compare difference between the two groups. Prevalence of orthoptic anomalies is compared between the two groups and compared with the norm data, using Chi-Square test. If the number of cases allows for estimating parameters, a logistic regression model is used, otherwise the outcomes are stratified by treatment arms. Pearson's correlation coefficients are calculated to determine a correlation between the VAS and the 2D photo grading and the VAS and the 3D photo grading per time point. For all validated instruments norm values are available, including cut-off levels. Comparison will be made for the outcomes of the instruments between the two treatment groups and with the norm data. For some of the above mentioned variables, different instruments are used at various time points to measure a single construct. In this case, the (ordinal) scores obtained from the instruments will be compared between the two groups at each time point using an independent-sample t-test. In case of repeated measures of a construct using the same instrument, we will use mixed-model analysis to compare the change of the given outcome over time between the two groups. In the case of multiple analyses that target the same research question, multiple testing correction will be applied. We will control the type-I error rate using Bonferroni correction. As far as possible, missing data will be imputed and the number of patients used for analysis at each stage of the study shall be reported.

Economic evaluation

An economic evaluation will be conducted from a societal perspective in accordance with the Dutch guidelines for economic evaluations in healthcare, in which healthcare costs, patient and family costs, and costs outside of the healthcare sector (i.e. productivity costs of the parents related to paid work absenteeism) will be considered (51). The time horizon is 8 years to include all relevant costs and effects. The primary outcome (i.e. head circumference) will be used as effect measure in the cost-effectiveness analysis. The incremental cost effectiveness ratio of surgery versus conservative treatment will be expressed as costs per case of decline in head circumference > 0.5 SD.

Data monitoring

In accordance with Erasmus MC guidelines, the conduct of the study will be monitored. Monitoring will be done by an independent resident or PhD candidate of the Plastic and Reconstructive Surgery Department of the Erasmus MC. Monitoring is performed yearly and includes the following: inclusion and dropout rates, informed consent, protocol compliance, and reporting of severe adverse events.

The intervention is not experimental but rather standard of care and is not expected to have a significant risk of potential harm to the patients, therefore there will be no data monitoring committee.

All adverse events reported spontaneously by the parent of the participant or observed by the investigator or the staff will be recorded and followed. Interim analysis is done for head growth in 2025 to verify that the prevalence of raised intracranial pressure is within the expected range, and continuation of the study is justified.

ETHICS AND DISSEMINATION

This study complies with the Declaration of Helsinki and is reviewed and approved by the MREC of the Erasmus MC, University Medical Center Rotterdam (MEC-2022-0142). This is a non-WMO study, which is an observational study in which no action or behavior is imposed on the participants in the study. All amendments will be notified to the MREC. This research adheres to the Code of Conduct for Health Research and Medical Treatment Contracts Act.

Written informed consent is obtained from both parents by the coordinating researcher. This is done sufficient time after study information was shared, and after answering any questions of the parents to satisfaction. The informed consent form also indicates how participant data is stored, shared, and used.

No provisions about ancillary and post-trial care are in place as the Dutch healthcare system ensures all participants get the care they need through health insurance. In accordance with Dutch law, Erasmus MC has a liability insurance and a human subject insurance which provides cover for damage to research subjects.

The results of this study will be published in international peer-reviewed journals and presented at international conferences. Parents and patients will be informed about any publication accompanied by a brief summary in Dutch. The published outcomes of this study will be implemented into clinical practice and the Dutch guideline for craniosynostosis will be updated accordingly.

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Patient consent for publication: not required. This is a study protocol.

Data statement: Technical appendix, statistical code, and raw data resulting from this research will be available from the corresponding and senior author upon reasonable request, in accordance with regulations.

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Supplement A – Psychometric characteristics instruments

A series of assessments and parent or self-reported measures were used to monitor neurocognitive and behavioral development, stress and impact on family and child:

ASQ-4 – Parent-report

The Ages and Stages Questionnaire-4 (ASQ-4) is a parent-reported computerized adaptive testing questionnaire for children aged 0-6 years which is adapted from the ASQ-3 (1). This questionnaire is used to screen the child's development in 5 domains: Communication, Gross Motor skills, Fine Motor skills, Problem-solving, and Personal-social development. Items are answered by parents with 'yes', 'sometimes, and 'never' and are clarified with images. Dutch norms and percentile scores are available. The development is determine based on cut-off values of percentile scores: percentile </= 3% slowest development, and percentile >/=90% is fastest development.

Bayley Scales of Infant and Toddler Development – Third edition (Dutch)

The Bayley Scales of Infant and Toddler Development (BSID-III-NL) is a widely used assessment for developmental functioning in children between the age of 2 weeks to 3.5 years (2). Normative data is present for all children aged 16 days to 42 months and 15 days and divided over 17 age-groups. The assessment is categorized into 5 domains: Cognition (91 items), Language (consists of the subscales Receptive language (49 items) and Expressive language (46 items)), Motor (consists of the subscales Fine motor (66 items) and Gross motor (72 items)), Social-Emotional, and Adaptive behavior. The assessment of the Social-Emotional and Adaptive behavior scales rely on the response of the caregiver, whereas the Cognition, Language and Motor scales are administered by a psychologist. The administration of a subscale starts at a specific starting item based on the age of the child. If the patient had failed to successfully complete the first three consecutive items, the administrator went back to a previous starting item until the infant completed the three consecutive items successfully of a starting point. Full credit is given for items prior to the starting item. The administration continued until the infant had a score of 0 on five items in a row. Index scores have a mean of 100 (*SD* = 15) and subscales have a mean of 10 (*SD* = 3).

Wechsler Preschool and Primary Scale of Intelligence – Fourth edition (Dutch)

The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV-NL) is an intelligence test that is validated for children between the ages of 2 years and 6 months to 6 years and 11 months (3). The WPPSI-IV-NL consists of 15 subtests that generates a Full Scale Intelligence Quotient (IQ) and five primary indexes: Verbal Comprehension Index (VCI), Verbal Spatial Index (VSI), Fluid Reasoning Index (FRI), Working Memory Index (WMI), and Processing Speed Index (PSI). Normative data is present for children aged 2 years and 6 months to 3 years and 11 months and for children aged 4 years to 6 years and 11 months. The mean scaled score for the Full Scale IQ and the indexes is 100 (*SD* = 15) and for the subtests 10 (*SD* = 3). This study includes the first 10 subtests to obtain a score on all five domains and a Full Score IQ. Each domain will be assessed with two subtests.

Wechsler Intelligence Scale for Children – Fifth edition (Dutch)

The Wechsler Intelligence Scale for Children (WISC-V-NL) is an intelligence test that is validated for children between the ages of 6 years and 16 years and 11 months (4). The WISC-V-NL consists of 14

subtests that generates a Full Scale IQ and five primary indexes: Verbal Comprehension Index (VCI), Visual Spatial Index (VSI), Fluid Reasoning Index (FRI), Working Memory Index (WMI), and the Processing Speed Index (PSI). The mean scaled score for the Full Scale IQ and the indexes is 100 (SD = 15) and for the subtests 10 (SD = 3). This study includes the first 10 subtests to obtain a score on all five domains and a Full Score IQ. Each domain will be assessed with two subtests.

SDQ – Parent-report

The Strength and Difficulties Questionnaire (SDQ) is a brief behavioral screening questionnaire, with a parent-report and teacher-report version (5, 6). This questionnaire has been validated for children aged 2-4 years and 4-16 years and has a parent- or teacher-report and a self-report version. The items are categorized into five subscales, each comprising five items. These subscales produce scores for Emotional Symptoms, Conduct Problems, Hyperactivity/Inattention, Peer Relationship Problems, and Pro-Social Behaviors. Each item is assessed on a three-point scale: "Not True," "Somewhat True," and "Certainly True." The total difficulties score is derived by summarizing the four scales mentioned above, excluding Pro-Social Behavior. The parent-report version of the SDQ is sent to the parents when their child is 2, 4, and 8 years old. Cut-off scores for the total difficulties score at 2 years old is 12 or higher, at 4 years old is 15 or higher and at 8 years old is 14 or higher. Cut-off scores for the Emotional Problem scale at 2 years old is 3 or higher, at 4 years old is 4 or higher and at 8 years old is 5 or higher. For the Conduct problem scale, the cut-off score at 2 years old is 4 or higher, at 4 and 8 years old its 3 or higher.

CBSK – self-report

The Self-perception Profile for Children (Dutch: Competentiebelevingsschaal voor kinderen (CBSK)) is a child-reported questionnaire validated for children between the age of 8 and 12 years, which is focused on how children perceive their own capabilities (7). The CBSK contains 36 items, which are divided over six scales: School Performance, Social Acceptance, Athletic Competence, Physical Appearance, Behavioral Conduct, and Self-Worth. Scale scores are converted to percentile scores. Scores lower than the 15th percentile or above the 85th percentile indicate an extreme high score or low score of the child's own capabilities. The reliability of each scale is moderate to high.

KJTS – Parent-report

The Kinder- en Jeugd Trauma Screener (KJTS) is used to screen for posttraumatic stress disorder (PTSD) in children (8). KJTS is the Dutch validated version of the Child and Adolescent Trauma Screen (CATS). This questionnaire has a self-report at the age of 7 years or older and two parent-report versions, between the age of 3-6 years and 7 years or older. The parent-report version is completed by the parents when their child is 0, 2, 4, and 8 years old. The KJTS is divided in 3 parts and consists of 41 items. The KJTS has 16 items measuring traumatic events, 20 items measuring DSM-5 PTSD symptoms, and 4 items measuring psychosocial functioning. Items are answered with 'Yes' and 'No' or with a four-point scale 'Never', 'Once in a while', 'Half of the time', and 'Almost always'. Cut-off values for this screening tool are determined for the parent-report version 3-6 years as 'Normal, not at risk' (=/<11), 'Increased trauma-related stress symptoms' (11-14), and 'Increased risk on PTSD' (>/=15). Cut-off values for this screening tool are determined for the parent-report version 7 years or older as 'Normal, not at risk' (<15), 'Possible trauma-related symptoms' (15-20), 'Increased trauma-related stress symptoms' (>/= 21), and 'Increased risk on PTSD' (>/=25).

PCL-5- Parent-report

The Dutch PTSD Checklist for DSM-5 (PCL-5) is a self-reported questionnaire used to screen for posttraumatic stress disorder in adults, which contains 20 items regarding PTSD symptoms (9). Items are rated by a Likert scale from 0 (not at all) to 4 (extremely), which results in a total score between 0-80. The items can be divided into four subscales which match the four symptom clusters for PTSD within the DSM-5: Cluster B (re-experiencing), Cluster C (Avoidance), Cluster D (negative alterations in cognition and mood) and Cluster E (hyper-arousal). The Dutch translation has an excellent internal consistency and reliability, and a high criterion validity (10). A score of 31 or higher and at least 1 symptom in cluster B and C and at least 2 symptoms in cluster D and E indicate PTSD.

OBVL – parent-report

The Parenting Stress Questionnaire (*Dutch*: Opvoedingsbelasting vragenlijst (OBVL)) is a questionnaire focused on child-parent relationship and parenting stress (11). The OBVL contains 34 items which are answered on a Likert scale from 0 (not true) to 4 (very true). The total score involves five subscales, including: Parent-Child Relationship Problems, Parenting Problems, Depressive Mood (parent), Parental Role Restriction, and Physical Problems (parent). The OBVL has an overall good reliability and a Cronback's alpha between 0.74 and 0.87. The total score is converted to aged-corrected T-scores. A T-score between 60-63 indicate mild problems and a T-score of 64 or higher indicates substantial problems.

Decisional Conflict Scale - Parent-report

The Decisional conflict scale (DCS) measures perceptions of uncertainty in choosing options and effective decision making (12, 13). The DCS contains 16 items which are rated from 0 (strongly agree) to 4 (strongly disagree). The Dutch version of the DCS is divided into three subscales with moderate to good reliability (12). The subscales include: uncertainty about choosing among alternatives, factors contributing to uncertainty, and perceived effectiveness of the decision. The DCS is sent to parents after the treatment decision with a window of 8 weeks.

Decision Regret Scale - Parent-report

The Decisional Regret Scale (DRS) measures distress or remorse after a treatment decision (14, 15). It contains 5 items which are scored on a Likert scale ranging from 1 (completely disagree) to 5 (completely agree). This scale has a good internal consistency with a Cronbach's alpha between 0.81 to 0.92.

PedsQL – Parent-report and self-report

The Pediatric Quality of Life Inventory (PedsQL) is a questionnaire measuring the health-related quality of life in children (16). This questionnaire contains 23 items divided over 4 subscales: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning. Three different summary scores can be calculated: Total Scale Score, Physical Health Summary Score, and Psychosocial Health Summary Score. Higher scores indicate a better health-related quality of life. Different versions are available based on the child's age and the respondent (child self-report and parent proxy-report). Both the Dutch version of the child self-report as well as the parent proxy-report show good reliability

(17, 18). The parent proxy-report form is sent to parents when their child is 2, 4, and 8 years old and the child proxy-report is sent to the child at the age of 8 years old.

Referral

The results of the assessments (BSID-III-NL, WPPSI-IV-NL, and WISC-V-NL) will be communicated to the parents via telephone within 3-4 weeks post-assessment. Additionally, a detailed report of the results will be recorded in the patient's medical file. In cases where infants score below -2 standard deviations, the psychologist will consult with the parents regarding the need for referral. The nature of the referral will depend on the specific index or subscale exhibiting the low score and may include a referral to a physiotherapist or further evaluation by a psychologist. Simultaneously, the psychologist will review the outcomes of the questionnaires with the parents, and any indicated referrals will be facilitated accordingly. Furthermore, if the psychologist suspects a behavioral disorder based on the anamnesis or behavioral observations during the assessments, this will be discussed with the parents to determine if further assessment is required.

Table 1. Overview of assessments and questionnaires

ASSESSMENT/QUESTIONNAIRE	0 Y	2 Y	4 Y	8 Y
DEVELOPMENT & COGNITION				
ASQ-4	x			
BSID-III-NL		x[a]		
WPPSI-IV-NL			x[a]	
WISC-V-NL				x[a]
SCHOOL PERFORMANCE (CITO)			x[b]	x[b]
EMOTION, BEHAVIOR & PSYCHOSOCIAL				
SDQ		x	x	x
POSTTRAUMATIC STRESS				
KJTS	x	x	x	x
PCL-5	x	x	x	x
IMPACT ON FAMILY & CHILD				
INTERVIEW	x	x	x	x
OBVL	x	x	x	x
CBSK				x[c]
DECISIONAL CONFLICT SCALE	x			
DECISIONAL REGRET SCALE				x
PEDSQL		x	x	x[d]
EQ-5D-Y-5L	x	x	x	x
COST-EFFECTIVENESS ANALYSIS				
IMCQ	x	x	x	x
IPCQ	x	x	x	x

[a] assessments by psychologist; [b] school reports provided by parents; [c] child-reported questionnaire; [d] both parent- and child-reported questionnaire

ASQ: Ages and Stages Questionnaire; BSID: Bayley Scales of Infant and Toddler Development; WPPSI: Wechsler Preschool and Primary Scale of Intelligence; WISC: Wechsler Intelligence Scale for Children; SDQ: Strength and Difficulties Questionnaire; KJTS: Kinder- en Jeugd Trauma Screener; PCL-5: posttraumatic stress disorder checklist for DSM-5; OBVL: Opvoedingsbelasting vragenlijst; CBSK: Competentiebelevingsschaal voor kinderen; PedsQL: Pediatric Quality of Life Inventory; EQ-5D-5L-Y: EuroQol five dimensions health questionnaire youth; iMCQ: medical consumption questionnaire; iPCQ: productivity costs questionnaire

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Complete List of Authors:	Tio, Pauline; Erasmus MC University Medical Center Rotterdam, Department of Plastic and Reconstructive Surgery van Staalduinen, Merel; Erasmus MC Sophia, Department of Child and Adolescent Psychiatry/Psychology Okkerse, Jolanda; Erasmus MC Sophia, Department of Child and Adolescent Psychiatry/Psychology Dulfer, K.; Erasmus MC Sophia, Department of Neonatal & Pediatric Intensive Care; Erasmus MC Sophia, Department of Child and Adolescent Psychiatry/Psychology Erler, Nicole; Erasmus MC University Medical Center Rotterdam, Department of Biostatistics; Erasmus MC University Medical Center Rotterdam, Department of Epidemiology Loudon, Sjoukje; Erasmus MC University Medical Center Rotterdam, Department of Ophthalmology Telleman, Marieke; Erasmus MC University Medical Center Rotterdam, Department of Ophthalmology Abdel-Alim, Tareq; Erasmus MC University Medical Center Rotterdam, Department of Neurosurgery; Erasmus MC University Medical Center Rotterdam, Department of Radiology and Nuclear Medicine Roshchupkin, Gennady; Erasmus MC University Medical Center Rotterdam, Department of Radiology and Nuclear Medicine; Erasmus MC University Medical Center Rotterdam, Department of Epidemiology Heemskerk, Stella; Erasmus MC University Medical Center Rotterdam, Department of Public Health Polinder, Suzanne; Erasmus MC University Medical Center Rotterdam, Department of Public Health van Veelen, Marie-Lise; Erasmus MC University Medical Center Rotterdam, Department of Neurosurgery; Erasmus MC Sophia, Child Brain Center Bannink, Natalja; Franciscus Gasthuis en Vlietland, Department of Pediatrics van Driel, Arianne; IJsselland Ziekenhuis, Department of Pediatrics Faasse, Mariët; Dutch Patient and Parent Society for Craniofacial Conditions Ista, Erwin; Erasmus MC Sophia, Department of Neonatal and Pediatric Intensive Care Joosten, K; Erasmus MC Sophia, Department of Neonatal and Pediatric

	Intensive Care Spoor, Jochem; Erasmus MC University Medical Center Rotterdam, Department of Neurosurgery Weissbach, Elin; Erasmus MC University Medical Center Rotterdam, Department of Plastic and Reconstructive Surgery Kats, Jacoba; Erasmus MC University Medical Center Rotterdam, Department of Plastic and Reconstructive Surgery Versnel, Sarah; Erasmus MC University Medical Center Rotterdam, Department of Plastic and Reconstructive Surgery Pleumeekers, Mieke; Erasmus MC University Medical Center Rotterdam, Department of Plastic and Reconstructive Surgery Mathijssen, Irene; Erasmus MC University Medical Center Rotterdam, Department of Plastic and Reconstructive Surgery
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Comparing Effectiveness of Conservative Policy to Craniofacial Surgery in Children with Metopic Synostosis: Protocol for an Observational Cohort Study on Clinical Outcomes, Psychosocial Wellbeing, and Costs in a Dutch Academic Hospital

AUTHORS

P.A.E. Tio[1], M.J.A. van Staalduinen[2], J.M.E. Okkerse[2], K. Dulfer[2,13], N.S. Erler[3,7], S.E. Loudon[4], M.A.J. Telleman[4], T. Abdel-Alim[5, 6], G. Roshchupkin[6, 7], S.C.M. Heemskerk[8], S. Polinder[8], M.L.C. van Veelen[5,9], N. Bannink[10], A.H.M. van Driel[11], M. Faasse[12], E. Ista[13], K.F.M. Joosten[13], J. Spoor[5], E. Weissbach[1], J. Kats[1], S.L. Versnel[1], M.M. Pleumeekers[1], I.M.J. Mathijssen[1]

INSTITUTIONAL AFFILIATIONS

1. Department of Plastic and Reconstructive Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands.
2. Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands.
3. Department of Biostatistics, Erasmus University Medical Center, Rotterdam, The Netherlands.
4. Department of Ophthalmology, Erasmus University Medical Center, Rotterdam, The Netherlands.
5. Department of Neurosurgery, Erasmus University Medical Center, Rotterdam, The Netherlands.
6. Department of Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands.
7. Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands
8. Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands.
9. Child Brain Center, Erasmus University Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands.
10. Department of Pediatrics, Franciscus Gasthuis and Vlietland, Rotterdam and Schiedam, The Netherlands
11. Department of Pediatrics, IJsselland Ziekenhuis, Capelle aan den IJssel, The Netherlands
12. Dutch Patient and Parent Society for Craniofacial Conditions (LAPOSA), The Netherlands
13. Department of Neonatal and Pediatric Intensive Care, Division of Pediatric intensive Care, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands.

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CORRESPONDING AUTHOR

P.A.E. Tio, Department of Plastic and Reconstructive Surgery, Erasmus University Medical Center, Sophia’s Children’s Hospital Rotterdam, Doctor Molewaterplein 40, 3015 GD Rotterdam, The Netherlands; email: p.tio@erasmusmc.nl

ABSTRACT

Introduction

Traditionally, surgical intervention has been the standard treatment for children with metopic synostosis, assuming that it reduces the risk of raised intracranial pressure, thereby preventing vision and cognitive impairment, and also restores the abnormal head shape. However, recent research suggests a sporadic occurrence of raised intracranial pressure in patients with metopic synostosis. In addition, following surgery, an overall tendency to have worse cognitive and behavioral outcomes, and more refractive errors compared to healthy peers is observed. Research on conservative (nonsurgical) treatment in metopic synostosis is limited and lacks a comparative design. The purpose of this study is to compare the (cost-)effectiveness of conservative and surgical treatment in patients with metopic synostosis.

Methods and analysis

This is the protocol for an observational cohort study with a duration of 8 years. A total of 450 patients with metopic synostosis will be included. The primary outcome is head growth as predictor for increased intracranial pressure. Non-inferiority with regard to head growth from 0-8 years (yearly difference in standard deviation) is determined using a linear mixed model adjusted for potential confounders. Secondary outcomes include papilledema, orthoptic outcomes, forehead shape, cognitive, behavioral, and psychological outcomes, and societal costs. A cost-effectiveness analysis will be performed.

Ethics and dissemination

The study has been reviewed and approved by the Medical Research Ethics Committee of the Erasmus MC, University Medical Centre Rotterdam (MEC-2022-0142). Written informed consent will be obtained from both parents of each participant. The results will be disseminated by publication in international peer-reviewed journals.

Trial registration

ClinicalTrials.gov NCT06069479

Keywords

Trigonocephaly, craniosynostosis, cohort studies, cost-benefit analysis, intracranial pressure, cognition

ARTICLE SUMMARY

Strengths and limitations of this study

1. This is the first prospective cohort study evaluating different treatment policies in patients with metopic synostosis.
2. This large cohort will provide information on clinical outcomes, psychosocial wellbeing, and costs.
3. This study will be conducted in a single academic center.
4. Randomization of the type of treatment was not accepted by parents, therefore an observational cohort study was chosen instead of a randomized trial.

INTRODUCTION

Premature closure of the metopic suture, also known as trigonocephaly or metopic synostosis, is the second most common type of craniosynostosis [1,2]. The head shape in these patients is characterized by a wedge-shaped forehead, hypotelorism, temporal retrusion, and biparietal widening [2,3]. In contrast to other sutures of the calvaria, the fusion of the metopic suture early in life is a normal developmental process, with physiological closure occurring before 9 months of age [4-6].

Traditionally, craniofacial surgery has been the standard treatment for these children, assuming that it reduces the risk of raised intracranial pressure, thereby preventing vision and cognitive impairment, and also restoring the abnormal head shape. There are two main options for surgical interventions, namely fronto-orbital advancement and endoscopic-strip craniectomy followed by helmet therapy. Recent research suggests that raised intracranial pressure occurs sporadically in these patients [7,8]. Predictors for raised intracranial pressure include a decline in head growth and the presence of papilledema at fundoscopy, which are described in 9% and 1.8% of surgically treated non-syndromic metopic synostosis patients, respectively [7]. Although the second aim of surgery is to correct the abnormal head shape, a common long-term outcome observed after surgery is the recurrence of forehead deformities, occasionally resulting in a second surgical procedure [8-10].

Patients with metopic synostosis have a higher risk of ophthalmologic, cognitive, and behavioral problems. A higher prevalence of refractive errors is seen in patients with metopic synostosis compared to healthy controls [11-13]. Patients with metopic synostosis experience hyperopia and astigmatism at rates of 22% and 23%, respectively, versus 8% and 4% in the age-matched norm population, which can contribute to headaches in these patients [13]. Following surgery, patients with metopic synostosis score worse compared to healthy peers on several domains of cognitive and behavioral functioning [14-19].

There are certain risks accompanying craniofacial surgery in these young patients. Complications occur sporadically but they do occur, and include dural tears and wound infections [8-10]. In addition, a blood transfusion is imperative in these patients when performing a fronto-orbital advancement. The coronal incision necessary with a fronto-orbital advancement results in a large scar for the child. Surgery is a stressful event not only for the child but also for the family and projects a significant amount of stress on the whole family [20]. Caregivers of whom the child is planned for a surgical procedure can experience emotional distress and anxiety, which influences the child's development [21-24].

In recent years, the indication for craniofacial surgery in patients with metopic synostosis, particularly those with mild to moderate severity, has become a subject of debate [25]. Conservative (nonsurgical) management, involving regular follow-up appointments without surgical intervention, has gained interest due to the sporadic occurrence of signs indicating raised intracranial pressure. In a small group of patients that did not undergo surgery (n=40), none of these patients required surgical intervention for increased intracranial pressure during their follow-up [8]. None of the existing literature has investigated the development of head shape overtime in conservatively treated patients with metopic synostosis. It is hypothesized that a conservative policy allows for natural improvement of the abnormal head shape over time, however the extent of the self-correction remains unknown [26]. Conservative treatment could probably also remove the additional stress on the child and the family and the risk of complications associated with craniofacial surgery. While literature concerning cognitive outcomes in conservatively treated patients with metopic synostosis is limited and heterogeneous, there is a

tendency for patients without surgical intervention to score slightly below average or exhibit a higher prevalence of concerns when compared to healthy controls [14,17,27,28]. No research has been conducted in a large sample that directly compares cognitive and behavioral functioning between patients with metopic synostosis treated conservatively and those treated surgically.

Over the course of the past six years at Erasmus Sophia Children's Hospital (Rotterdam, The Netherlands), approximately two-thirds (142/216) of parents of patients with metopic synostosis chose conservative treatment, while the remaining one-third opted for surgical treatment. None of the conservatively treated patients developed signs of increased intracranial pressure nor required craniofacial surgery. The choice of conservative treatment extends beyond its clinical consequences, influencing financial expenses associated with the management of patients with craniosynostosis. Although studies in the field of craniosynostosis have compared costs and established the cost-effectiveness of various surgical techniques [29-31], an evident gap exists in the literature concerning cost-effectiveness analyses comparing conservative and surgical treatments, particularly in patients with metopic synostosis.

Taking into account the sporadic occurrence of increased intracranial pressure and the overall tendency to have worse cognitive, behavioral, and ophthalmologic outcomes even after surgery, the functional indication for surgical intervention for patients with metopic synostosis seems uncertain. In the existing literature, all outcomes following conservative treatment for patients with metopic synostosis are hard to determine due to small sample sizes, relatively short duration of follow-up, and mild characteristics in the majority of the conservatively treated patients [14,26-28,32]. Therefore, a prospective cohort study with adequate follow-up is needed to determine if a conservative policy is as effective as surgical intervention. We present the study protocol for an observational cohort study on the effectiveness of a conservative policy compared to craniofacial surgery in metopic synostosis. This study presents a unique opportunity to assess differences in outcomes between conservatively and surgically treated patients with metopic synostosis in domains including intracranial pressure, vision, cognitive and behavioral functioning, impact on family and child, aesthetic outcomes, and societal costs.

METHODS

Patient and Public involvement

The Dutch Patient and Parent Society for Craniofacial Conditions (LAPOSA) is a partner in the proposal and was involved in the design of the study. LAPOSA will also be involved in the dissemination of the results.

Study design

Based on discussions with the patient society LAPOSA, an observational cohort design was chosen as study design instead of a randomized trial, because randomization of the type of treatment is not accepted by parents.

Setting

In the Netherlands, treatment for craniosynostosis is fully reimbursed by the National Health Insurance program. The care for patients with craniosynostosis is centralized in the Netherlands in two centers,

with Erasmus Sophia Children's Hospital treating over 80% of the Dutch population. This study is taking place at Erasmus Sophia Children's Hospital. To evaluate the feasibility of transitioning a portion of follow-up care to non-specialized centers, follow-up appointments at the ages of 5 and 7 years are conducted in non-specialized hospitals (Franciscus Gasthuis and Vlietland, Rotterdam and Schiedam, The Netherlands and IJsselland Ziekenhuis, Capelle aan den IJssel, The Netherlands).

Eligibility criteria

Patients diagnosed with metopic synostosis at Erasmus Sophia Children's Hospital will be recruited in the clinic. Eligible patients are up to 3 years of age and are diagnosed with either non-syndromic or syndromic metopic synostosis. These patients will be offered the opportunity to participate in the study by their clinician. Patients are excluded if they present with a metopic ridge only. Patient with multi-suture craniosynostosis are excluded.

Interventions

The study protocol aligns with our current clinical protocol up until the age of 8 years, except for additional questionnaires. At our center, as of 2017, treatment decisions are made through a shared decision-making process in which parents can choose between two treatment options: conservative treatment or surgical treatment. Conservative treatment involves a nonsurgical approach with yearly routine follow-up appointments. The choice of the type of surgical treatment depends on the age at presentation and parental preferences, with two options available: fronto-orbital advancement and endoscopic-strip craniectomy with helmet therapy. If parents opt for a conservative policy, surgery is only performed if raised intracranial pressure occurs.

All patients with metopic synostosis receive identical follow-up care, irrespective of whether they undergo surgical or conservative treatment. This entails yearly hospital visits until the age of 8 years, followed by subsequent visits every 3 years until the age of 18 when craniofacial growth is considered to have reached its final stage. Head growth is measured every visit and fundoscopy is performed annually up to the age of 4 years. Assessment of refractive errors occurs at 1, 4, and 8 years of age. Psychological screening is routinely offered between the ages of 2 to 8 years. 2D- and 3D-imaging is performed every other year at the ages of 0, 2, 4, 6, and 8 years.

Outcomes

Clinical outcomes

Supplement A provides a visual overview of the clinical outcomes. When available, supplementary retrospective patient data will be collected in addition to prospective data.

Head circumference

The primary outcome is the change in head circumference, as head growth decline is an indicator for raised intracranial pressure. Head circumference is repeatedly measured every year from age 0-8 years. Measurements are performed manually with a measuring tape by skilled clinicians. Head circumference is defined in cm and corresponding standard deviation based on national normative values. A decline in head circumference of more than 0.5 SD is considered clinically relevant.

Papilledema

Fundoscopies are performed annually by a pediatric ophthalmologist in children up to the age of 4 years to detect the presence (or absence) of papilledema, as an indicator for raised intracranial pressure.

Orthoptic outcomes

A full orthoptic examination is performed at the age of 1, 4 and 8 years by a pediatric orthoptist. The examination provides data on the refractive error (myopia, hyperopia, astigmatism), visual acuity, strabismus and amblyopia. Visual acuity scores are converted to logMAR; hyperopia, myopia, and astigmatism are measured in diopters; presence of strabismus is measured in degrees; amblyopia is assessed as present or absent.

Forehead shape

Forehead shape is assessed at the ages of 0, 2, 4, 6, and 8 years using 2D and 3D photogrammetry and a visual analogue scale (VAS) score determined by the parents. Within the ERN CRANIO, a core outcome set for metopic synostosis has been developed, based on 2D photos [33]. Serial 2D and 3D photos during follow-up will illustrate and quantify the growth pattern of the forehead over time. Comparison of the objective data (2D and 3D photos) with the subjective data (VAS score) will show how realistic parents experience their child's forehead shape.

Cognitive, behavioral and psychological instruments

Table 1 offers an overview of the cognitive, behavioral and psychological instruments. For a more detailed description of all psychometric properties, see Supplement B. Questionnaires will be sent through email at pre-specified times and completed online using GemsTracker.

Table 1. Cognitive, behavioral and psychological instruments

ASSESSMENT/QUESTIONNAIRE	0 Y	2 Y	4 Y	8 Y
DEVELOPMENT & COGNITION				
ASQ-4	x			
BSID-III-NL		x[a]		
WPPSI-IV-NL			x[a]	
WISC-V-NL				x[a]
SCHOOL PERFORMANCE (CITO)			x[b]	x[b]
EMOTION, BEHAVIOR & PSYCHOSOCIAL				
SDQ		x	x	x
POSTTRAUMATIC STRESS				
KJTS	x	x	x	x
PCL-5	x	x	x	x
IMPACT ON FAMILY & CHILD				
INTERVIEW	x	x	x	x
OBVL	x	x	x	x
CBSK				x[c]
DECISIONAL CONFLICT SCALE	x			
DECISIONAL REGRET SCALE				x
PEDSQL		x	x	x[d]
EQ-5D-Y-5L	x	x	x	x

[a] assessments by psychologist; [b] school reports provided by parents; [c] child-reported questionnaire; [d] both parent- and child-reported questionnaire

ASQ: Ages and Stages Questionnaire; BSID: Bayley Scales of Infant and Toddler Development; WPPSI: Wechsler Preschool and Primary Scale of Intelligence; WISC: Wechsler Intelligence Scale for Children; SDQ: Strength and Difficulties Questionnaire; KJTS: Kinder- en Jeugd Trauma Screener; PCL-5: posttraumatic stress disorder checklist for DSM-5; OBVL: Opvoedingsbelasting vragenlijst; CBSK: Competentiebelevingsschaal voor kinderen; PedsQL: Pediatric Quality of Life Inventory; EQ-5D-5L-Y: EuroQol five dimensions health questionnaire youth

Development & cognition

The cognitive and behavioral development of the children is evaluated at different ages using the following modalities:

At the age of 0 years old, the Ages and Stages Questionnaire-4 (ASQ-4), a parent-reported computerized adaptive testing questionnaire for children aged 0-6 years which is adapted from the ASQ-3, is used to screen the child's development [34]. At the age of 2, 4 and 8-years, respectively the Bayley Scales of Infant and Toddler Development (BSID-III-NL), Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV-NL) and Wechsler Intelligence Scale for Children (WISC-V-NL) are assessed by a psychologist. The BSID-III-NL is validated for children between the age of 2 weeks to 3.5 years and is widely used to assess neurodevelopment [35]. The WPPSI-IV-NL is an intelligence test that is validated for children between the ages of 2 years and 6 months and 6 years and 11 months [36]. The WISC-V-NL is an intelligence test that is validated for children between the ages of 6 years and 16 years and 11 months [37]. At the age of 4- and 8-years old, school performance is assessed with the nationwide Centraal Instituut voor Toetsontwikkeling (CITO) score to determine performance in elementary school [38]. The CITO scores are provided by parents.

Emotional, behavioral and psychosocial functioning

The Strength and Difficulties Questionnaire (SDQ) is a brief behavioral screening questionnaire [39]. The parent-reported version of the SDQ will be sent to parents when their child is 2, 4, and 8 years. The Self-perception Profile for Children (*Dutch*: Competentiebelevingsschaal voor kinderen (CBSK)) is a child-reported questionnaire validated for children between the age of 8 and 12 years, which is focused on how children perceive their own capabilities [40]. The questionnaire is filled in by the child at the age of 8 years old.

Posttraumatic stress

The Kinder- en Jeugd Trauma Screener (KJTS) is used to screen for posttraumatic stress disorder (PTSD) in the child [41]. KJTS is the Dutch validated version of the Child and Adolescent Trauma Screen (CATS). The parent-report version is completed by the parents when their child is 0, 2, 4, and 8 years old. The Dutch PTSD Checklist for DSM-5 (PCL-5) is a self-reported questionnaire used to screen for posttraumatic stress disorder in adults [42]. The PCL-5 is sent to the parents when their child is 0, 2, 4, and 8 years old.

Impact on family and child

Multiple questionnaires are used to measure the impact on the family and the child. The Parenting Stress Questionnaire (*Dutch*: Opvoedingsbelasting vragenlijst (OBVL)) is a questionnaire focused on child-parent relationship and parenting stress [43]. The OBVL is sent to parents when their child is 0, 2, 4, and 8 years old. The Dutch Decisional conflict scale (DCS) measures parental perceptions of uncertainty in choosing options and effective decision making [44,45]. The DCS is sent to parents after the treatment decision with a window of 8 weeks. The Decisional Regret Scale (DRS) is distributed to parents when the child is 8 years old to measure distress or remorse after the treatment decision [46,47]. The Pediatric Quality of Life Inventory (PedsQL) is a questionnaire measuring the health-related quality of life in children [48]. The parent proxy-report form is sent to parents at the age of 2, 4, and 8 years old and the child proxy-report to the child at the age of 8 years old. The EuroQol Five Dimensions Health Questionnaire Youth (EQ-5D-Y-5L) measure the quality of life of children validated from 4 to 15 years [49]. The parent-reported version is sent to parents when the child is 0, 2, 4, and 8 years old. Semi-structured interviews with both parents separate are performed when their child is 0, 2, 4 and 8 years old, discussing the following aspects: parental concerns, parental stress indicators, traumatic experiences, hospital experience, relevant family factors, relation between parents and child, impact of disease on the child and family, and decision making process.

Resource use and costs

All related societal costs will be taken into account, including costs related to healthcare resource use and loss of productivity for the parents for sick leave. This will allow for a comparison of the costs for both types of treatment. Healthcare resource use is extracted from the medical system and in addition the validated parent-reported iMTA Medical Consumption Questionnaire (iMCQ) will be used to measure healthcare consumption (i.e. medical specialist care, hospitalization, and extramural healthcare consumption) and other costs directly associated with the treatment. Productivity losses are assessed by the iMTA Productivity Costs Questionnaire (iPCQ). Costs will be calculated by multiplication of healthcare consumption volumes by the cost prices per resource unit. Cost prices for healthcare resources use will be primarily derived from the Dutch manual on costing research [50]. Cost prices of surgery will be determined by bottom-up micro-costing method. Productivity costs will be assessed using the friction cost method [51].

Power & sample size considerations

Due to the minimal extra time required from participants and parents, the inclusion rate is expected to be high and the loss to follow-up is expected to be low. Annually, around 50 new patients with metopic synostosis are referred to our center, with an anticipated consent rate of 90% among parents, demonstrating their recognition of this observational study's significance and their willingness to participate. In addition, within the first study year children aged 1-3 years old will be included for follow-up with sufficient available retrospective data. Because at Erasmus Sophia Children's Hospital, standard care for patients with metopic synostosis includes follow-up until the age of 18 years, drop-out rates are expected to be low. Inclusion will add up to 450 patients total.

A power calculation for the primary endpoint was performed using simulation. To obtain parameters for the simulation, a linear mixed model for age-adjusted standard deviation scores (SD) of head circumference was fitted on existing data of children who underwent surgery. The model included a random intercept and (linear) slope for the child's age at the time of the measurement to account for correlation between repeated measurements of the same child and to allow for child-specific

trajectories. To take into account the non-linear shape of the children's SD over time, a natural cubic spline with four degrees of freedom for age at the time of measurement was used in the fixed effects. The parameters from this model formed the assumption for the surgery arm in the power analysis simulation. For the conservative treatment arm, we assumed the SD at baseline follows the same distribution as in the surgery arm, but assumed linearly decreasing SD values over time. The rate of SD decrease in the conservative arm was increased over different simulation scenarios to find the most extreme scenario for which non-inferiority of the conservative arm could be shown with sufficient power.

Each simulated data set contained 245 and 195 children in the conservative and surgery arm, respectively. The number of available observations at each measurement time decreased with increasing age, taking into account the sequential inclusion of children throughout the study period (and resulting differences in length of follow-up). The differences in SD scores between subsequent measurements were calculated and modelled using a random-intercept linear mixed model that had the treatment arm as only fixed effect. The resulting parameter estimate for the treatment arm describes the difference in the yearly decline of SD score in the conservative arm compared to the surgery arm. Non-inferiority was defined as the lower bound of the 95% confidence interval of the treatment effect estimate being larger than -0.5 SD.

Assuming an average yearly decline in head-circumference SD score of -0.25 in the conservative arm resulted in 90% power to demonstrate non-inferiority of the conservative arm at a 2.5% one-sided significance, with a non-inferiority margin of -0.5 yearly SD difference.

Patient recruitment and timeline

Patients are informed by their clinician about the ongoing research and are offered the opportunity to participate in the study. Upon expressing interest, parents will be approached by an independent researcher who will provide them with detailed information about the study. Interested parents will be asked to sign the consent form indicating their willingness to participate with their child (Consent Form, see Supplement C). For all parents who decline participations or withdraw from the study, their reasoning for making this decision will be documented. In order to promote participant retention, parents will receive 10 euro gift cards for every complete set of questionnaires.

Enrollment of participants and their parents has started in September 2022. The study follow-up period will extend until either participants reach the age of 8 years or until the end of the inclusion period (September 2030), whichever comes first. Currently, there are 90 participants included in this study (September 2024).

Data collection & management

Data will be handled confidentially and anonymously. After receiving the signed consent form from the parents, every participant receives a unique study number that is used to link the data to the child. The coordinating researcher safeguards the key to the code.

All data from the questionnaires will be collected with GemsTracker, a software package for the distribution of digital questionnaires. Parents of patients receive emails at appropriate times with a secured link to GemsTracker's website to answer questionnaires digitally. Both the emails as well as reminders, if questionnaires remain incomplete, are sent automatically with a maximum of 2 reminders.

All data from clinical follow-up will be collected from the medical records. The coordinating researcher will regularly monitor whether all data are registered timely and properly. The combined data from both GemsTracker and the medical records are collected in Castor, a secured database. Daily back-ups are made automatically. Storage of personal data will be in line with the Dutch General Data Protection Regulation. Data access control will be in the hands of the principal investigator. Research data will be preserved for 10 years, according to national law. In the case of discontinuation of a participant, only data collected up until that point will be included.

Statistical methods

Primary outcome

The primary outcome measurement of the head circumference is transformed to an age- and sex-specific standard deviation score, according to national norms. The yearly decline in head growth is chosen as the primary outcome since this continuous measure has more power, allowing us to adjust for possible confounders. This would not be possible when using binary outcomes with low prevalence (e.g. presence/absence of papilledema at fundoscopy). Non-inferiority with regard to head growth from 0-8 years (yearly difference in SD score) is determined using a linear mixed model adjusted for potential confounders (including severity of phenotype, sex, syndrome, and parental factors) and comparing the lower bound of the 95% confidence interval of the treatment effect estimate (conservative vs surgery) to the non-inferiority margin of -0.5 SD.

Secondary outcomes

The presence or absence of papilledema on fundoscopy is analyzed with a repeated measures logistic regression to compare difference between the two groups. Prevalence of orthoptic anomalies is compared between the two groups and compared with the norm data, using Chi-Square test. If the number of cases allows for estimating parameters, a logistic regression model is used, otherwise the outcomes are stratified by treatment arms. Pearson's correlation coefficients are calculated to determine a correlation between the VAS and the 2D photo grading and the VAS and the 3D photo grading per time point. For all validated instruments norm values are available, including cut-off levels. Comparison will be made for the outcomes of the instruments between the two treatment groups and with the norm data. For some of the above mentioned variables, different instruments are used at various time points to measure a single construct. In this case, the (ordinal) scores obtained from the instruments will be compared between the two groups at each time point using an independent-sample t-test. In case of repeated measures of a construct using the same instrument, we will use mixed-model analysis to compare the change of the given outcome over time between the two groups. In the case of multiple analyses that target the same research question, multiple testing correction will be applied. We will control the type-I error rate using Bonferroni correction. As far as possible, missing data will be imputed and the number of patients used for analysis at each stage of the study shall be reported.

Economic evaluation

An economic evaluation will be conducted from a societal perspective in accordance with the Dutch guidelines for economic evaluations in healthcare, in which healthcare costs, patient and family costs, and costs outside of the healthcare sector (i.e. productivity costs of the parents related to paid work absenteeism) will be considered [51]. The time horizon is 8 years to include all relevant costs and

effects. The primary outcome (i.e. head circumference) will be used as effect measure in the cost-effectiveness analysis. The incremental cost effectiveness ratio of surgery versus conservative treatment will be expressed as costs per case of decline in head circumference > 0.5 SD.

Data monitoring

In accordance with Erasmus MC guidelines, the conduct of the study will be monitored. Monitoring will be done by an independent resident or PhD candidate of the Plastic and Reconstructive Surgery Department of the Erasmus MC. Monitoring is performed yearly and includes the following: inclusion and dropout rates, informed consent, protocol compliance, and reporting of severe adverse events.

The intervention is not experimental but rather standard of care and is not expected to have a significant risk of potential harm to the patients, therefore there will be no data monitoring committee.

All adverse events reported spontaneously by the parent of the participant or observed by the investigator or the staff will be recorded and followed. Interim analysis is done for head growth in 2025 to verify that the prevalence of raised intracranial pressure is within the expected range, and continuation of the study is justified.

ETHICS AND DISSEMINATION

This study complies with the Declaration of Helsinki and is reviewed and approved by the MREC of the Erasmus MC, University Medical Center Rotterdam (MEC-2022-0142). This is a non-WMO study, which is an observational study in which no action or behavior is imposed on the participants in the study. All amendments will be notified to the MREC. This research adheres to the Code of Conduct for Health Research and Medical Treatment Contracts Act.

Written informed consent is obtained from the child's parent/legal guardian by the coordinating researcher. This is done sufficient time after study information was shared, and after answering any questions of the parents to satisfaction. The informed consent form also indicates how participant data is stored, shared, and used.

No provisions about ancillary and post-trial care are in place as the Dutch healthcare system ensures all participants get the care they need through health insurance. In accordance with Dutch law, Erasmus MC has a liability insurance and a human subject insurance which provides cover for damage to research subjects.

The results of this study will be published in international peer-reviewed journals and presented at international conferences. Parents and patients will be informed about any publication accompanied by a brief summary in Dutch. The published outcomes of this study will be implemented into clinical practice and the Dutch guideline for craniosynostosis will be updated accordingly.

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Data statement: Technical appendix, statistical code, and raw data resulting from this research will be available from the corresponding and senior author upon reasonable request, in accordance with regulations.

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Supplement A – Clinical outcomes

CLINICAL OUTCOMES	0 Y	1Y	2 Y	3 Y	4 Y	5 Y	6 Y	7Y	8 Y
HEAD CIRCUMFERENCE	X	X	X	X	X	X	X	X	X
PAPILLEDEMA		X	X	X	X	*	*	*	*
ORTHOPTIC OUTCOMES		X			X				X
FOREHEAD SHAPE	X		X		X		X		X

*only if a decline in head circumference occurs or the child experiences headaches.

Supplement A – Psychometric characteristics instruments

A series of assessments and parent or self-reported measures were used to monitor neurocognitive and behavioral development, stress and impact on family and child:

ASQ-4 – Parent-report

The Ages and Stages Questionnaire-4 (ASQ-4) is a parent-reported computerized adaptive testing questionnaire for children aged 0-6 years which is adapted from the ASQ-3 (1). This questionnaire is used to screen the child's development in 5 domains: Communication, Gross Motor skills, Fine Motor skills, Problem-solving, and Personal-social development. Items are answered by parents with 'yes', 'sometimes, and 'never' and are clarified with images. Dutch norms and percentile scores are available. The development is determine based on cut-off values of percentile scores: percentile </= 3% slowest development, and percentile >/=90% is fastest development.

Bayley Scales of Infant and Toddler Development – Third edition (Dutch)

The Bayley Scales of Infant and Toddler Development (BSID-III-NL) is a widely used assessment for developmental functioning in children between the age of 2 weeks to 3.5 years (2). Normative data is present for all children aged 16 days to 42 months and 15 days and divided over 17 age-groups. The assessment is categorized into 5 domains: Cognition (91 items), Language (consists of the subscales Receptive language (49 items) and Expressive language (46 items)), Motor (consists of the subscales Fine motor (66 items) and Gross motor (72 items)), Social-Emotional, and Adaptive behavior. The assessment of the Social-Emotional and Adaptive behavior scales rely on the response of the caregiver, whereas the Cognition, Language and Motor scales are administered by a psychologist. The administration of a subscale starts at a specific starting item based on the age of the child. If the patient had failed to successfully complete the first three consecutive items, the administrator went back to a previous starting item until the infant completed the three consecutive items successfully of a starting point. Full credit is given for items prior to the starting item. The administration continued until the infant had a score of 0 on five items in a row. Index scores have a mean of 100 (*SD* = 15) and subscales have a mean of 10 (*SD* = 3).

Wechsler Preschool and Primary Scale of Intelligence – Fourth edition (Dutch)

The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV-NL) is an intelligence test that is validated for children between the ages of 2 years and 6 months to 6 years and 11 months (3). The WPPSI-IV-NL consists of 15 subtests that generates a Full Scale Intelligence Quotient (IQ) and five primary indexes: Verbal Comprehension Index (VCI), Verbal Spatial Index (VSI), Fluid Reasoning Index (FRI), Working Memory Index (WMI), and Processing Speed Index (PSI). Normative data is present for children aged 2 years and 6 months to 3 years and 11 months and for children aged 4 years to 6 years and 11 months. The mean scaled score for the Full Scale IQ and the indexes is 100 (*SD* = 15) and for the subtests 10 (*SD* = 3). This study includes the first 10 subtests to obtain a score on all five domains and a Full Score IQ. Each domain will be assessed with two subtests.

Wechsler Intelligence Scale for Children – Fifth edition (Dutch)

The Wechsler Intelligence Scale for Children (WISC-V-NL) is an intelligence test that is validated for children between the ages of 6 years and 16 years and 11 months (4). The WISC-V-NL consists of 14

subtests that generates a Full Scale IQ and five primary indexes: Verbal Comprehension Index (VCI), Visual Spatial Index (VSI), Fluid Reasoning Index (FRI), Working Memory Index (WMI), and the Processing Speed Index (PSI). The mean scaled score for the Full Scale IQ and the indexes is 100 (SD = 15) and for the subtests 10 (SD = 3). This study includes the first 10 subtests to obtain a score on all five domains and a Full Score IQ. Each domain will be assessed with two subtests.

SDQ – Parent-report

The Strength and Difficulties Questionnaire (SDQ) is a brief behavioral screening questionnaire, with a parent-report and teacher-report version (5, 6). This questionnaire has been validated for children aged 2-4 years and 4-16 years and has a parent- or teacher-report and a self-report version. The items are categorized into five subscales, each comprising five items. These subscales produce scores for Emotional Symptoms, Conduct Problems, Hyperactivity/Inattention, Peer Relationship Problems, and Pro-Social Behaviors. Each item is assessed on a three-point scale: "Not True," "Somewhat True," and "Certainly True." The total difficulties score is derived by summarizing the four scales mentioned above, excluding Pro-Social Behavior. The parent-report version of the SDQ is sent to the parents when their child is 2, 4, and 8 years old. Cut-off scores for the total difficulties score at 2 years old is 12 or higher, at 4 years old is 15 or higher and at 8 years old is 14 or higher. Cut-off scores for the Emotional Problem scale at 2 years old is 3 or higher, at 4 years old is 4 or higher and at 8 years old is 5 or higher. For the Conduct problem scale, the cut-off score at 2 years old is 4 or higher, at 4 and 8 years old its 3 or higher.

CBSK – self-report

The Self-perception Profile for Children (Dutch: Competentiebelevingsschaal voor kinderen (CBSK)) is a child-reported questionnaire validated for children between the age of 8 and 12 years, which is focused on how children perceive their own capabilities (7). The CBSK contains 36 items, which are divided over six scales: School Performance, Social Acceptance, Athletic Competence, Physical Appearance, Behavioral Conduct, and Self-Worth. Scale scores are converted to percentile scores. Scores lower than the 15th percentile or above the 85th percentile indicate an extreme high score or low score of the child's own capabilities. The reliability of each scale is moderate to high.

KJTS – Parent-report

The Kinder- en Jeugd Trauma Screener (KJTS) is used to screen for posttraumatic stress disorder (PTSD) in children (8). KJTS is the Dutch validated version of the Child and Adolescent Trauma Screen (CATS). This questionnaire has a self-report at the age of 7 years or older and two parent-report versions, between the age of 3-6 years and 7 years or older. The parent-report version is completed by the parents when their child is 0, 2, 4, and 8 years old. The KJTS is divided in 3 parts and consists of 41 items. The KJTS has 16 items measuring traumatic events, 20 items measuring DSM-5 PTSD symptoms, and 4 items measuring psychosocial functioning. Items are answered with 'Yes' and 'No' or with a four-point scale 'Never', 'Once in a while', 'Half of the time', and 'Almost always'. Cut-off values for this screening tool are determined for the parent-report version 3-6 years as 'Normal, not at risk' (=/<11), 'Increased trauma-related stress symptoms' (11-14), and 'Increased risk on PTSD' (>/=15). Cut-off values for this screening tool are determined for the parent-report version 7 years or older as 'Normal, not at risk' (<15), 'Possible trauma-related symptoms' (15-20), 'Increased trauma-related stress symptoms' (>/= 21), and 'Increased risk on PTSD' (>/=25).

PCL-5- Parent-report

The Dutch PTSD Checklist for DSM-5 (PCL-5) is a self-reported questionnaire used to screen for posttraumatic stress disorder in adults, which contains 20 items regarding PTSD symptoms (9). Items are rated by a Likert scale from 0 (not at all) to 4 (extremely), which results in a total score between 0-80. The items can be divided into four subscales which match the four symptom clusters for PTSD within the DSM-5: Cluster B (re-experiencing), Cluster C (Avoidance), Cluster D (negative alterations in cognition and mood) and Cluster E (hyper-arousal). The Dutch translation has an excellent internal consistency and reliability, and a high criterion validity (10). A score of 31 or higher and at least 1 symptom in cluster B and C and at least 2 symptoms in cluster D and E indicate PTSD.

OBVL – parent-report

The Parenting Stress Questionnaire (*Dutch*: Opvoedingsbelasting vragenlijst (OBVL)) is a questionnaire focused on child-parent relationship and parenting stress (11). The OBVL contains 34 items which are answered on a Likert scale from 0 (not true) to 4 (very true). The total score involves five subscales, including: Parent-Child Relationship Problems, Parenting Problems, Depressive Mood (parent), Parental Role Restriction, and Physical Problems (parent). The OBVL has an overall good reliability and a Cronback's alpha between 0.74 and 0.87. The total score is converted to aged-corrected T-scores. A T-score between 60-63 indicate mild problems and a T-score of 64 or higher indicates substantial problems.

Decisional Conflict Scale - Parent-report

The Decisional conflict scale (DCS) measures perceptions of uncertainty in choosing options and effective decision making (12, 13). The DCS contains 16 items which are rated from 0 (strongly agree) to 4 (strongly disagree). The Dutch version of the DCS is divided into three subscales with moderate to good reliability (12). The subscales include: uncertainty about choosing among alternatives, factors contributing to uncertainty, and perceived effectiveness of the decision. The DCS is sent to parents after the treatment decision with a window of 8 weeks.

Decision Regret Scale - Parent-report

The Decisional Regret Scale (DRS) measures distress or remorse after a treatment decision (14, 15). It contains 5 items which are scored on a Likert scale ranging from 1 (completely disagree) to 5 (completely agree). This scale has a good internal consistency with a Cronbach's alpha between 0.81 to 0.92.

PedsQL – Parent-report and self-report

The Pediatric Quality of Life Inventory (PedsQL) is a questionnaire measuring the health-related quality of life in children (16). This questionnaire contains 23 items divided over 4 subscales: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning. Three different summary scores can be calculated: Total Scale Score, Physical Health Summary Score, and Psychosocial Health Summary Score. Higher scores indicate a better health-related quality of life. Different versions are available based on the child's age and the respondent (child self-report and parent proxy-report). Both the Dutch version of the child self-report as well as the parent proxy-report show good reliability

(17, 18). The parent proxy-report form is sent to parents when their child is 2, 4, and 8 years old and the child proxy-report is sent to the child at the age of 8 years old.

Referral

The results of the assessments (BSID-III-NL, WPPSI-IV-NL, and WISC-V-NL) will be communicated to the parents via telephone within 3-4 weeks post-assessment. Additionally, a detailed report of the results will be recorded in the patient's medical file. In cases where infants score below -2 standard deviations, the psychologist will consult with the parents regarding the need for referral. The nature of the referral will depend on the specific index or subscale exhibiting the low score and may include a referral to a physiotherapist or further evaluation by a psychologist. Simultaneously, the psychologist will review the outcomes of the questionnaires with the parents, and any indicated referrals will be facilitated accordingly. Furthermore, if the psychologist suspects a behavioral disorder based on the anamnesis or behavioral observations during the assessments, this will be discussed with the parents to determine if further assessment is required.

Table 1. Overview of assessments and questionnaires

ASSESSMENT/QUESTIONNAIRE	0 Y	2 Y	4 Y	8 Y
DEVELOPMENT & COGNITION				
ASQ-4	x			
BSID-III-NL		x[a]		
WPPSI-IV-NL			x[a]	
WISC-V-NL				x[a]
SCHOOL PERFORMANCE (CITO)			x[b]	x[b]
EMOTION, BEHAVIOR & PSYCHOSOCIAL				
SDQ		x	x	x
POSTTRAUMATIC STRESS				
KJTS	x	x	x	x
PCL-5	x	x	x	x
IMPACT ON FAMILY & CHILD				
INTERVIEW	x	x	x	x
OBVL	x	x	x	x
CBSK				x[c]
DECISIONAL CONFLICT SCALE	x			
DECISIONAL REGRET SCALE				x
PEDSQL		x	x	x[d]
EQ-5D-Y-5L	x	x	x	x
COST-EFFECTIVENESS ANALYSIS				
IMCQ	x	x	x	x
IPCQ	x	x	x	x

[a] assessments by psychologist; [b] school reports provided by parents; [c] child-reported questionnaire; [d] both parent- and child-reported questionnaire

ASQ: Ages and Stages Questionnaire; BSID: Bayley Scales of Infant and Toddler Development; WPPSI: Wechsler Preschool and Primary Scale of Intelligence; WISC: Wechsler Intelligence Scale for Children; SDQ: Strength and Difficulties Questionnaire; KJTS: Kinder- en Jeugd Trauma Screener; PCL-5: posttraumatic stress disorder checklist for DSM-5; OBVL: Opvoedingsbelasting vragenlijst; CBSK: Competentiebelevingsschaal voor kinderen; PedsQL: Pediatric Quality of Life Inventory; EQ-5D-5L-Y: EuroQol five dimensions health questionnaire youth; iMCQ: medical consumption questionnaire; iPCQ: productivity costs questionnaire

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Complete List of Authors:	Tio, Pauline; Erasmus MC University Medical Center Rotterdam, Department of Plastic and Reconstructive Surgery van Staalduinen, Merel; Erasmus MC Sophia, Department of Child and Adolescent Psychiatry/Psychology Okkerse, Jolanda; Erasmus MC Sophia, Department of Child and Adolescent Psychiatry/Psychology Dulfer, K.; Erasmus MC Sophia, Department of Neonatal & Pediatric Intensive Care; Erasmus MC Sophia, Department of Child and Adolescent Psychiatry/Psychology Erler, Nicole; Erasmus MC University Medical Center Rotterdam, Department of Biostatistics; Erasmus MC University Medical Center Rotterdam, Department of Epidemiology Loudon, Sjoukje; Erasmus MC University Medical Center Rotterdam, Department of Ophthalmology Telleman, Marieke; Erasmus MC University Medical Center Rotterdam, Department of Ophthalmology Abdel-Alim, Tareq; Erasmus MC University Medical Center Rotterdam, Department of Neurosurgery; Erasmus MC University Medical Center Rotterdam, Department of Radiology and Nuclear Medicine Roshchupkin, Gennady; Erasmus MC University Medical Center Rotterdam, Department of Radiology and Nuclear Medicine; Erasmus MC University Medical Center Rotterdam, Department of Epidemiology Heemskerk, Stella; Erasmus MC University Medical Center Rotterdam, Department of Public Health Polinder, Suzanne; Erasmus MC University Medical Center Rotterdam, Department of Public Health van Veelen, Marie-Lise; Erasmus MC University Medical Center Rotterdam, Department of Neurosurgery; Erasmus MC Sophia, Child Brain Center Bannink, Natalja; Franciscus Gasthuis en Vlietland, Department of Pediatrics van Driel, Arianne; IJsselland Ziekenhuis, Department of Pediatrics Faasse, Mariët; Dutch Patient and Parent Society for Craniofacial Conditions Ista, Erwin; Erasmus MC Sophia, Department of Neonatal and Pediatric Intensive Care Joosten, K; Erasmus MC Sophia, Department of Neonatal and Pediatric

	Intensive Care Spoor, Jochem; Erasmus MC University Medical Center Rotterdam, Department of Neurosurgery Weissbach, Elin; Erasmus MC University Medical Center Rotterdam, Department of Plastic and Reconstructive Surgery Kats, Jacoba; Erasmus MC University Medical Center Rotterdam, Department of Plastic and Reconstructive Surgery Versnel, Sarah; Erasmus MC University Medical Center Rotterdam, Department of Plastic and Reconstructive Surgery Pleumeekers, Mieke; Erasmus MC University Medical Center Rotterdam, Department of Plastic and Reconstructive Surgery Mathijssen, Irene; Erasmus MC University Medical Center Rotterdam, Department of Plastic and Reconstructive Surgery
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Comparing Effectiveness of Conservative Policy to Craniofacial Surgery in Children with Metopic Synostosis: Protocol for an Observational Cohort Study on Clinical Outcomes, Psychosocial Wellbeing, and Costs in a Dutch Academic Hospital

AUTHORS

P.A.E. Tio[1], M.J.A. van Staalduinen[2], J.M.E. Okkerse[2], K. Dulfer[2,13], N.S. Erler[3,7], S.E. Loudon[4], M.A.J. Telleman[4], T. Abdel-Alim[5, 6], G. Roshchupkin[6, 7], S.C.M. Heemskerk[8], S. Polinder[8], M.L.C. van Veelen[5,9], N. Bannink[10], A.H.M. van Driel[11], M. Faasse[12], E. Ista[13], K.F.M. Joosten[13], J. Spoor[5], E. Weissbach[1], J. Kats[1], S.L. Versnel[1], M.M. Pleumeekers[1], I.M.J. Mathijssen[1]

INSTITUTIONAL AFFILIATIONS

1. Department of Plastic and Reconstructive Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands.
2. Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands.
3. Department of Biostatistics, Erasmus University Medical Center, Rotterdam, The Netherlands.
4. Department of Ophthalmology, Erasmus University Medical Center, Rotterdam, The Netherlands.
5. Department of Neurosurgery, Erasmus University Medical Center, Rotterdam, The Netherlands.
6. Department of Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands.
7. Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands
8. Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands.
9. Child Brain Center, Erasmus University Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands.
10. Department of Pediatrics, Franciscus Gasthuis and Vlietland, Rotterdam and Schiedam, The Netherlands
11. Department of Pediatrics, IJsselland Ziekenhuis, Capelle aan den IJssel, The Netherlands
12. Dutch Patient and Parent Society for Craniofacial Conditions (LAPOSA), The Netherlands
13. Department of Neonatal and Pediatric Intensive Care, Division of Pediatric intensive Care, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands.

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CORRESPONDING AUTHOR

P.A.E. Tio, Department of Plastic and Reconstructive Surgery, Erasmus University Medical Center, Sophia’s Children’s Hospital Rotterdam, Doctor Molewaterplein 40, 3015 GD Rotterdam, The Netherlands; email: p.tio@erasmusmc.nl

ABSTRACT

Introduction

Traditionally, surgical intervention has been the standard treatment for children with metopic synostosis, assuming that it reduces the risk of raised intracranial pressure, thereby preventing vision and cognitive impairment, and also restores the abnormal head shape. However, recent research suggests a sporadic occurrence of raised intracranial pressure in patients with metopic synostosis. In addition, following surgery, an overall tendency to have worse cognitive and behavioral outcomes, and more refractive errors compared to healthy peers is observed. Research on conservative (nonsurgical) treatment in metopic synostosis is limited and lacks a comparative design. The purpose of this study is to compare the (cost-)effectiveness of conservative and surgical treatment in patients with metopic synostosis.

Methods and analysis

This is the protocol for an observational cohort study with a duration of 8 years. A total of 450 patients with metopic synostosis will be included. The primary outcome is head growth as predictor for increased intracranial pressure. Non-inferiority with regard to head growth from 0-8 years (yearly difference in standard deviation) is determined using a linear mixed model adjusted for potential confounders. Secondary outcomes include papilledema, orthoptic outcomes, forehead shape, cognitive, behavioral, and psychological outcomes, and societal costs. A cost-effectiveness analysis will be performed.

Ethics and dissemination

The study has been reviewed and approved by the Medical Research Ethics Committee of the Erasmus MC, University Medical Centre Rotterdam (MEC-2022-0142). Written informed consent will be obtained from both parents of each participant. The results will be disseminated by publication in international peer-reviewed journals.

Trial registration

ClinicalTrials.gov NCT06069479

Keywords

Trigonocephaly, craniosynostosis, cohort studies, cost-benefit analysis, intracranial pressure, cognition

ARTICLE SUMMARY

Strengths and limitations of this study

1. This is the first prospective cohort study evaluating different treatment policies in patients with metopic synostosis.
2. This large cohort will provide information on clinical outcomes, psychosocial wellbeing, and costs.
3. This study will be conducted in a single academic center.
4. Randomization of the type of treatment was not accepted by parents, therefore an observational cohort study was chosen instead of a randomized trial.

INTRODUCTION

Premature closure of the metopic suture, also known as trigonocephaly or metopic synostosis, is the second most common type of craniosynostosis [1,2]. The head shape in these patients is characterized by a wedge-shaped forehead, hypotelorism, temporal retrusion, and biparietal widening [2,3]. In contrast to other sutures of the calvaria, the fusion of the metopic suture early in life is a normal developmental process, with physiological closure occurring before 9 months of age [4-6].

Traditionally, craniofacial surgery has been the standard treatment for these children, assuming that it reduces the risk of raised intracranial pressure, thereby preventing vision and cognitive impairment, and also restoring the abnormal head shape. There are two main options for surgical interventions, namely fronto-orbital advancement and endoscopic-strip craniectomy followed by helmet therapy. Recent research suggests that raised intracranial pressure occurs sporadically in these patients [7,8]. Predictors for raised intracranial pressure include a decline in head growth and the presence of papilledema at fundoscopy, which are described in 9% and 1.8% of surgically treated non-syndromic metopic synostosis patients, respectively [7]. Although the second aim of surgery is to correct the abnormal head shape, a common long-term outcome observed after surgery is the recurrence of forehead deformities, occasionally resulting in a second surgical procedure [8-10].

Patients with metopic synostosis have a higher risk of ophthalmologic, cognitive, and behavioral problems. A higher prevalence of refractive errors is seen in patients with metopic synostosis compared to healthy controls [11-13]. Patients with metopic synostosis experience hyperopia and astigmatism at rates of 22% and 23%, respectively, versus 8% and 4% in the age-matched norm population, which can contribute to headaches in these patients [13]. Following surgery, patients with metopic synostosis score worse compared to healthy peers on several domains of cognitive and behavioral functioning [14-19].

There are certain risks accompanying craniofacial surgery in these young patients. Complications occur sporadically but they do occur, and include dural tears and wound infections [8-10]. In addition, a blood transfusion is imperative in these patients when performing a fronto-orbital advancement. The coronal incision necessary with a fronto-orbital advancement results in a large scar for the child. Surgery is a stressful event not only for the child but also for the family and projects a significant amount of stress on the whole family [20]. Caregivers of whom the child is planned for a surgical procedure can experience emotional distress and anxiety, which influences the child's development [21-24].

In recent years, the indication for craniofacial surgery in patients with metopic synostosis, particularly those with mild to moderate severity, has become a subject of debate [25]. Conservative (nonsurgical) management, involving regular follow-up appointments without surgical intervention, has gained interest due to the sporadic occurrence of signs indicating raised intracranial pressure. In a small group of patients that did not undergo surgery (n=40), none of these patients required surgical intervention for increased intracranial pressure during their follow-up [8]. None of the existing literature has investigated the development of head shape overtime in conservatively treated patients with metopic synostosis. It is hypothesized that a conservative policy allows for natural improvement of the abnormal head shape over time, however the extent of the self-correction remains unknown [26]. Conservative treatment could probably also remove the additional stress on the child and the family and the risk of complications associated with craniofacial surgery. While literature concerning cognitive outcomes in conservatively treated patients with metopic synostosis is limited and heterogeneous, there is a

tendency for patients without surgical intervention to score slightly below average or exhibit a higher prevalence of concerns when compared to healthy controls [14,17,27,28]. No research has been conducted in a large sample that directly compares cognitive and behavioral functioning between patients with metopic synostosis treated conservatively and those treated surgically.

Over the course of the past six years at Erasmus Sophia Children's Hospital (Rotterdam, The Netherlands), approximately two-thirds (142/216) of parents of patients with metopic synostosis chose conservative treatment, while the remaining one-third opted for surgical treatment. None of the conservatively treated patients developed signs of increased intracranial pressure nor required craniofacial surgery. The choice of conservative treatment extends beyond its clinical consequences, influencing financial expenses associated with the management of patients with craniosynostosis. Although studies in the field of craniosynostosis have compared costs and established the cost-effectiveness of various surgical techniques [29-31], an evident gap exists in the literature concerning cost-effectiveness analyses comparing conservative and surgical treatments, particularly in patients with metopic synostosis.

Taking into account the sporadic occurrence of increased intracranial pressure and the overall tendency to have worse cognitive, behavioral, and ophthalmologic outcomes even after surgery, the functional indication for surgical intervention for patients with metopic synostosis seems uncertain. In the existing literature, all outcomes following conservative treatment for patients with metopic synostosis are hard to determine due to small sample sizes, relatively short duration of follow-up, and mild characteristics in the majority of the conservatively treated patients [14,26-28,32]. Therefore, a prospective cohort study with adequate follow-up is needed to determine if a conservative policy is as effective as surgical intervention. We present the study protocol for an observational cohort study on the effectiveness of a conservative policy compared to craniofacial surgery in metopic synostosis. This study presents a unique opportunity to assess differences in outcomes between conservatively and surgically treated patients with metopic synostosis in domains including intracranial pressure, vision, cognitive and behavioral functioning, impact on family and child, aesthetic outcomes, and societal costs.

METHODS

Patient and Public involvement

The Dutch Patient and Parent Society for Craniofacial Conditions (LAPOSA) is a partner in the proposal and was involved in the design of the study. LAPOSA will also be involved in the dissemination of the results.

Study design

Based on discussions with the patient society LAPOSA, an observational cohort design was chosen as study design instead of a randomized trial, because randomization of the type of treatment is not accepted by parents.

Setting

In the Netherlands, treatment for craniosynostosis is fully reimbursed by the National Health Insurance program. The care for patients with craniosynostosis is centralized in the Netherlands in two centers,

with Erasmus Sophia Children's Hospital treating over 80% of the Dutch population. This study is taking place at Erasmus Sophia Children's Hospital. To evaluate the feasibility of transitioning a portion of follow-up care to non-specialized centers, follow-up appointments at the ages of 5 and 7 years are conducted in non-specialized hospitals (Franciscus Gasthuis and Vlietland, Rotterdam and Schiedam, The Netherlands and IJsselland Ziekenhuis, Capelle aan den IJssel, The Netherlands).

Eligibility criteria

Patients diagnosed with metopic synostosis at Erasmus Sophia Children's Hospital will be recruited in the clinic. Eligible patients are up to 3 years of age and are diagnosed with either non-syndromic or syndromic metopic synostosis. These patients will be offered the opportunity to participate in the study by their clinician. Patients are excluded if they present with a metopic ridge only. Patient with multi-suture craniosynostosis are excluded.

Interventions

The study protocol aligns with our current clinical protocol up until the age of 8 years, except for additional questionnaires. At our center, as of 2017, treatment decisions are made through a shared decision-making process in which parents can choose between two treatment options: conservative treatment or surgical treatment. Conservative treatment involves a nonsurgical approach with yearly routine follow-up appointments. The choice of the type of surgical treatment depends on the age at presentation and parental preferences, with two options available: fronto-orbital advancement and endoscopic-strip craniectomy with helmet therapy. If parents opt for a conservative policy, surgery is only performed if raised intracranial pressure occurs.

All patients with metopic synostosis receive identical follow-up care, irrespective of whether they undergo surgical or conservative treatment. This entails yearly hospital visits until the age of 8 years, followed by subsequent visits every 3 years until the age of 18 when craniofacial growth is considered to have reached its final stage. Head growth is measured every visit and fundoscopy is performed annually up to the age of 4 years. Assessment of refractive errors occurs at 1, 4, and 8 years of age. Psychological screening is routinely offered between the ages of 2 to 8 years. 2D- and 3D-imaging is performed every other year at the ages of 0, 2, 4, 6, and 8 years.

Outcomes

Clinical outcomes

Supplement A provides a visual overview of the clinical outcomes. When available, supplementary retrospective patient data will be collected in addition to prospective data.

Head circumference

The primary outcome is the change in head circumference, as head growth decline is an indicator for raised intracranial pressure. Head circumference is repeatedly measured every year from age 0-8 years. Measurements are performed manually with a measuring tape by skilled clinicians. Head circumference is defined in cm and corresponding standard deviation based on national normative values. A decline in head circumference of more than 0.5 SD is considered clinically relevant. Head circumference is a significant predictor of intracranial volume making it a very useful clinical measurement to monitor skull growth [33, 34]. As a non-invasive measurement accessible at every age, it serves as a valuable and

efficient measurement to initiate further screening if abnormal in metopic synostosis patients [7]. Patients with stagnation of the head circumference require further screening for raised ICP. Serial head circumference measurements, combined with a comprehensive screening protocol if necessary, provide a robust and clinically relevant approach to monitoring these patients. This method allows for regular, non-invasive assessment while minimizing radiation exposure, which is particularly important in pediatric populations.

Papilledema

Fundoscopies are performed annually by a pediatric ophthalmologist in children up to the age of 4 years to detect the presence (or absence) of papilledema, as an indicator for raised intracranial pressure.

Orthoptic outcomes

A full orthoptic examination is performed at the age of 1, 4 and 8 years by a pediatric orthoptist. The examination provides data on the refractive error (myopia, hyperopia, astigmatism), visual acuity, strabismus and amblyopia. Visual acuity scores are converted to logMAR; hyperopia, myopia, and astigmatism are measured in diopters; presence of strabismus is measured in degrees; amblyopia is assessed as present or absent.

Forehead shape

Forehead shape is assessed at the ages of 0, 2, 4, 6, and 8 years using 2D and 3D photogrammetry and a visual analogue scale (VAS) score determined by the parents. Within the ERN CRANIO, a core outcome set for metopic synostosis has been developed, based on 2D photos [35]. Serial 2D and 3D photos during follow-up will illustrate and quantify the growth pattern of the forehead over time. Comparison of the objective data (2D and 3D photos) with the subjective data (VAS score) will show how realistic parents experience their child's forehead shape.

Cognitive, behavioral and psychological instruments

Table 1 offers an overview of the cognitive, behavioral and psychological instruments. For a more detailed description of all psychometric properties, see Supplement B. Questionnaires will be sent through email at pre-specified times and completed online using GemsTracker.

Table 1. Cognitive, behavioral and psychological instruments

ASSESSMENT/QUESTIONNAIRE	0 Y	2 Y	4 Y	8 Y
DEVELOPMENT & COGNITION				
ASQ-EXTENDED	x			
BSID-III-NL		x[a]		
WPPSI-IV-NL			x[a]	
WISC-V-NL				x[a]
SCHOOL PERFORMANCE (CITO)			x[b]	x[b]
EMOTION, BEHAVIOR & PSYCHOSOCIAL				
SDQ		x	x	x
POSTTRAUMATIC STRESS				
KJTS	x	x	x	x

PCL-5	x	x	x	x
IMPACT ON FAMILY & CHILD				
INTERVIEW	x	x	x	x
OBVL	x	x	x	x
CBSK				x[c]
DECISIONAL CONFLICT SCALE	x			
DECISIONAL REGRET SCALE				x
PEDSQL		x	x	x[d]
EQ-5D-Y-5L	x	x	x	x

[a] assessments by psychologist; [b] school reports provided by parents; [c] child-reported questionnaire; [d] both parent- and child-reported questionnaire

ASQ: Ages and Stages Questionnaire; BSID: Bayley Scales of Infant and Toddler Development; WPPSI: Wechsler Preschool and Primary Scale of Intelligence; WISC: Wechsler Intelligence Scale for Children; SDQ: Strength and Difficulties Questionnaire; KJTS: Kinder- en Jeugd Trauma Screener; PCL-5: posttraumatic stress disorder checklist for DSM-5; OBVL: Opvoedingsbelasting vragenlijst; CBSK: Competentiebelevingsschaal voor kinderen; PedsQL: Pediatric Quality of Life Inventory; EQ-5D-5L-Y: EuroQol five dimensions health questionnaire youth

Development & cognition

The cognitive and behavioral development of the children is evaluated at different ages using the following modalities:

At the age of 0 years old, the Ages and Stages Questionnaire-extended (ASQ-extended), a Dutch parent-reported computerized adaptive testing questionnaire for children aged 0-6 years which is adapted from the ASQ, is used to screen the child's development [36, 37]. At the age of 2, 4 and 8-years, respectively the Bayley Scales of Infant and Toddler Development (BSID-III-NL), Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV-NL) and Wechsler Intelligence Scale for Children (WISC-V-NL) are assessed by a psychologist. The BSID-III-NL is validated for children between the age of 2 weeks to 3.5 years and is widely used to assess neurodevelopment [38]. The WPPSI-IV-NL is an intelligence test that is validated for children between the ages of 2 years and 6 months and 6 years and 11 months [39]. The WISC-V-NL is an intelligence test that is validated for children between the ages of 6 years and 16 years and 11 months [40]. For this study design, the ages of 4 and 8 years were selected for cognitive assessments due to their significance in the Dutch school system and the comprehensive set of outcomes measured at age 8. For further clarification on this decision see Supplement B. At the age of 4- and 8-years old, school performance is assessed with the nationwide Centraal Instituut voor Toetsontwikkeling (CITO) score to determine performance in elementary school [41]. The CITO scores are provided by parents.

Emotional, behavioral and psychosocial functioning

The Strength and Difficulties Questionnaire (SDQ) is a brief behavioral screening questionnaire [42]. The parent-reported version of the SDQ will be sent to parents when their child is 2, 4, and 8 years. The Self-perception Profile for Children (*Dutch*: Competentiebelevingsschaal voor kinderen (CBSK)) is a child-reported questionnaire validated for children between the age of 8 and 12 years, which is focused on how children perceive their own capabilities [43]. The questionnaire is filled in by the child at the age of 8 years old.

Posttraumatic stress

The Kinder- en Jeugd Trauma Screener (KJTS) is used to screen for posttraumatic stress disorder (PTSD) in the child [44]. KJTS is the Dutch validated version of the Child and Adolescent Trauma Screen (CATS). The parent-report version is completed by the parents when their child is 0, 2, 4, and 8 years old. The Dutch PTSD Checklist for DSM-5 (PCL-5) is a self-reported questionnaire used to screen for posttraumatic stress disorder in adults [45]. The PCL-5 is sent to the parents when their child is 0, 2, 4, and 8 years old.

Impact on family and child

Multiple questionnaires are used to measure the impact on the family and the child. The Parenting Stress Questionnaire (*Dutch*: Opvoedingsbelasting vragenlijst (OBVL)) is a questionnaire focused on child-parent relationship and parenting stress [46]. The OBVL is sent to parents when their child is 0, 2, 4, and 8 years old. The Dutch Decisional conflict scale (DCS) measures parental perceptions of uncertainty in choosing options and effective decision making [47,48]. The DCS is sent to parents after the treatment decision with a window of 8 weeks. The Decisional Regret Scale (DRS) is distributed to parents when the child is 8 years old to measure distress or remorse after the treatment decision [49,50]. The Pediatric Quality of Life Inventory (PedsQL) is a questionnaire measuring the health-related quality of life in children [51]. The parent proxy-report form is sent to parents at the age of 2, 4, and 8 years old and the child proxy-report to the child at the age of 8 years old. The EuroQol Five Dimensions Health Questionnaire Youth (EQ-5D-Y-5L) measure the quality of life of children validated from 4 to 15 years [52]. The parent-reported version is sent to parents when the child is 0, 2, 4, and 8 years old. Semi-structured interviews with both parents separate are performed when their child is 0, 2, 4 and 8 years old, discussing the following aspects: parental concerns, parental stress indicators, traumatic experiences, hospital experience, relevant family factors, relation between parents and child, impact of disease on the child and family, and decision making process.

Resource use and costs

All related societal costs will be taken into account, including costs related to healthcare resource use and loss of productivity for the parents for sick leave. This will allow for a comparison of the costs for both types of treatment. Healthcare resource use is extracted from the medical system and in addition the validated parent-reported iMTA Medical Consumption Questionnaire (iMCQ) will be used to measure healthcare consumption (i.e. medical specialist care, hospitalization, and extramural healthcare consumption) and other costs directly associated with the treatment. Productivity losses are assessed by the iMTA Productivity Costs Questionnaire (iPCQ). Costs will be calculated by multiplication of healthcare consumption volumes by the cost prices per resource unit. Cost prices for healthcare resources use will be primarily derived from the Dutch manual on costing research [53]. Cost prices of surgery will be determined by bottom-up micro-costing method. Productivity costs will be assessed using the friction cost method [54].

Power & sample size considerations

Due to the minimal extra time required from participants and parents, the inclusion rate is expected to be high and the loss to follow-up is expected to be low. Annually, around 50 new patients with metopic synostosis are referred to our center, with an anticipated consent rate of 90% among parents,

demonstrating their recognition of this observational study's significance and their willingness to participate. In addition, within the first study year children aged 1-3 years old will be included for follow-up with sufficient available retrospective data. Because at Erasmus Sophia Children's Hospital, standard care for patients with metopic synostosis includes follow-up until the age of 18 years, drop-out rates are expected to be low. Inclusion will add up to 450 patients total.

A power calculation for the primary endpoint was performed using simulation. To obtain parameters for the simulation, a linear mixed model for age-adjusted standard deviation scores (SD) of head circumference was fitted on existing data of children who underwent surgery. The model included a random intercept and (linear) slope for the child's age at the time of the measurement to account for correlation between repeated measurements of the same child and to allow for child-specific trajectories. To take into account the non-linear shape of the children's SD over time, a natural cubic spline with four degrees of freedom for age at the time of measurement was used in the fixed effects. The parameters from this model formed the assumption for the surgery arm in the power analysis simulation. For the conservative treatment arm, we assumed the SD at baseline follows the same distribution as in the surgery arm, but assumed linearly decreasing SD values over time. The rate of SD decrease in the conservative arm was increased over different simulation scenarios to find the most extreme scenario for which non-inferiority of the conservative arm could be shown with sufficient power.

Each simulated data set contained 245 and 195 children in the conservative and surgery arm, respectively. The number of available observations at each measurement time decreased with increasing age, taking into account the sequential inclusion of children throughout the study period (and resulting differences in length of follow-up). The differences in SD scores between subsequent measurements were calculated and modelled using a random-intercept linear mixed model that had the treatment arm as only fixed effect. The resulting parameter estimate for the treatment arm describes the difference in the yearly decline of SD score in the conservative arm compared to the surgery arm. Non-inferiority was defined as the lower bound of the 95% confidence interval of the treatment effect estimate being larger than -0.5 SD.

Assuming an average yearly decline in head-circumference SD score of -0.25 in the conservative arm resulted in 90% power to demonstrate non-inferiority of the conservative arm at a 2.5% one-sided significance, with a non-inferiority margin of -0.5 yearly SD difference.

Patient recruitment and timeline

Patients are informed by their clinician about the ongoing research and are offered the opportunity to participate in the study. Upon expressing interest, parents will be approached by an independent researcher who will provide them with detailed information about the study. Interested parents will be asked to sign the consent form indicating their willingness to participate with their child (Consent Form, see Supplement C). For all parents who decline participations or withdraw from the study, their reasoning for making this decision will be documented. In order to promote participant retention, parents will receive 10 euro gift cards for every complete set of questionnaires.

Enrollment of participants and their parents has started in September 2022. The study follow-up period will extend until either participants reach the age of 8 years or until the end of the inclusion period

(September 2030), whichever comes first. Currently, there are 90 participants included in this study (September 2024).

Data collection & management

Data will be handled confidentially and anonymously. After receiving the signed consent form from the parents, every participant receives a unique study number that is used to link the data to the child. The coordinating researcher safeguards the key to the code.

All data from the questionnaires will be collected with GemsTracker, a software package for the distribution of digital questionnaires. Parents of patients receive emails at appropriate times with a secured link to GemsTracker's website to answer questionnaires digitally. Both the emails as well as reminders, if questionnaires remain incomplete, are sent automatically with a maximum of 2 reminders. All data from clinical follow-up will be collected from the medical records. The coordinating researcher will regularly monitor whether all data are registered timely and properly. The combined data from both GemsTracker and the medical records are collected in Castor, a secured database. Daily back-ups are made automatically. Storage of personal data will be in line with the Dutch General Data Protection Regulation. Data access control will be in the hands of the principal investigator. Research data will be preserved for 10 years, according to national law. In the case of discontinuation of a participant, only data collected up until that point will be included.

Statistical methods

Primary outcome

The primary outcome measurement of the head circumference is transformed to an age- and sex-specific standard deviation score, according to national norms. The yearly decline in head growth is chosen as the primary outcome since this continuous measure has more power, allowing us to adjust for possible confounders. This would not be possible when using binary outcomes with low prevalence (e.g. presence/absence of papilledema at fundoscopy). Non-inferiority with regard to head growth from 0-8 years (yearly difference in SD score) is determined using a linear mixed model adjusted for potential confounders (including severity of phenotype, sex, syndrome, and parental factors) and comparing the lower bound of the 95% confidence interval of the treatment effect estimate (conservative vs surgery) to the non-inferiority margin of -0.5 SD.

Secondary outcomes

The presence or absence of papilledema on fundoscopy is analyzed with a repeated measures logistic regression to compare difference between the two groups. Prevalence of orthoptic anomalies is compared between the two groups and compared with the norm data, using Chi-Square test. If the number of cases allows for estimating parameters, a logistic regression model is used, otherwise the outcomes are stratified by treatment arms. Pearson's correlation coefficients are calculated to determine a correlation between the VAS and the 2D photo grading and the VAS and the 3D photo grading per time point. For all validated instruments norm values are available, including cut-off levels. Comparison will be made for the outcomes of the instruments between the two treatment groups and with the norm data. For some of the above mentioned variables, different instruments are used at various time points to measure a single construct. In this case, the (ordinal) scores obtained from the instruments will be compared between the two groups at each time point using an independent-sample

t-test. In case of repeated measures of a construct using the same instrument, we will use mixed-model analysis to compare the change of the given outcome over time between the two groups. In the case of multiple analyses that target the same research question, multiple testing correction will be applied. We will control the type-I error rate using Bonferroni correction. As far as possible, missing data will be imputed and the number of patients used for analysis at each stage of the study shall be reported.

Economic evaluation

An economic evaluation will be conducted from a societal perspective in accordance with the Dutch guidelines for economic evaluations in healthcare, in which healthcare costs, patient and family costs, and costs outside of the healthcare sector (i.e. productivity costs of the parents related to paid work absenteeism) will be considered [54]. The time horizon is 8 years to include all relevant costs and effects. The primary outcome (i.e. head circumference) will be used as effect measure in the cost-effectiveness analysis. The incremental cost effectiveness ratio of surgery versus conservative treatment will be expressed as costs per case of decline in head circumference > 0.5 SD.

Data monitoring

In accordance with Erasmus MC guidelines, the conduct of the study will be monitored. Monitoring will be done by an independent resident or PhD candidate of the Plastic and Reconstructive Surgery Department of the Erasmus MC. Monitoring is performed yearly and includes the following: inclusion and dropout rates, informed consent, protocol compliance, and reporting of severe adverse events.

The intervention is not experimental but rather standard of care and is not expected to have a significant risk of potential harm to the patients, therefore there will be no data monitoring committee.

All adverse events reported spontaneously by the parent of the participant or observed by the investigator or the staff will be recorded and followed. Interim analysis is done for head growth in 2025 to verify that the prevalence of raised intracranial pressure is within the expected range, and continuation of the study is justified.

ETHICS AND DISSEMINATION

This study complies with the Declaration of Helsinki and is reviewed and approved by the MREC of the Erasmus MC, University Medical Center Rotterdam (MEC-2022-0142). This is a non-WMO study, which is an observational study in which no action or behavior is imposed on the participants in the study. All amendments will be notified to the MREC. This research adheres to the Code of Conduct for Health Research and Medical Treatment Contracts Act.

Written informed consent is obtained from the child's parent/legal guardian by the coordinating researcher. This is done sufficient time after study information was shared, and after answering any questions of the parents to satisfaction. The informed consent form also indicates how participant data is stored, shared, and used.

No provisions about ancillary and post-trial care are in place as the Dutch healthcare system ensures all participants get the care they need through health insurance. In accordance with Dutch law, Erasmus

MC has a liability insurance and a human subject insurance which provides cover for damage to research subjects.

The results of this study will be published in international peer-reviewed journals and presented at international conferences. Parents and patients will be informed about any publication accompanied by a brief summary in Dutch. The published outcomes of this study will be implemented into clinical practice and the Dutch guideline for craniosynostosis will be updated accordingly.

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Competing interests: This observational cohort study is investigator-initiated. No competing interests to declare.

Patient consent for publication: not required. This is a study protocol.

Data statement: Technical appendix, statistical code, and raw data resulting from this research will be available from the corresponding and senior author upon reasonable request, in accordance with regulations.

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Supplement A – Clinical outcomes

CLINICAL OUTCOMES	0 Y	1Y	2 Y	3 Y	4 Y	5 Y	6 Y	7Y	8 Y
HEAD CIRCUMFERENCE	X	X	X	X	X	X	X	X	X
PAPILLEDEMA		X	X	X	X	*	*	*	*
ORTHOPTIC OUTCOMES		X			X				X
FOREHEAD SHAPE	X		X		X		X		X

*only if a decline in head circumference occurs or the child experiences headaches.

Supplement A – Psychometric characteristics instruments

A series of assessments and parent or self-reported measures were used to monitor neurocognitive and behavioral development, stress and impact on family and child:

ASQ-extended – Parent-report

The Ages and Stages Questionnaire is a parent-reported validated questionnaire used to screen the child's development (1). The Dutch adapted version of the ASQ is used, which is a computerized adaptive testing questionnaire for children aged 0-6 years, showing good reliability and validity (2). This questionnaire is used to screen the child's development in 5 domains: Communication, Gross Motor skills, Fine Motor skills, Problem-solving, and Personal-social development. Items are answered by parents with 'yes', 'sometimes, and 'never' and are clarified with images. Dutch norms and percentile scores are available. The development is determine based on cut-off values of percentile scores: percentile </= 3% slowest development, and percentile >/=90% is fastest development.

Bayley Scales of Infant and Toddler Development – Third edition (Dutch)

The Bayley Scales of Infant and Toddler Development (BSID-III-NL) is a widely used assessment for developmental functioning in children between the age of 2 weeks to 3.5 years (3). Normative data is present for all children aged 16 days to 42 months and 15 days and divided over 17 age-groups. The assessment is categorized into 5 domains: Cognition (91 items), Language (consists of the subscales Receptive language (49 items) and Expressive language (46 items)), Motor (consists of the subscales Fine motor (66 items) and Gross motor (72 items)), Social-Emotional, and Adaptive behavior. The assessment of the Social-Emotional and Adaptive behavior scales rely on the response of the caregiver, whereas the Cognition, Language and Motor scales are administered by a psychologist. The administration of a subscale starts at a specific starting item based on the age of the child. If the patient had failed to successfully complete the first three consecutive items, the administrator went back to a previous starting item until the infant completed the three consecutive items successfully of a starting point. Full credit is given for items prior to the starting item. The administration continued until the infant had a score of 0 on five items in a row. Index scores have a mean of 100 (*SD* = 15) and subscales have a mean of 10 (*SD* = 3).

Wechsler Preschool and Primary Scale of Intelligence – Fourth edition (Dutch)

The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV-NL) is an intelligence test that is validated for children between the ages of 2 years and 6 months to 6 years and 11 months (4). The WPPSI-IV-NL consists of 15 subtests that generates a Full Scale Intelligence Quotient (IQ) and five primary indexes: Verbal Comprehension Index (VCI), Verbal Spatial Index (VSI), Fluid Reasoning Index (FRI), Working Memory Index (WMI), and Processing Speed Index (PSI). Normative data is present for children aged 2 years and 6 months to 3 years and 11 months and for children aged 4 years to 6 years and 11 months. The mean scaled score for the Full Scale IQ and the indexes is 100 (*SD* = 15) and for the subtests 10 (*SD* = 3). This study includes the first 10 subtests to obtain a score on all five domains and a Full Score IQ. Each domain will be assessed with two subtests.

Wechsler Intelligence Scale for Children – Fifth edition (Dutch)

The Wechsler Intelligence Scale for Children (WISC-V-NL) is an intelligence test that is validated for children between the ages of 6 years and 16 years and 11 months (5). The WISC-V-NL consists of 14 subtests that generates a Full Scale IQ and five primary indexes: Verbal Comprehension Index (VCI), Visual Spatial Index (VSI), Fluid Reasoning Index (FRI), Working Memory Index (WMI), and the Processing Speed Index (PSI). The mean scaled score for the Full Scale IQ and the indexes is 100 (SD = 15) and for the subtests 10 (SD = 3). This study includes the first 10 subtests to obtain a score on all five domains and a Full Score IQ. Each domain will be assessed with two subtests.

Note: For this study design, the ages of 4 and 8 years were selected for cognitive assessments due to their significance in the Dutch school system and the comprehensive set of outcomes measured at age 8. While we acknowledge the potential discrepancies between WPPSI and WISC scores, as highlighted by Salonen et al. (2023), our primary objective is to compare cognitive development between conservative and surgical groups rather than analyze longitudinal changes (6). Both the WPPSI and WISC demonstrate good reliability for this purpose. We opted against an additional assessment at age 6 to avoid potential ceiling effects, as the WPPSI-IV-NL's upper age limit of 6 years and 11 months could impact results for children tested closer to age 7. Our approach ensures consistent and reliable cognitive assessments at key developmental stages while aligning with the study's main comparative goals.

SDQ – Parent-report

The Strength and Difficulties Questionnaire (SDQ) is a brief behavioral screening questionnaire, with a parent-report and teacher-report version (7, 8). This questionnaire has been validated for children aged 2-4 years and 4-16 years and has a parent- or teacher-report and a self-report version. The items are categorized into five subscales, each comprising five items. These subscales produce scores for Emotional Symptoms, Conduct Problems, Hyperactivity/Inattention, Peer Relationship Problems, and Pro-Social Behaviors. Each item is assessed on a three-point scale: "Not True," "Somewhat True," and "Certainly True." The total difficulties score is derived by summarizing the four scales mentioned above, excluding Pro-Social Behavior. The parent-report version of the SDQ is sent to the parents when their child is 2, 4, and 8 years old. Cut-off scores for the total difficulties score at 2 years old is 12 or higher, at 4 years old is 15 or higher and at 8 years old is 14 or higher. Cut-off scores for the Emotional Problem scale at 2 years old is 3 or higher, at 4 years old is 4 or higher and at 8 years old is 5 or higher. For the Conduct problem scale, the cut-off score at 2 years old is 4 or higher, at 4 and 8 years old its 3 or higher.

CBSK – self-report

The Self-perception Profile for Children (Dutch: Competentiebelevingsschaal voor kinderen (CBSK)) is a child-reported questionnaire validated for children between the age of 8 and 12 years, which is focused on how children perceive their own capabilities (9). The CBSK contains 36 items, which are divided over six scales: School Performance, Social Acceptance, Athletic Competence, Physical Appearance, Behavioral Conduct, and Self-Worth. Scale scores are converted to percentile scores. Scores lower than the 15th percentile or above the 85th percentile indicate an extreme high score or low score of the child's own capabilities. The reliability of each scale is moderate to high.

KJTS – Parent-report

The Kinder- en Jeugd Trauma Screener (KJTS) is used to screen for posttraumatic stress disorder (PTSD) in children (10). KJTS is the Dutch validated version of the Child and Adolescent Trauma Screen (CATS).

This questionnaire has a self-report at the age of 7 years or older and two parent-report versions, between the age of 3-6 years and 7 years or older. The parent-report version is completed by the parents when their child is 0, 2, 4, and 8 years old. The KJTS is divided in 3 parts and consists of 41 items. The KJTS has 16 items measuring traumatic events, 20 items measuring DSM-5 PTSD symptoms, and 4 items measuring psychosocial functioning. Items are answered with 'Yes' and 'No' or with a four-point scale 'Never', 'Once in a while', 'Half of the time', and 'Almost always'. Cut-off values for this screening tool are determined for the parent-report version 3-6 years as 'Normal, not at risk' (=/<11), 'Increased trauma-related stress symptoms' (11-14), and 'Increased risk on PTSD' (>/=15). Cut-off values for this screening tool are determined for the parent-report version 7 years or older as 'Normal, not at risk' (<15), 'Possible trauma-related symptoms' (15-20), 'Increased trauma-related stress symptoms' (>/= 21), and 'Increased risk on PTSD' (>/=25).

PCL-5- Parent-report

The Dutch PTSD Checklist for DSM-5 (PCL-5) is a self-reported questionnaire used to screen for posttraumatic stress disorder in adults, which contains 20 items regarding PTSD symptoms (11). Items are rated by a Likert scale from 0 (not at all) to 4 (extremely), which results in a total score between 0-80. The items can be divided into four subscales which match the four symptom clusters for PTSD within the DSM-5: Cluster B (re-experiencing), Cluster C (Avoidance), Cluster D (negative alterations in cognition and mood) and Cluster E (hyper-arousal). The Dutch translation has an excellent internal consistency and reliability, and a high criterion validity (12). A score of 31 or higher and at least 1 symptom in cluster B and C and at least 2 symptoms in cluster D and E indicate PTSD.

OBVL – parent-report

The Parenting Stress Questionnaire (*Dutch*: Opvoedingsbelasting vragenlijst (OBVL)) is a questionnaire focused on child-parent relationship and parenting stress (13). The OBVL contains 34 items which are answered on a Likert scale from 0 (not true) to 4 (very true). The total score involves five subscales, including: Parent-Child Relationship Problems, Parenting Problems, Depressive Mood (parent), Parental Role Restriction, and Physical Problems (parent). The OBVL has an overall good reliability and a Cronback's alpha between 0.74 and 0.87. The total score is converted to aged-corrected T-scores. A T-score between 60-63 indicate mild problems and a T-score of 64 or higher indicates substantial problems.

Decisional Conflict Scale - Parent-report

The Decisional conflict scale (DCS) measures perceptions of uncertainty in choosing options and effective decision making (14, 15). The DCS contains 16 items which are rated from 0 (strongly agree) to 4 (strongly disagree). The Dutch version of the DCS is divided into three subscales with moderate to good reliability (14). The subscales include: uncertainty about choosing among alternatives, factors contributing to uncertainty, and perceived effectiveness of the decision. The DCS is sent to parents after the treatment decision with a window of 8 weeks.

Decision Regret Scale - Parent-report

The Decisional Regret Scale (DRS) measures distress or remorse after a treatment decision (16, 17). It contains 5 items which are scored on a Likert scale ranging from 1 (completely disagree) to 5

(completely agree). This scale has a good internal consistency with a Cronbach's alpha between 0.81 to 0.92.

PedsQL – Parent-report and self-report

The Pediatric Quality of Life Inventory (PedsQL) is a questionnaire measuring the health-related quality of life in children (18). This questionnaire contains 23 items divided over 4 subscales: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning. Three different summary scores can be calculated: Total Scale Score, Physical Health Summary Score, and Psychosocial Health Summary Score. Higher scores indicate a better health-related quality of life. Different versions are available based on the child's age and the respondent (child self-report and parent proxy-report). Both the Dutch version of the child self-report as well as the parent proxy-report show good reliability (19, 20). The parent proxy-report form is sent to parents when their child is 2, 4, and 8 years old and the child proxy-report is sent to the child at the age of 8 years old.

Referral

The results of the assessments (BSID-III-NL, WPPSI-IV-NL, and WISC-V-NL) will be communicated to the parents via telephone within 3-4 weeks post-assessment. Additionally, a detailed report of the results will be recorded in the patient's medical file. In cases where infants score below -2 standard deviations, the psychologist will consult with the parents regarding the need for referral. The nature of the referral will depend on the specific index or subscale exhibiting the low score and may include a referral to a physiotherapist or further evaluation by a psychologist. Simultaneously, the psychologist will review the outcomes of the questionnaires with the parents, and any indicated referrals will be facilitated accordingly. Furthermore, if the psychologist suspects a behavioral disorder based on the anamnesis or behavioral observations during the assessments, this will be discussed with the parents to determine if further assessment is required.

Table 1. Overview of assessments and questionnaires

ASSESSMENT/QUESTIONNAIRE	0 Y	2 Y	4 Y	8 Y
DEVELOPMENT & COGNITION				
ASQ-EXTENDED	x			
BSID-III-NL		x[a]		
WPPSI-IV-NL			x[a]	
WISC-V-NL				x[a]
SCHOOL PERFORMANCE (CITO)			x[b]	x[b]
EMOTION, BEHAVIOR & PSYCHOSOCIAL				
SDQ		x	x	x
POSTTRAUMATIC STRESS				
KJTS	x	x	x	x
PCL-5	x	x	x	x
IMPACT ON FAMILY & CHILD				
INTERVIEW	x	x	x	x
OBVL	x	x	x	x
CBSK				x[c]
DECISIONAL CONFLICT SCALE	x			

DECISIONAL REGRET SCALE				x
PEDSQL		x	x	x[d]
EQ-5D-Y-5L	x	x	x	x
COST-EFFECTIVENESS ANALYSIS				
IMCQ	x	x	x	x
IPCQ	x	x	x	x

[a] assessments by psychologist; [b] school reports provided by parents; [c] child-reported questionnaire; [d] both parent- and child-reported questionnaire

ASQ: Ages and Stages Questionnaire; BSID: Bayley Scales of Infant and Toddler Development; WPPSI: Wechsler Preschool and Primary Scale of Intelligence; WISC: Wechsler Intelligence Scale for Children; SDQ: Strength and Difficulties Questionnaire; KJTS: Kinder- en Jeugd Trauma Screener; PCL-5: posttraumatic stress disorder checklist for DSM-5; OBVL: Opvoedingsbelasting vragenlijst; CBSK: Competentiebelevingsschaal voor kinderen; PedsQL: Pediatric Quality of Life Inventory; EQ-5D-5L-Y: EuroQol five dimensions health questionnaire youth; iMCQ: medical consumption questionnaire; iPCQ: productivity costs questionnaire

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Supplement B – Consent form parent/guardian

Children with trigonocephaly: is surgery necessary?

I have been asked to give consent for my child's participation in this medical-scientific study:

Participant name (child):…….. Date of birth: __ / __ / __

- I have read the information letter for the participant/parents/caregivers. I was also able to ask questions. My questions were answered sufficiently. I had enough time to decide whether I want my child to participate.
- I understand that participation is voluntary. I also understand that I can decide at any time to withdraw my child from the study. I do not need to provide a reason for this decision.
- I give permission for the researcher to inform my child's general practitioner/specialist(s) about their participation in this study.
- I give permission for the researchers to collect and use my child's data. The researchers will only use this data to answer the research question of this study.
- I understand that, for research monitoring purposes, certain individuals may have access to all of my child's data. These individuals are mentioned in the information letter. I give them permission to review my child's data for this purpose.
- Please check "yes" or "no" in the table below:

I give permission for my child's data to be stored and used for other research conducted by Erasmus MC, as described in the information letter.	Yes ☐	No☐
I give permission for my child's data to be stored and used for other research on metopic ridges by Erasmus MC and other European craniofacial centers, as described in the information letter.	Yes ☐	No☐

- I agree that my child will participate in this study.

Name parent/guardian**: ……

Signature: …… Date: __ / __ / __

Name parent/guardian **: ……..

Signature: …… Date: __ / __ / __

I declare that I have fully informed the above-mentioned person(s) about this study.

If any new information arises during the study that may influence the parent's or guardian's consent, I will inform them in a timely manner.

Researcher (or representative) name: ……

Signature: …… Date: __ / __ / __

<if applicable>

Additional information provided by:

Name: ……..

Role: ……

Signature: …… Date: __ / __ / __

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* Cross out what does not apply

** If the child is younger than 16 years old, the parent(s) with legal custody or guardian(s) must sign this form. In addition, children aged 12 to 15 years who are capable of making independent decisions must also sign their own consent form.

The parent/guardian will receive a full information letter along with a signed copy of the consent form.