Risk factors for developing recurrent raised intracranial pressure post cranial vault remodelling in nonsyndromic craniosynostosis in children: a systematic review protocol

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Review question/objective
The objective of this review is to identify the factors associated with an increased risk for developing recurrent raised intracranial pressure in nonsyndromic children who have had previous cranial vault remodelling surgery.

Background
An infant's skull is made up of several pairs of floating bone plates connected by fibrous tissues called sutures. The sutures allow for deformation during birth and expansion of the cranial vault in relation to brain volume growth. Brain growth pushes the two sides of the patent sutures apart, thereby enabling growth of the skull. The main sutures are named sagittal, metopic, coronal and lambdoid sutures. These sutures close at different ages by ossification; the metopic closes between three to nine months of age and the sagittal, lambdoid and coronal sutures close between 22 to 39 years of age.¹

The term craniosynostosis was first described by Otto in 1830² and is defined as premature fusion of one or more cranial sutures which occur in isolation or in the context of a craniodystopic syndrome. It affects approximately one in 2000 births.³ There are several classifications of craniosynostosis; isolated or compound, primary or secondary and either syndromic or nonsyndromic.⁴ Isolated craniosynostosis refers to fusion of a single suture and compound refers to premature fusion of multiple cranial sutures.

Syndromic synostosis typically involves premature fusion of multiple sutures and are hereditary forms of craniosynotosis with extracranial features which are associated with mutations of fibroblast growth factor receptor family (FGFR1, FGFR2, FGFR3), TWIST1 and MSX2 gene.¹ The well known syndromes associated with craniosynostosis include Pfeiffer, Apert, Crouzon, Muenke and Saethre-Chotzen.⁴ Nonsyndromic craniosynostosis relates to sporadic cases without the presence of extracranial features. Primary craniosynostosis occurs in the absence of an associated syndrome or
known cause, whereas secondary craniosynostosis refers to premature fusion secondary to a craniofacial syndrome or intracranial, metabolic, teratogenic or haematological causes.\textsuperscript{4}

Sagittal synostosis is seen in 40-55\% of nonsyndromic cases and is therefore the most commonly affected.\textsuperscript{5} The second most common is coronal synostosis seen in 20-25\% of nonsyndromic cases, followed by metopic synostosis in 5-15\%. Lambdoid suture synostosis is extremely rare and makes up less than 5\% of nonsyndromic cases.\textsuperscript{4}

Craniosynostosis causes a characteristic cranial deformity. Virchow's law dictates that when a suture fuses prematurely, growth of the skull is typically restricted perpendicular to the fused suture and enhanced in a plane parallel to it in an attempt to compensate to provide adequate space for the growing brain.\textsuperscript{5} This knowledge allows clinicians to diagnose which suture has prematurely fused based on the distinct morphologic characteristics of the affected infant's head shape. Craniosynostosis is commonly evident at birth and is usually diagnosed in the first few months of life commonly due to the characteristic cranial deformity. In some cases, the synostosis is already evident in the antenatal ultrasound. Previously, skull radiographs alone were adequate to diagnose a single suture craniosynostosis. This is no longer acceptable as the only radiographic investigation because it often does not allow for adequate visualisation of the entire suture and also some of the sutures may not have completely fused. A 3D computed tomography CT scan is regarded as the current gold standard in the diagnosis of craniosynostosis as it not only allows for clear visualisation of the suture patency but also to exclude any underlying or associated intracranial abnormalities.\textsuperscript{6} The 3D CT scan is also utilised in the preoperative stage to plan the extent of cranial vault remodelling required.

Craniosynostosis is also a potential source of neural dysfunction. The premature ossification of cranial sutures does not merely cause facial symmetry and a dysmorphic head shape, it most importantly can cause raised intracranial pressure which can lead to visual impairment, deafness and possibly cognitive impairment.\textsuperscript{7,8} There is considerable debate in the literature on whether neurodevelopmental impairment exist in patients with nonsyndromic, single suture craniosynostosis. It remains challenging to clarify this controversy because the battery of tests used to gauge neurodevelopmental status and assess function at a specific point in time in infancy have poor long term predictive value as they relate to neurologic function.\textsuperscript{9} Even though Renier et al\textsuperscript{10} found increased intracranial pressure ICP in up to one third of patients older than one year with craniosynostosis, attributing intracranial pressure to neurodevelopmental delay is challenging considering the absence of "normative" data on paediatric ICP. Therefore the interpretation of increased ICP in the absence of clinical symptoms remains dubious.\textsuperscript{11} Contemporary neuropsychologic tests have been developed to detect subtle learning disabilities and studies utilising these methods have demonstrated that patients with nonsyndromic craniosynostosis tend to have decreased processing speed and difficulty performing tasks involving learning or memory, visual-spatial planning and problem solving. Magge et al\textsuperscript{9} suggested that surgery before the age of six months may be beneficial to improve IQ and mathematical performance.

Currently, most experts agree that surgery should be performed before the age of 12 months to take advantage of the normal period of rapid brain growth which occurs in the first year of life to splint open and remodel the cranial vault.\textsuperscript{12,13} Some authors strongly support surgery within three to nine months but ideally before six months to prevent further progression of the deformity, neurodevelopmental delay and the potential of developing raised ICP.\textsuperscript{8,11}
Despite significant advances in the management of craniosynostosis, surgical treatment remains the only treatment. There are many variations of surgical treatment performed and some are more extensive than others. Essentially, the goals of surgery include excising the fused suture, normalising the skull shape and expanding the cranial vault to allow for normal brain growth and prevent refusion as well as the potential sequelae of increased intracranial pressure. The literature remains divided whether or not a more extensive calvarial remodelling surgery as opposed to a limited suturectomy plays a role in the development recurrent raised ICP.

The rate of reoperation is an important outcome variable in the surgical treatment of craniosynostosis. Currently the literature reports a reoperation rate between 5-75%. However, only few papers distinguish between reoperation for aesthetic reasons or due to recurrent synostosis causing raised intracranial pressure. We aim to review specifically those risk factors associated with reoperation for recurrent synostosis causing raised intracranial pressure, as this is clinically more pertinent. Reoperation should not be taken lightly as it is associated with higher morbidity. In an older child, the skull is much thicker and does not lend itself to remodelling as easily as in infants. Additionally, the dura is often strongly adherent to areas of previous craniectomy and therefore more prone to tears and the risk of wound breakdown is higher in repeat surgery.

Many theories have been proposed as to why some children develop recurrent craniosynostosis associated with raised intracranial pressure following cranial vault remodelling surgery. These include involvement of more than one suture, patient's age at initial operation, stenosis of the coronal suture, the extent of the operation performed and whether the diagnosis of craniosynotosis was made antenatally or after birth. No previous systematic reviews have been performed on risk factors for reoperation for recurrent raised intracranial pressure.

The results of this review will inform clinical practice by helping surgeons minimise those modifiable factors which contribute to developing recurrent raised ICP in nonsyndromic children. When we are able to identify those factors associated with a higher probability of recurrent raised ICP, we may be able to minimise each patient's risk in order to prevent the need for a repeat operation with its associated morbidity. Additionally, we will be able to target those patients at higher risk with closer monitoring and investigations whilst concurrently reduce the frequency of outpatient reviews in those patients with a lower risk of developing recurrent raised ICP from restenosis. This will facilitate a more efficient use of the limited services available in the public health sector.

**Keywords**

craniosynostosis; recurrence; restenosis; refusion; reoperation

**Inclusion criteria**

**Types of participants**

This review will consider studies that include:

1. Male and female children up to the age of 18 years old who have had previous cranial vault remodelling surgery for craniosynostosis.
2. Patients diagnosed with primary, nonsyndromic craniosynostosis.
3. Patients who have undergone reoperation for signs and symptoms of raised intracranial pressure.

This review will exclude studies that include:

1. Patients with any genetic abnormalities.

**Types of intervention(s)/phenomena of interest**

This review will consider studies that evaluate the factors that may be associated with increased risk for developing recurrent raised intracranial pressure, including:

1. Patient's age at the time of first surgery
2. The extent of cranial vault remodelling surgery undertaken.
3. The involvement of single or multiple sutures.
4. The specific suture involved.
5. The timing of initial suture closure (antenatal vs postnatal).

Other risk factors identified during the course of the review will also be considered.

**Types of outcomes**

Recurrent raised intracranial pressure leading to repeat cranial vault operation.

We will consider studies that report raised ICP by objective measures such as papilloedema which is swelling of the optic discs caused by raised ICP and/or 24 hour ICP monitoring via any intracranial pressure monitoring device.

**Types of studies**

This review will consider both analytical and descriptive epidemiological study designs including prospective and retrospective cohort studies, case control studies, case series, individual case reports and cross sectional studies for inclusion.

**Search strategy**

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilised in this review. An initial limited search of MEDLINE and CINAHL will be undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference list of all identified reports and articles will be searched for additional studies. Studies published in English will be considered for inclusion in this review. Studies published from 1967 will be considered for inclusion in this review as that was when the cranial vault remodelling operation was first described. The search strategy will be performed with appropriate species and study filters.

The databases to be searched include:

PubMed, Embase, Web of Knowledge.
The search for unpublished studies will include:

Scirus, Mednar, ProQuest theses and dissertations and Grey Source, Index to Theses, Libraries Australia.

Initial keywords to be used will be:

craniosynostos*[mh] OR premature cranial suture closure[mh] OR craniostenosis[mh]

AND


AND

raised intracranial pressure [tw]

**Assessment of methodological quality**

Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardised critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix I). Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

**Data collection**

Data will be extracted from papers included in the review using the standardised data extraction tool from JBI-MAStARI (Appendix I). The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

**Data synthesis**

Quantitative data will, where possible, be pooled in statistical meta-analysis using JBI-MAStARI. All results will be subject to double data entry. Effect sizes expressed as relative risk for cohort studies and odds ratio for case control studies (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. A random effects model will be used and heterogeneity will be assessed statistically using the standard Chi-square. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate. Subgroup analysis will be considered where appropriate.

**Conflicts of interest**

No conflict of interest to be reported

**Acknowledgements**

Omar Breik BDSc (Hons), MBBS
References


Appendix I: Appraisal instruments

MAStARI appraisal instrument

JBI Critical Appraisal Checklist for Descriptive / Case Series

Reviewer __________________ Date ___________________

Author __________________ Year _______ Record Number _______

1. Was study based on a random or pseudo-random sample?  Yes ☐ No ☐ Unclear ☐ Not Applicable ☐
2. Were the criteria for inclusion in the sample clearly defined?  Yes ☐ No ☐ Unclear ☐ Not Applicable ☐
3. Were confounding factors identified and strategies to deal with them stated?  Yes ☐ No ☐ Unclear ☐ Not Applicable ☐
4. Were outcomes assessed using objective criteria?  Yes ☐ No ☐ Unclear ☐ Not Applicable ☐
5. If comparisons are being made, was there sufficient descriptions of the groups?  Yes ☐ No ☐ Unclear ☐ Not Applicable ☐
6. Was follow up carried out over a sufficient time period?  Yes ☐ No ☐ Unclear ☐ Not Applicable ☐
7. Were the outcomes of people who withdrew described and included in the analysis?  Yes ☐ No ☐ Unclear ☐ Not Applicable ☐
8. Were outcomes measured in a reliable way?  Yes ☐ No ☐ Unclear ☐ Not Applicable ☐
9. Was appropriate statistical analysis used?  Yes ☐ No ☐ Unclear ☐ Not Applicable ☐

Overall appraisal:  Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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JBI Critical Appraisal Checklist for Comparable Cohort/Case Control

Reviewer ___________________________ Date ___________________________

Author ___________________________ Year _______ Record Number ______

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<td>Is sample representative of patients in the population as a whole?</td>
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<td>Are the patients at a similar point in the course of their condition/illness?</td>
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<td>Are confounding factors identified and strategies to deal with them stated?</td>
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Overall appraisal:  Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)
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Appendix II: Data extraction instruments

MAStARI data extraction instrument

**JBI Data Extraction Form for Experimental / Observational Studies**

Reviewer ............................................. Date .............................................

Author ............................................... Year .............................................

Journal, ............................................... Record Number ..............................

**Study Method**

RCT □ Quasi-RCT □ Longitudinal □
Retrospective □ Observational □ Other □

**Participants**

Setting

Population

**Sample size**

Group A ............................................. Group B .................................

**Interventions**

Intervention A

Intervention B

Authors Conclusions:

Reviewers Conclusions:

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### Study results

#### Dichotomous data

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#### Continuous data

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