Comparative outcomes of craniectomy versus cranial remodelling in the human infant with isolated sagittal synostosis

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ABSTRACT

BACKGROUND

Craniosynostosis is a congenital condition characterised by the premature closure of one or more cranial sutures. The sagittal suture is the most common site, comprising 40-60% of cases. Premature fusion of this suture can cause scaphocephaly, seen morphologically as a narrow elongated skull with a decreased cephalic index. Diagnosis is made clinically and/or radiologically. The goals of surgical correction and the techniques used have evolved over time. Whilst there has been a general move from limited craniectomy to calvarial remodelling, in recent times there has been a return towards less invasive methods.

OBJECTIVES

The objectives were to identify and synthesize the best available evidence on the morphological, functional and neurological outcomes of craniectomy compared to cranial vault remodelling and compare this to existing results.

METHODS

A systematic review of the literature was conducted using the Joanna Briggs Institute methodology. The review considered studies of infants with primary isolated sagittal synostosis operated on before a mean of two years of age. The intervention of interest
was sagittal craniectomy; this was compared to cranial vault remodelling. Morphological, functional and neurological outcomes were included. Mortality, complications and aesthetic outcome were included as tertiary outcomes. A comprehensive search was undertaken across major databases. Retrieved studies were assessed by two independent reviewers for methodological validity. Data was extracted and where possible, pooled in statistical meta-analysis. Where this was not possible, findings were presented in narrative form.

RESULTS

Based on critical appraisal 27 studies, all descriptive in nature, were of suitable quality for inclusion. Meta-analysis was only possible for the primary morphological outcome (mean change in cephalic index post-operatively) based on two studies. This showed that at one year post-operative follow-up remodelling offers an advantage over craniectomy ($Z = 4.16, P<0.0001$). Narrative synthesis suggests that improvements of cephalic index to varying degrees were seen in patients receiving either procedure; whilst the mean change appears to peak early in patients who have undergone remodelling procedures, the trend suggests it may improve in the longer term after craniectomy.

Whilst global IQ scores may be comparable to an age-matched population, narrative review suggests that patients with sagittal synostosis who have undergone a surgical correction of any type may have discrepancies in specific domains and may be at risk of developing learning disorders. There is insufficient primary research with inter-
procedure comparison of pre-operative and post-operative cognitive or neurological outcome.

CONCLUSIONS

At one year follow-up, remodelling is superior to craniectomy in terms of mean change in cephalic index. However both procedures were seen to give improvements in the short, medium and long term. Neither procedure offers a distinct sustained advantage; longer follow-up is required to assess the comparative improvement over time.

There is insufficient evidence whether craniectomy or remodelling procedures offer superior functional or neurological outcome. Patients who have had surgical repair (any type) may have deficiencies in different subdomains and be at risk of learning disorders, whilst maintaining an age-appropriate global IQ and school performance. It is unknown if either surgery impart any restorative or protective benefit.
DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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May Thwin
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DEDICATION

To my father.
CHAPTER 1

INTRODUCTION
CHAPTER 1

1.1 INTRODUCTION

1.1.1 Sutural pathology

Craniosynostosis, also known as cranial synostosis, is a congenital condition characterized by the premature closure of one (the so-called “simple” synostosis) or more (“compound” synostosis) of the cranial sutures.\(^1\)\(^2\) It predominantly affects male infants, with an approximate male:female ratio of 4:1.\(^3\) The condition is commonly present at birth and is usually diagnosed during the first few months of life as a cranial deformity, noticed by the parents and/or healthcare workers.

Synostosis may occur as a primary condition, either in isolation or in its syndromic form in association with other congenital defects.\(^4\) The latter scenario is not as common, comprising only 20% of all cases of craniosynostosis.\(^2\) Alternatively the synostosis may be secondary to an identifiable underlying cause that may be intracranial, metabolic, teratogenic or haematological.\(^(4)\) The focus of this dissertation and the systematic review at its heart will be primary non-syndromic cases.

The sagittal suture is the most commonly affected, forming a reported 40-60% of all cases of craniosynostosis.\(^2\) It is estimated to have a birth prevalence of 190:1,000,000.\(^5\) Most cases of non-syndromic synostosis are sporadic. Whilst potential risk factors have previously been identified in the literature, the etiology remains largely unknown.\(^2\) The
familial form of non-syndromic craniosynostosis is rare; an autosomal dominant disorder, it is responsible for only 2-6% of sagittal synostosis. Scaphocephaly is reported as the most common presentation of craniosynostosis to craniofacial units.

Inconsistent terminology and definitions are a problematic area in this field of research. For example, whilst the two terms are often used interchangeably in the literature, it is important to understand that “scaphocephaly” should not be considered synonymous with “sagittal synostosis”. The word “scaphocephaly” refers only to the morphology or appearance of the skull, usually a result of sagittal synostosis. The term was originally introduced by von Baer in 1860 and literally means “skiff” or “keel-shaped” head. It does not make any inference to the underlying cause. Though it is less common, there have been documented cases of patients who are morphologically scaphocephalic without diagnosed sagittal synostosis. Likewise, sagittal synostosis does not always result in scaphocephaly. The lack of consistency in terminology in this area risks progress in understanding and treating the condition.

1.1.2 Anatomy

To understand the natural history and management of synostotic disease, we must first discuss the relevant anatomy and development of the human cranium. The word “cranium” is not synonymous with the “skull”. The skull consists of both the cranium and the mandible. The cranium, or cranial cavity has a roof, the cranial (calvarial) vault; and a floor, the so-called “base” of skull. The cranial vault consists of the frontal and
occipital bones, and the paired parietal, temporal and sphenoid bones. These bones articulate with each other at cartilaginous joints that are commonly known as sutures.

There are several slightly different definitions of the term suture, though all describe a similar process. One such definition describes the suture as a ‘craniofacial articulation in which contiguous margins of bone approximate each other and are united by a thin layer of fibrous tissue’.

The concept of the suture can be further divided into the proper suture, that is the soft tissue or mesenchyme of the suture and the suture ‘area’, which includes the osteogenic fronts of the adjoining bony plates. The suture ‘complex’ goes on to include not only these two components but also the dura mater beneath the suture and the overlying pericranium.

The cranial sutures are comprised of the sagittal, metopic, coronal, lambdoid, squamosal, sphenofrontal, sphenoparietal, sphenotemporal and masto-occipital sutures. In the skull of the normal human newborn, the sagittal suture lies in the centre of the cranial vault, running anterior to posterior from the anterior to the posterior fontanelle, separating the left and right parietal bones (Figure 1).
Figure 1. Cranial bones and sutures$^{12}$
Normal cranial sutures are regarded as “open” at birth, that is, the tissue of the suture ‘proper’ is not yet ossified. It is this characteristic that allows the overlapping of the calvarial bones necessary to permit passage of the infant through the birth canal. After birth there is a period of physiological remodelling where the head resumes a more “normal” shape. During this post-natal remodelling period and beyond, sutures facilitate the ongoing growth of the skull. This process if thought to be secondary to brain development. Over time, sutures may differentially close through a process of bony bridging. The histological content of the suture has been observed to change with the aging process, with a decrease in the number of fibroblasts and an increasingly irregular spacing of the collagen fibres.\(^{10}\) The details of the exact mechanism/s controlling the ultimate fate of the sutures is yet to be discovered.\(^{11}\)

In the human, the closure of the sagittal suture is thought to begin around 22 years of age through a proposed combination of local and systemic factors including biomechanical forces.\(^{10}\) As mentioned, the exact trigger that initiates this process remains to be elucidated. It is, however, known that bony bridging can begin at any point along the length of the suture, either anterior, middle or posterior.\(^{10}\) It is not uncommon for a suture to remain partially patent throughout adult life.

### 1.1.3 Pathogenesis

Premature fusion of the suture begins at one point before spreading throughout the remaining length of the suture, mirroring the physiological process of sutural bridging. It too can begin at either the anterior or posterior end, or in the middle of the suture.
proper. Its onset may be pre- or post-natal. Like the mechanisms of physiological suture ossification, the mechanisms for pathologic synostosis are heterogeneous and yet to be fully understood, although a number of different hypotheses have been suggested. Understandably, it has been already proposed that synostosis may merely represent an abnormally early variant of normal development.

The premature fusion of suture lines typically results in characteristic changes to the morphology and appearance of the calvarium. Early understanding of this was based largely on the 19th century writings of Sommering, who described the structure of sutures and the consequences of their premature closure, and Rudolf Ludwig Carl Virchow, a German pathologist, who was the first to use the term “craniostenosis” in the literature. It should be noted that craniostenosis refers not just to the premature closure of the sutures, but also implies an element of stenosis to the underlying brain itself. Further understanding in this area came from Virchow, whose law famously dictated that when a suture closes prematurely, subsequent cranial growth becomes specifically restricted in a plane perpendicular to the affected suture. Over time this simplistic view has been refined, and we now know that while growth is predominantly restricted in this plane, compensatory mechanisms occur in the unaffected sutures, including bone deposition in sutures adjacent to the affected suture and asymmetric bone deposition away from the bone plate. These mechanisms allow compensatory, albeit pathological, growth of the skull in an unrestricted direction.
Fusion of the sagittal synostosis can therefore result in the limited medial-lateral growth of the cranium with subsequent narrowing of the bi-temporal dimensions and an elongated skull (Figure 2). This in turn produces the characteristic “boat” or canoe appearance of scaphocephaly (Figure 3).
Figure 3. Unoperated sagittal synostosis at 3 months; photo courtesy of PJ Anderson, Australian Craniofacial Unit, with parental consent

With ongoing antero-posterior growth there may also be development of frontal and occipital bossing and a ridged sagittal suture line, features that are palpable on examination.²
1.1.4 Diagnosis

Diagnosis of craniosynostosis is usually based on clinical assessment and physical examination and radiological studies, including plain x-ray and/or computed tomography (CT). Plain radiography may be sufficient in diagnosis of single suture craniosynostosis (Figure 4).²

Figure 4. Sagittal synostosis on plain XR demonstrating occipital bossing and thickening and ridging of the sagittal suture line.¹⁷

Previous studies have shown that imaging is not required for the diagnosis of isolated sagittal synostosis, and that this diagnosis can be made based on clinical findings alone. However, imaging is generally indicated where there is the possibility of an alternate diagnosis, or where doing so may save the child from unnecessary surgery and the inherent risks.¹⁸ Radiological studies are particularly useful in so-called “mild” cases where the phenotype may not be obvious from appearance alone. It is important to differentiate between cranial deformity that is due to synostosis and that which is positional e.g. in the case of positional plagiocephaly, as the latter may be managed
successfully without the need for surgical intervention. Imaging may also be useful to look for other explanations for the phenotype when the clinical features are atypical.\textsuperscript{18}

Other appropriate investigations at the time of diagnosis may include genetic screening and neurodevelopmental analysis.\textsuperscript{19} Genetic counselling is more likely to be offered in the case of craniosynostosis syndromes, where the synostosis occurs in association with other anomalies e.g. digital and skeletal. Alternatively genetic testing may be appropriate in situations where there are multiple affected patients in the same family.

\textbf{1.1.5 Summary}

The introduction has described the relevant anatomy and physiology of the calvarial bones and cranial sutures, and the basic pathology necessary to understanding the natural history of craniosynostosis, with particular regard to the sagittal suture. It has described the epidemiology of sagittal synostosis and defined the terms pertinent to this field of study and the diagnosis of craniosynostosis by imaging and other investigations.
1.2 LITERATURE REVIEW

1.2.1 The history of surgery

Although the earliest descriptions of craniosynostosis can be traced back to the times of Galen and Hippocrates,\textsuperscript{20} the first recorded surgical procedure for sagittal synostosis did not occur until Lannelongue during the 1800s.\textsuperscript{20} In 1890, Odilon Lannelongue, a French surgeon and Professor, performed bilateral strip craniectomies to correct sagittal synostosis. Around the same time, LC Lane, an American surgeon, performed a strip craniectomy of a diseased sagittal suture accompanied by perpendicular craniectomies, which were designed to allow remodelling of the skull towards a normal shape. Unfortunately the latter procedure resulted in the patient’s death less than 24 hours after the operation. In addition to this poor outcome, a scathing paper published by Jacobi in 1894 described a high mortality rate in a sample of 33 microcephalic patients operated on for presumed craniosynostosis (15 of 33 patients died as a result of their operation).\textsuperscript{20} In addition to the published paper he also delivered the following speech to his contemporaries of the time, condemning what he perceived as inappropriate surgical practices;

“The relative impunity of operative interference accomplished by modern asepsis and antisepsis has developed an undue tendency to, and rashness in, handling the knife. The hands take too frequently the place of brains…Is it sufficient glory to don a white apron and swing a carbonized knife, and is therein a sufficient indication to let daylight into a deformed cranium and on top of the hopelessly defective brain, and to proclaim a success because the victim consented not to die of the assault? Such rash feats of
indiscriminate surgery…are stains on your hands and sins on your soul. No ocean of soap and water will clean those hands, no power of corrosive sublimate will disinfect the souls. – Jacobi, 1894

Due to these highly unfavourable results the concept of surgery for craniosynostosis fell out of favour and was discontinued for many years during the early part of the 20th century. It would take nearly 30 years for surgery to make a return, heralded by Mehner who in 1921 successfully performed a craniectomy to remove a fused suture. By the 1940s there was widespread support of strip craniectomy and suturectomy as accepted practices for the treatment of synostosis, along with a developing awareness of the need for early intervention. The so-called “modern” concepts of synostosis treatment were not established until the 1970s, when craniofacial surgery teams were formed through the union of neurosurgeons and plastic surgeons who worked together to address the dual goals of morphological and functional restoration.

1.2.2 Aims and rationale for intervention

As understanding of the disease process and its natural history changed, so too the indications for surgery and the goals of treatment have evolved over time. Compared to the syndromic form, isolated craniosynostoses are considered to pose simpler and more straightforward problems. However, this also means that the role of surgery for isolated non-syndromic craniosynostosis is less well-defined. It may be harder to justify invasive treatment for a perceived “mild” problem than it is for an obvious multi-suture syndromic anomaly.
As identified above, early reports suggested that surgical treatment was needed to prevent brain injury due to restricted growth. It was Virchow who first noted an association between brain pathology and abnormal calvarial shape. Such was the perception not only by clinicians but by patient’s families; Lane once famously quoted one such mother who approached him and pleaded for him to “unlock my poor child’s brain and let it grow”. Faber and Towne too, advocated the role of early prophylactic craniectomy to preserve neurological function, as well as improve aesthetic outcome. At least one modern study has found persistent behavioural defects in 45% of their sample of patients with so-called “mild” non-syndromic craniosynostosis who did not have corrective surgery (presumably because of the perceived severity or rather lack thereof).

It has already been proposed that all of the synostoses conditions, even those involving a single suture in isolation, can cause an increase in intracranial pressure (ICP), although it is more commonly seen in cases where there are multiple sutures involved or in syndromic cases. Studies have shown that up to 24% of patients with single suture synostosis may have raised ICP on examination. The exact mechanism by which synostosis contributes to intracranial hypertension is yet to be identified. One proposed mechanism points to an imbalance between brain growth and relative skull growth.

Intracranial hypertension has been implicated as the cause of the detrimental neurological effects observed in synostosis, as opposed to the synostosis condition
itself. Untreated craniosynostoses have been implicated in problems with vision in addition to mental function.\textsuperscript{22} Even without the development of its associated complications, raised ICP may be an indicator for surgical correction;\textsuperscript{23} so much so that in some centres the measurement of ICP is part of the pre-operative assessment before patients undergo remodelling.

Unfortunately, intracranial hypertension can be difficult to diagnose and may go unnoticed.\textsuperscript{22} Signs and symptoms are uncommon and often only occur in later stages of craniosynostosis.\textsuperscript{24} Direct measurement can provide clarity in situations when the clinical signs and symptoms are not distinct enough to diagnose ICP based on clinical assessment alone.\textsuperscript{26} Where it does cause symptoms, raised ICP has the potential to confound functional outcomes. It may be difficult to separate neurological complications as a result of the underlying synostosis from those due to raised ICP. The only way to truly diagnose raised ICP is to measure it directly through invasive means. In addition, intracranial pressure varies depending on age, can be altered by the position of the patient and whether or not they are relaxed or agitated. It can also be altered by certain anaesthetic drugs.\textsuperscript{26}

Despite the perception that surgery can relieve intracranial hypertension, the current indication for operative intervention has been centred on aesthetic or cosmetic merit.\textsuperscript{22} It is often perceived in the absence of intracranial hypertension that surgery serves a primarily aesthetic purpose.\textsuperscript{24} However, even if this is the case, and surgery is only beneficial for a “cosmetic” reason, this in itself is not without merit. It has previously
been shown that in general, children who do not undergo repair of their scaphocephaly have greater negative psychosocial sequelae compared with those who do, with head shape playing a significant role. Surgery is therefore undertaken with the goal of correcting the physical deformity in order to prevent stigmatisation of the child in later life.

There is a general consensus that the repair of craniosynostosis should occur as early as possible. Eighty percent of brain growth occurs in the first 2 years of life, and most of that occurs in the first 12 months. As discussed earlier this growth plays an important role in the remodelling of the infant skull. Based on this knowledge arguments have been made in support of earlier surgical intervention to allow reconfiguration of the skull towards a more normal morphology after correction of the synostosis. Suggested ranges for intervention are within the first 6-12 months, with the intention of preventing further progression of the deformity and possible complications associated with increased intracranial pressure.

1.2.3 Variations in operative technique

Broadly, we may think of synostosis treatment as surgical or non-surgical. Surgical treatment may be further divided into single or multi-stage; conservative craniectomy or more extensive remodelling; endoscopic or open procedure; with or without adjuncts (this may include positioning and orthotics such as helmet therapy); with or without hardware including different methods of fixation. The procedures used in the surgical management of non-syndromic sagittal synostosis are many and varied, and have evolved over time. It has been proposed that whilst syndromic craniosynostoses may
require multiple corrective procedures, isolated synostosis should ideally be managed with a single step operation, performed as early as possible.\textsuperscript{22} Unfortunately despite the advent of many new techniques, no single procedure to date has been identified as the “gold standard”. The reasons for this may in part be explained by the broad variability between patients, centres and clinicians.

The earliest and most conservative technique of treating synostosis involves excision of the diseased suture; this is known as strip craniectomy or suturectomy. Studies have shown that in many cases simply removing the diseased suture alone (in a strip craniectomy) was not adequate in patients who were being treated in later life, and did not give sustained results, with evidence of disease recurrence.\textsuperscript{27} The reasons for re-stenosis are unclear, but one mechanism proposed is that the disease itself does not originate in the bony tissue, but rather from the underlying dura mater of the sutural complex.\textsuperscript{27}

In attempt to delay or prevent re-stenosis, the technique has been modified and amended over time, with surgeons opting to trial different materials to interposition between the cut bony edges. However when it became apparent that this too was insufficient to achieve adequate correction, surgeons began resorting to more invasive and extensive procedures, which we now come to recognise as different types of remodelling.\textsuperscript{27}

Cranial vault remodelling is usually indicated in patients who are treated later in infancy and childhood to manage the phenotypic changes that may have already
occurred, as these techniques are designed not only to excise the diseased suture, but also to definitively resolve any cranial abnormalities that have resulted from the synostosis (Figure 5). 4,6

Figure 5. Frontal bone being replaced as part of cranial remodelling; photo courtesy of PJ Anderson, Australian Craniofacial Unit, with parental consent

However, some centres may elect to perform one of these more invasive procedures even in their younger populations, in favour of a more limited craniectomy, citing previous experience with disease recurrence as their rationale.

Other recent advances in synostosis treatment include spring-mediated cranioplasty, which was introduced in the early part of the 21st century. The rationale behind this
technique is to allow remodelling of the skull through gradual expansion in specific areas using springs. This technique was not explored within the confines of the systematic review forming the basis of this dissertation, as there is little consistency in its application between centres and this heterogeneity in technique makes it difficult to draw comparison.

Surgery in all areas continues to evolve as new techniques and new technology come to light. In the area of synostosis surgery it has come full circle; from limited craniectomy and excision of the diseased suture, to remodelling of the cranial vault to varying extents, and now back to limited procedures with various adjuncts such as helmet therapy. However lack of longitudinal comparison between these procedures limits the surgeon's ability to select the appropriate procedure for a particular patient and advise one procedure over another in terms of outcomes and complications.

1.2.4 Outcomes in the literature

As surgical management and indeed medical care worldwide moves more and more towards evidence-based models of care, it is more important than ever to have clearly defined goals of treatment. But how do we measure the relative success or failure of a surgical intervention? We must ask the question of which indicators can be used as objective markers of surgical outcome.
Previously used markers of clinical performance include mortality and morbidity and complications (blood loss, infection), operative time, length of admission, rate of disease recurrence and rate of re-operation. But outcomes can also be functional and aesthetic, and measure the more subjective outcomes including the quality of life.\textsuperscript{30} The outcome of synostosis surgery has been reported in a highly variable way in the literature. Such variability can create challenges to drawing comparisons between procedures and can make meta-analysis of results difficult.\textsuperscript{30} To add to this difficulty, there is no clearly defined baseline condition to be targeted and therefore surrogate markers for relative success or failure must be established.\textsuperscript{30} In the case of sagittal synostosis the surrogate markers used for success are commonly morphological; a reflection of the primary aim of surgery from its inception as a restoration of “normality”.

Cephalic index is a widely used measure of head growth of the infant skull, calculated using the ratio of the short and long axis of the head (short axis / long axis x 100).\textsuperscript{31} As it is a ratio, cephalic index is dimensionless. The index was first described by Swedish anatomist Andreas Retzius in 1842.\textsuperscript{32} In the early period after its introduction, cephalic index was used largely by anthropologists in discussion when describing and comparing human populations. Retzius used the terms “gentes dolichocephalae” and “gentes brachycephalae” to describe elongated and shortened skull shape respectively, but did not assign numerical values to his descriptions.\textsuperscript{33}
Cephalic index can be calculated using direct measurement and/or radiologically. Where cephalic index is greater than 70 it is unlikely there will be any noticeable deformity; while a cephalic index of less than or equal to 66 is usually noticeable.

There are some discrepancies in the literature regarding classification ranges for various head shapes. One of the earliest papers to provide “normal” ranges for cephalic index was by the March of Dimes group in 1980, who defined dolichocephaly (or scaphocaphly) as a cephalic index of 75.9 or less, normocephaly (or mesocephaly) as cephalic index 76-80.9 and brachycephaly as cephalic index of 81 or more. Since that time different centres have used variations of these figures to assign patients to different morphological categories. The average cephalic index of children with isolated sagittal synostosis has been quoted between 60 to 67, with normocephaly reported from 76 to 78.

Unfortunately, despite its widespread use, the cephalic index is far from perfect as a means of measurement. Even with a “standardized” tool it can still be challenging to compare outcomes for a number of reasons. One such reason is the apparent variation in degrees of sagittal synostosis morphology, which the cephalic index, when used as a single tool, may not be able to take into account. Even in the presence of a cephalic index in the so-called “normal” range there may be other associated morphological features which impact on the appearance of the patient, for example frontal and occipital bossing.
1.2.5 Summary

This section has described the history of surgery and the rationale for surgical intervention, including an explanation of how and why this has evolved over time. It has described the different techniques that have been utilized to correct sagittal synostosis, including different types of surgery, and the outcomes that other authors have previously used as surrogate markers of surgical “success”.

1.3 OBJECTIVES

1.3.1 Aims of review

The introduction has shown that synostosis surgery is beneficial and that these benefits may be both aesthetic and functional, though the full nature and extent remain to be seen. The extent to which single suture craniosynostosis can impair function remains as yet unclear. There is a range of procedures available to repair sagittal synostosis however there is little understanding whether the outcomes differ between procedures, and if so, how they differ. Therefore the systematic review central to this dissertation was designed with the presumption that a patient with isolated sagittal synostosis would undergo surgical repair. The aims of the review were to compare the post-operative outcomes of paediatric patients with isolated sagittal synostosis who underwent a limited craniectomy procedure with those who had cranial vault remodelling for the same problem. The outcomes of interest were in the areas of morphology, function and neurology.
1.3.2 Systematic review

Surgical research is fraught with inherent difficulties; “blinding” of the surgeon involved is not possible, and the process of randomization is often open debate, both ethical and otherwise. We cannot easily account for variability of technique and skill level between surgeons, even when it is the same procedure being performed. Therefore in many circumstances the best evidence we may be able to gain is through the systematic review process.

Systematic review methodology has certain advantages over traditional literature review in that it allows for more objective appraisal of the evidence. It is a transparent process, designed to be robust and reproducible. It provides a framework in which to summarise the existing evidence, allowing clinicians to efficiently access the current best available evidence and employ it in clinical practice. Compared with primary research, systematic review provides a broader “world view”. Where possible, meta-analysis aims to produce a single estimate of a treatment effect by combining the results of multiple studies, therefore reducing bias (which may occur by chance, especially if sample sizes are low) and improving statistical power. When appropriate a systematic review should also highlight a particular area of health care where further research is needed.
CHAPTER 2

METHODS
CHAPTER 2

2.1 INCLUSION AND EXCLUSION CRITERIA

The methods described here have previously been published as a systematic review protocol available through the Joanna Briggs Library; there will be some repetition of content with minor amendments to better suit the format of the thesis.

2.1.1 Population

The review considered studies that included male and female human infants with primary isolated sagittal synostosis diagnosed clinically and/or radiologically.

Studies concerning patients with secondary sagittal synostosis resulting from other causes were not included in the review. Likewise the review did not include cases with multiple sutures involved or syndromic cases with anomalies other than sagittal synostosis. However, studies that also included other suture types were included as long as sagittal synostosis (in its isolated form) formed the majority of cases and the results for these patients were available to be extracted separately. The review did not seek to include cases of scaphocephaly from causes other than sagittal synostosis (if they were explicitly declared as such). Studies that did not explicitly declare that sagittal synostosis was the sole diagnosis were included. Where identified, studies of children with mental and developmental impairments from causes other than sagittal synostosis were not included, as this would pose a confounding factor on these outcomes.
The review considered studies with mean age at time of surgery less than 24 months. This cutoff was selected with the intention of preventing further deformity, in order to minimise the potential for complications and to enable the theoretical normal reconfiguration of the growing skull. Although it was already identified that surgery should ideally be done in the first 12 months, the longer timeframe accommodates any potential administrative and clinical delays in treatment.

2.1.2 Intervention and comparator

The review included studies evaluating the outcomes of craniectomy methods; craniectomy versus cranial vault remodelling. For craniectomy, variations in method were accepted (including endoscopic versus non-endoscopic, linear versus extended, post-operative helmet therapy versus no helmet therapy) as long as the underlying technique involved only removal of the affected suture. Limited modification of surrounding cranial bones was permitted, as long as there was no significant re-shaping of the other bones. Whilst extended craniectomy was permitted in this category, barrel-staving and barrel-stave osteotomies were regarded as re-shaping and therefore this operation was classified in the remodelling category (see below for more detail) (Figure 6).
The comparator intervention used was cranial vault remodelling (CVR). This included any operation that involves modifying or re-shaping the bones of the calvarial vault, regardless of the extent (barrel-staving, subtotal remodelling, total remodelling were therefore all regarded as a variation of cranial vault remodelling). Depending on the exact technique used, CVR was referred to in the literature as any number of different names, including cranial or calvarial vault remodelling. There was a broader range of techniques used and greater variation in terminology in the comparator group (Table 1). Note that many times the techniques listed in the ‘remodelling’ column also combined the technique with some form of craniectomy to remove the diseased suture (Table 1).
### Table 1. Techniques and terminologies included in the craniectomy and remodelling interventions

<table>
<thead>
<tr>
<th>Craniectomy</th>
<th>Remodelling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic sagittal suture strip craniectomy</td>
<td>Barrel-stave osteotomies</td>
</tr>
<tr>
<td>Endoscopic-assisted extended strip craniectomy</td>
<td>Bifrontal craniectomy</td>
</tr>
<tr>
<td>Endoscopically assisted wide-vertex strip</td>
<td>Biparietal cranial vault remodelling</td>
</tr>
<tr>
<td>craniectomy</td>
<td></td>
</tr>
<tr>
<td>Extended craniectomy</td>
<td>Cranial vault reshaping</td>
</tr>
<tr>
<td>Extended strip craniectomy</td>
<td>Endoscopy-assisted wide-vertex craniectomy, barrel</td>
</tr>
<tr>
<td></td>
<td>vault osteotomies</td>
</tr>
<tr>
<td></td>
<td>Greenstick fracturing</td>
</tr>
<tr>
<td>Linear craniectomy</td>
<td>Melbourne method of total vault remodelling</td>
</tr>
<tr>
<td>Minimally invasive strip craniectomy</td>
<td>Modified pi plasty</td>
</tr>
<tr>
<td>Modified strip craniectomy</td>
<td>Modified pi procedure</td>
</tr>
<tr>
<td>Partial sagittal craniectomy</td>
<td>Nonendoscopic minimally invasive calvarial vault</td>
</tr>
<tr>
<td>Sagittal suturectomy</td>
<td>remodelling</td>
</tr>
<tr>
<td>Strip craniectomy</td>
<td>Open calvarial vault reconstruction</td>
</tr>
<tr>
<td></td>
<td>Pi procedure</td>
</tr>
<tr>
<td></td>
<td>Reversal exchange technique of total calvarial</td>
</tr>
<tr>
<td></td>
<td>reconstruction</td>
</tr>
<tr>
<td></td>
<td>Reverse pi procedure</td>
</tr>
<tr>
<td></td>
<td>Subtotal calvarectomy</td>
</tr>
<tr>
<td></td>
<td>Subtotal cranial vault remodelling</td>
</tr>
<tr>
<td></td>
<td>Subtotal remodeled calvarectomy</td>
</tr>
<tr>
<td></td>
<td>Wedge craniectomy</td>
</tr>
<tr>
<td></td>
<td>Wide-vertex suturectomy and biparietal barrel stave</td>
</tr>
<tr>
<td></td>
<td>osteotomies</td>
</tr>
</tbody>
</table>

Where there was significant deviation from the intervention of interest the study was excluded. For example, dynamic techniques including distraction osteogenesis and spring mediated cranioplasty, and so-called microscopic methods were excluded from review. The review did not include studies of non-surgical interventions e.g. helmet therapy without prior surgical intervention, a technique that is used more often in cases of positional deformity such as positional plagiocephaly, as opposed to deformities due to underlying synostosis.

Where there was confusion regarding the classification of a particular method or type of procedure, clarification was sought from a consultant craniofacial surgeon and the study classified as the intervention of interest or comparator. If it was still unclear at this point the paper was excluded from the further review as it was regarded as too divergent from
the other procedures. Studies including other intervention types were only included where the intervention of interest formed the majority of cases, and only if the results were presented in such a way that allowed extraction of the data separately.

2.1.3 Study types

The review considered both experimental and epidemiological study designs, including randomised controlled trials, and in their absence, non-randomised controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case control studies. Descriptive epidemiological study designs, including case series, were also considered for inclusion. The use of such wide inclusion criteria ensured adequate capture of data, given the widely heterogeneous nature of reporting in this field, and the scarcity of quality information.
2.1.4 Outcomes

The primary outcome of interest was the post-operative change in cephalic index at three time periods; short (0-6 months inclusive), medium (6-12 months) and long term (greater than 12 months). Cephalic index was used as a benchmark of restoration of “normal” morphology, with “normality’ being defined as cephalic index from 76.0 to 80.9%, while acknowledging the ongoing debate as to what “normal” really is, as some studies have accepted a much broader range of cephalic index values as their concept of “normal.”.

Cephalic index was chosen as the primary outcome due to its widespread use in the literature, meaning there were results readily available. It is easily and non-invasively measured and provides an objective measure that theoretically allows statistical comparison within and between study populations. Cephalic index values were accepted from either direct measurement or from radiologic studies. Previous studies have shown that there is good correlation between direct and indirectly measured cephalic index (from radiology images). There is no known correlation between the patient’s age at time of surgery and the percentage of difference achieved, allowing comparisons to be made between studies where patients have been operated on at different ages. It has been previously observed that although the improvement in cephalic index is most marked in the early post-operative period, improvements can persist in longer-term follow-up.
Despite its widespread use the cephalic index system is not without its flaws. As mentioned in the introduction, one particular weakness is that it does not take into account morphological variation, such as frontal bossing or bony ridging of the skull. These features may be present even when the cephalic index is in the “normal” range. It has also been shown that there may be poor correlation between the measured cephalic index and the patient’s own perceptions of their appearance.\(^6\) The reasons for this are unclear, but may reflect variations in perception of head shape and body image between different communities and cultures. Harkening back to its anthropological origins, it is possible that what is regarded “normal” may vary between different human populations depending on ethnicity.\(^45\) Therefore it is possible that in some groups, people may be “normally” scaphocephalic on objective measurement.

As the morphologic outcome does not take into account the patient’s level of development, nor their cognitive performance, the secondary outcomes were function (development), through the use of developmental scales, and the assessment of cognitive (neurological) outcome, using different tests for IQ. No limitations were put on which instruments and tools used in assessing these outcomes, as the preliminary search of the literature highlighted that there was wide variability across different centres. Even in situations where the same tool had been used, different components were often selected depending on the goals of the study and the focus taken by the researchers. Due to this widespread variation it was anticipated that meta-analysis would not be possible, and the aim was to gather as much information as possible to allow for narrative analysis of the data if this was the case.
Although they were not explicitly sought in the initial search strategy, tertiary outcomes were extracted from the data where possible. These included mortality, morbidity and the assessment of aesthetic outcome. Mortality was a dichotomous outcome of peri-operative all-cause mortality. This approach assumed the reporting of surgery-related mortality.

Morbidity was defined through complications including the need for peri-operative transfusion, surgical site infection, peri-operative raised intracranial pressure and the rate of re-operation. Preliminary reading had indicated that blood loss was measured in various ways. While some studies used the absolute amount of blood lost (and measured this in different ways which may or may not be accurate), others used the percentage of total blood volume lost, average amount transfused or number of patients transfused. This review used the latter i.e. rate of transfusion, as a surrogate marker for this outcome, simultaneously acknowledging that whilst the need for transfusion is useful as a marker of blood loss outcome and by extension the extent of surgery, in some cases transfusion may have been administered “prophylactically” and/or without clear clinical indication.

Peri-operative infection was documented as a dichotomous outcome (present/absent). This was defined as either microbiological evidence of surgical site infection (as opposed to systemic infection e.g. respiratory of urinary tract) and/or a clearly documented need for antibiotics.
Re-operation was only considered appropriate for inclusion where it was necessary for further correction or in the case of disease recurrence, not where the return to theatre was to treat post-operative complications such as drainage of haematoma or raised ICP.

Raised intracranial pressure (so-called intracranial hypertension) was included as a secondary outcome, with or without its associated neurological sequelae. As previously identified there is no clearly defined normal range of ICP, and no definitive figures or ranges were attached to this outcome. However as preliminary searching revealed that authors did not report figures, it could only be included as a dichotomous outcome. The estimated incidence of intracranial hypertension in sagittal synostosis has been reported elsewhere as 15-17%\(^{28}\) and it was predicted that a portion of patients of either group would have documented peri- or post-operative raised ICP. No guidelines were made to assess aesthetic outcome as it was predicted there would be wide variation in method of assessment and significant subjectivity.

As previously mentioned, the following time periods were investigated for all primary and secondary outcomes; short, medium and long-term.

<table>
<thead>
<tr>
<th>Table 2. Summary of Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
</tr>
<tr>
<td>Cephalic index</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
</tr>
<tr>
<td>Function (development)</td>
</tr>
<tr>
<td>Cognition (neurological)</td>
</tr>
<tr>
<td><strong>Tertiary</strong></td>
</tr>
<tr>
<td>Mortality</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Raised intracranial pressure</td>
</tr>
<tr>
<td>Re-operation</td>
</tr>
<tr>
<td>Aesthetic outcome</td>
</tr>
</tbody>
</table>
2.2 SEARCH STRATEGY

Initially the search strategy was intended to locate both published and unpublished studies; however, the initial search of published data returned a relatively large number of studies for appraisal from a variety of sources. It was therefore decided not to include the unpublished literature. Conference proceedings, where results were not published in the literature, were also excluded for this reason. It is acknowledged that this places potentially undue emphasis on published data. A three-step search strategy was utilised in this review. Search grids were constructed with the disease and the primary and secondary outcomes in mind and an initial limited search of MEDLINE and CINAHL was undertaken, followed by analysis of the text words contained in the title and abstract of relevant studies, and of the index terms used to describe the article. A second search, using all identified keywords and index terms, was undertaken across the included databases (Appendix I. Search Strategy). Thirdly, the reference lists of the included articles were cross-checked to search for any additional studies not found on initial searching. Only studies published in English were considered for inclusion in this review. It was accepted that this would exclude the potential impact of non-English studies. No time frame was imposed on the search.

The databases searched included: PubMed, Embase and Web of Knowledge. The search strategy was designed to look specifically at the interventions of interest and the primary and secondary outcomes; tertiary outcomes such as mortality, morbidity, re-operation and satisfaction were not included as search terms, but the data was extracted if these were mentioned in the included papers. Likewise searches for specific complications were not done e.g. anaesthetic complications; where a paper examined
only a particular complication these studies were excluded unless they also reported on the outcomes of interest.

Where articles were not immediately available further attempts were made through library resources, through the journals themselves and by contacting authors. Extra data for the included papers was sought by contacting the authors, however, this was not successful.
2.3 CRITICAL APPRAISAL

Quantitative papers selected for retrieval were assessed by two independent reviewers for methodological validity prior to inclusion in the review. This was done using the standardised critical appraisal instruments supplied by the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix II. Appraisal Instruments). Guidelines for appraisal were provided by the primary to the secondary reviewer to assist with clarifying particular points, especially those regarding different types of intervention and comparator. To be included in the review a study had to fulfill six of the nine criteria. In situations where it was not clear whether the answer to a particular question was ‘yes’ or ‘no’ it was deemed ‘unclear’; this was given the same score as a ‘no’. Where a particular point for inclusion was regarded as ‘not applicable’ this criterion was removed from the final score i.e. the total possible became eight instead of nine. When this was the case, the minimum number of points for inclusion was adjusted accordingly i.e. five out of eight. The absolute minimum for inclusion was four out of seven. The final decision for inclusion or exclusion of a paper when the two reviewers disagreed was at the discretion of the primary reviewer. It was regarded that due to the highly specialized nature of the subject matter, the primary reviewer was the better judge of appropriateness for inclusion.
2.4 DATA EXTRACTION AND META ANALYSIS

Where possible, quantitative data were extracted from included papers using the standardised data extraction tool from the JBI-MAStARI software (APPENDIX III. Data extraction instruments). Data extracted included specific details about the study methods, included populations, intervention types and outcomes significant to the review question and its specific objectives.

Due to the nature of the (observational) study types and the data that were available, the JBI-MAStARI tool was not always appropriate for extraction; in these cases proforma worksheets constructed using Microsoft Excel were used to manually extract data.

Quantitative data were, where possible, pooled in statistical meta-analysis using JBI-MAStARI. Otherwise, narrative synthesis was conducted. All results were subject to double data entry. Effect sizes were expressed as odds ratio (for categorical data) and weighted mean differences (for continuous data using the same measure) and standardized mean differences (for continuous data using different measures) and their 95% confidence intervals were calculated for analysis. Heterogeneity was assessed statistically using the standard Chi-square. A random effects, DerSimonian and Laird model, was selected for meta-analysis of continuous data. Due to the small size of the studies and the heterogeneity between them, it was not appropriate to use a fixed effect model and therefore assume that all studies were measuring the same effect size. Standardised mean difference was considered for use where different scales were utilized to measure the same concept. Where statistical pooling was not possible, the findings have been presented in narrative form including tables to aid in data presentation where appropriate.
CHAPTER 3

RESULTS
CHAPTER 3

3.1 SEARCH RESULTS

3.1.1 Search results

Collectively, 450 studies were identified from the various searches. After excluding 249 duplicate studies, 201 references remained. After further review of abstracts, 42 were excluded based on their content and 159 remained to be retrieved in full. Unfortunately, despite best efforts nine papers could not be retrieved. After full retrieval, 96 were excluded from the critical appraisal stage for reasons including:

- Language of the paper (criteria required the paper to be in English or at least provide a translation)
- Age of patients; in some situations only the range was given and not the mean, in others the mean was provided and was older than the criterion of 24 months.
- Outcome type; papers were only included where they reported either the primary and/or secondary outcomes. Where a study only reported tertiary outcome/s it was excluded from critical appraisal.
- Study type; in some cases the information in the abstract was incomplete or unintentionally misleading.
- Where results were repeated from another included paper; this was the case for several of the larger papers out of the USA, where the results of a study have been published in more than one resource, or else the subsequent results of the same cohort have been reported and published over a period of time at different points. Where this was the case usually the latter paper was used for the review and the earlier result excluded.
• Type of surgery; despite attempts at clarification by an expert craniofacial surgeon, some of the techniques were considered too anomalous to be categorized as either intervention or comparator.

• Insufficient details regarding the suture type, the nature of the operation performed and homogeneity/heterogeneity within the study sample.

This ultimately resulted in 55 studies deemed appropriate for critical appraisal. Of these, seven were excluded from appraisal based on the quality of the study or the nature of the intervention, found on closer inspection to be inappropriate to include in either category. Twenty-one were excluded after appraisal, leaving 27 papers regarded as being high enough quality for inclusion in the review (Figure 7).
450 studies identified from various searches

201 studies after discarding duplicates
• 42 excluded based on title/abstract

159 from full retrieval
• 148 able to be retrieved; 9 unable to be retrieved in full
• 95 excluded based on age, language, outcome, study type, repeated results, surgery type, suture type

55 for critical appraisal
• 7 papers excluded based on quality or type of procedure or outcomes
• 21 excluded after secondary and final appraisal

27 for data extraction and analysis

Figure 7. Studies identified from search, retrieval and appraisal
3.1.2 Critical Appraisal

The studies were generally of low quality, many scoring below the required number of points for inclusion (Table 3). Even many of the papers that were eventually included achieved the very minimum score required for inclusion. None of the papers scored perfectly across all nine criteria (Table 3). There are several possible reasons for the low scores seen in critical appraisal:

- Some criteria were not applicable to certain papers depending on the study design. These criteria were therefore excluded out of the final score, reducing the possible total.
- In cases where the authors were unclear in their methodology, a particular criterion would be marked as “unclear” and therefore according to the review protocol scored the equivalent of a “no”.

None of the included papers met the first criteria (that the sample was representative of the whole population (Table 3). In some ways this was expected due to the nature of the review. Likewise none of the included papers scored a “yes” for question seven (Table 3): “did the study report on outcomes of patients who were lost to follow-up?”. The most likely reason for this was that the design of retrospective studies only included those patients who were available for follow-up assessment at the time of the data collection, therefore automatically excluding those who were not. Unfortunately this also meant that it is unknown how many patients were lost to follow-up and what the outcomes of these patients were.
Table 3. Critical appraisal results by study and question number

<table>
<thead>
<tr>
<th>Study (Citation)</th>
<th>Question</th>
<th>Total Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Engel et al (2012) (49)</td>
<td>NA</td>
<td>Y</td>
</tr>
<tr>
<td>Engel et al (b) (2012) (50)</td>
<td>NA</td>
<td>Y</td>
</tr>
<tr>
<td>Guimaraes-Ferreira (2001) (56)</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Mutchnick et al (2012) (64)</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Sikorski (2007) (68)</td>
<td>N</td>
<td>Y</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study (Citation)</th>
<th>Question</th>
<th>Total Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Total Yes</td>
<td>20 (74.1)</td>
</tr>
<tr>
<td></td>
<td>Total No</td>
<td>7 (25.9)</td>
</tr>
<tr>
<td></td>
<td>Total NA</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
3.2 INCLUDED STUDIES

3.2.1 Study characteristics

The majority of the included papers came from the USA. Most of them had small sample sizes, less than 100 patients (mean 44.3, range 2-139) (Table 4). The paper with the least number of patients was a one to one comparison of two twin boys who underwent different procedures; craniectomy vs cranial vault remodelling. The largest sample size (139 patients) were all undergoing the same remodelling procedure by the same operative team.

In 11 of the papers the diagnosis was stated as clinical and/or radiological (Table 4). Two papers explicitly stated that diagnosis was radiological and did not mention clinical diagnosis, although it is inherently assumed that clinical suspicion was the driving force behind radiological investigation. Three of the papers stated that diagnosis was made on clinical assessment, without explicit mention of imaging. Eleven papers did not elaborate on method of diagnosis – where not specified it is assumed that the diagnosis was made on clinical grounds alone (Table 4). As stated in the inclusion criteria, radiological confirmation of diagnosis, though common in clinical practice, was not necessary. Due to low numbers of papers, sensitivity analysis could not be performed to compare studies where diagnosis was established radiologically versus those where method of diagnosis was not explicitly stated. Where studies specified gender, the patients were predominantly male, consistent with established knowledge of sagittal synostosis (Table 4). Eight of the papers did not give a breakdown of the gender in the study population (Table 4).
Five papers directly compared the intervention of interest (craniectomy) with remodelling which was the primary objective of the systematic review (Table 4). The remainder reported results of either craniectomy or cranial vault remodelling in isolation (while the study itself may have looked at other interventions, these papers did not provide a direct comparison between the intervention of interest and comparator according to the review protocol). As previously discussed, both the intervention of interest and the comparator categories each encompass a variety of techniques, all of which were deemed appropriate to be placed in either category through independent review and, where needed, expert clarification.

While there is an undeniable large variation between craniectomy methods e.g. endoscopic vs non endoscopic and choice of ongoing post-operative management e.g. helmet vs no helmet therapy, further subgroup analysis was not able to be performed in this review due to limitations of data, and all of these studies have been regarded as the same for the purposes of data extraction and analysis.

3.2.2 Intervention types in included studies

Five papers looked at both craniectomy and remodelling; six studied craniectomy patients alone and the remaining 16 studied remodelling on its own (Table 4). Some of the papers separated patients into different subgroups and drew comparison between them e.g. limited vs more invasive skin incision for essentially the same cranial procedure\textsuperscript{63} or limited vs more extensive craniectomy.\textsuperscript{58} For the purposes of this review the patients in both of these studies were classified as the one procedure i.e.

45
remodelling and craniectomy respectively. A number of procedures were categorised together in this manner, despite some differences in technique. Kaiser et al looked at three different types of craniectomy; their category “a” (limited) and “b” (extended) procedures were deemed to be appropriate to place in the craniectomy category, whereas their category “c” procedure was deemed to fit neither category and therefore this subgroup of patients from this category have not been included in further extraction and analysis.58

Massimi et al looked at 94 patients who all underwent a similar procedure of cranial vault remodelling; however within their cohort they split their patients into two groups – those who underwent limited incision and those who underwent more invasive or what was regarded as a traditional incision.63 As the underlying bony procedures performed were essentially the same, regardless of approach, these patients were all regarded as one group for the purposes of this review and placed in the remodelling category.

3.2.3 Outcomes of included studies

Twenty-four of the 27 included papers reported on the primary outcome, post-operative improvement in cephalic index (Table 4). Three of these papers did not define how they calculated the cephalic index values reported in their study population. The remainder reached this figure either by clinical or anthropomorphic measurements and/or radiological methods; the latter usually involved the use of computed tomography (Table 4). However one paper calculated cephalic index through the use of laser scanning.54
In three of 24 papers it was unclear whether the cephalic index had been measured in the entire cohort or a portion of it. Of the remainder, 11 papers reported on post-operative cephalic index of a sample of their patients; 10 papers gave the cephalic index values for all patients in their study population (Table 4).

Each of the outcomes will be discussed individually. Results are presented in meta-analysis format first and then as narrative, using tables accompanied by explanation. This will be followed a comparison of the results of meta-analysis to those of the narrative where possible.
Table 4. Summary of included studies including details of all sagittal synostosis patients

<table>
<thead>
<tr>
<th>Study (Citation)</th>
<th>Country</th>
<th>Numbera (Gender breakdown)</th>
<th>Diag.d</th>
<th>No. remodeled</th>
<th>No. craniectomy</th>
<th>CI</th>
<th>Methodd</th>
<th>Develop.</th>
<th>Cognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agrawal et al (2006)(44)</td>
<td>Canada</td>
<td>90b</td>
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<td>90</td>
<td>Yes</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amm et al (2005)(46)</td>
<td>USA</td>
<td>22 (17M : 5F)</td>
<td></td>
<td></td>
<td>22</td>
<td>Yes</td>
<td>C+R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brichtova et al (2010)(47)</td>
<td>Czech Republic</td>
<td>29 (19M : 10F)</td>
<td></td>
<td></td>
<td>4</td>
<td>Yes</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chieffo et al (2010)(48)</td>
<td>Italy</td>
<td>35 (27M : 8F)</td>
<td></td>
<td></td>
<td>35</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engel et al (2012)(49)</td>
<td>Germany</td>
<td>38 (34M : 4F)</td>
<td></td>
<td></td>
<td>38</td>
<td>Yes</td>
<td>?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engel et al (b)(2012)(50)</td>
<td>Germany</td>
<td>46 (37M : 9F)</td>
<td></td>
<td></td>
<td>46</td>
<td>Yes</td>
<td>C</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Fata et al (2001)(51)</td>
<td>USA</td>
<td>23</td>
<td></td>
<td></td>
<td>23</td>
<td>Yes</td>
<td>R</td>
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<td></td>
</tr>
<tr>
<td>Gociman et al (2012)(54)</td>
<td>USA</td>
<td>46</td>
<td></td>
<td></td>
<td>67 (with helmet)</td>
<td>Yes</td>
<td>Laser*</td>
<td></td>
<td></td>
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<tr>
<td>Greensmith et al (2008)(55)</td>
<td>Australia</td>
<td>30 (22M : 8F)</td>
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<td></td>
<td>30</td>
<td>Yes</td>
<td>R</td>
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<tr>
<td>Jimenez et al (2004)(57)</td>
<td>USA</td>
<td>139 (99M : 40F)</td>
<td></td>
<td></td>
<td>139</td>
<td>Yes</td>
<td>C</td>
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<td></td>
</tr>
<tr>
<td>Kaiser (1988)(58)</td>
<td>Switzerland</td>
<td>50</td>
<td></td>
<td></td>
<td>39 (linear + extended)</td>
<td>Yes</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kandasamy et al (2011)(59)</td>
<td>UK</td>
<td>66 (54M : 12F)</td>
<td></td>
<td></td>
<td>66</td>
<td>Yes</td>
<td>?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kohan et al (2008)(60)</td>
<td>USA</td>
<td>2 (2M : 0F)</td>
<td></td>
<td></td>
<td>1</td>
<td>Yes</td>
<td>R</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Notes:
- a Number includes all included patients regardless of synostosis type.
- b Number does not include patients with additional synostoses.
- C = Cranial Index
- R = Resection
- C+R = Combined Cranial Index and Resection
- Laser* = Laser-assisted craniectomy
- CI = Craniofacial Index
- Develop. = Development
- Cognition = Cognition

48
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Total No.</th>
<th>Gender Breakdown</th>
<th>No. of Patients</th>
<th>Methodology</th>
<th>Diagnosis Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magge et al (2002)(61)</td>
<td>USA</td>
<td>16</td>
<td></td>
<td>16 (extended)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Massimi et al (2007)(63)</td>
<td>Italy</td>
<td>94 (76M : 18F)</td>
<td>C</td>
<td>94</td>
<td>Yes</td>
<td>C</td>
</tr>
<tr>
<td>Mutchnick et al (2012)(64)</td>
<td>USA</td>
<td>18 (11M : 7F)</td>
<td>C + R</td>
<td>18</td>
<td>Yes</td>
<td>C+R</td>
</tr>
<tr>
<td>Panchal et al (1999)(65)</td>
<td>USA</td>
<td>40</td>
<td>C + R</td>
<td>28 (extended)</td>
<td>Yes</td>
<td>R</td>
</tr>
<tr>
<td>Ridgway et al (2011)(66)</td>
<td>USA</td>
<td>56 (47M : 9F)</td>
<td>C</td>
<td>56 (with helmet)</td>
<td>Yes</td>
<td>C</td>
</tr>
<tr>
<td>Shah et al (2011)(67)</td>
<td>USA</td>
<td>89 (63M : 26F)</td>
<td>R</td>
<td>42 (endoscopic; with helmet)</td>
<td>Yes</td>
<td>C</td>
</tr>
<tr>
<td>Sikorski et al (2007)(68)</td>
<td>USA</td>
<td>21</td>
<td>R</td>
<td>21</td>
<td>Yes</td>
<td>R</td>
</tr>
</tbody>
</table>

a Total number of sagittal synostosis patients within a study who fulfilled the inclusion criteria.
b Italic text indicates that gender breakdown was not reported by the study authors.
c Includes all patients in this study who underwent remodelling, regardless of the approach used by the authors to do so e.g. traditional open technique, limited invasive approach.
d Indicates how sagittal synostosis was diagnosed and/or how cephalic index (cephalic index) was measured. C = clinical diagnosis, R = radiological diagnosis (of any modality e.g. plain x-ray, computed tomography)
? Indicates where method of CI measurement was unclear
3.3 PRIMARY OUTCOME

The results of the primary outcome will be presented in three ways in descending order of power. Firstly, meta-analysis will compare the mean change in cephalic index between craniectomy and remodelling. This will be followed by narrative synthesis consisting of those papers which report mean change in cephalic index, but whose data was not appropriate for meta-analysis. Lastly, those papers that reported on cephalic index, but not mean change, will be presented and discussed.

3.3.1 Meta analysis

Figure 8. Forrest plot of medium term (6-12 months) post-operative cephalic index

Meta-synthesis of post-operative change in cephalic index demonstrates that at one year follow-up after synostosis surgery the comparator (control) procedure, cranial vault remodelling is superior to the intervention of interest, limited craniectomy (Figure 8).
The meta-analysis was derived from two out of five possible studies that directly compared the intervention of interest with the comparator, by Marsh et al and Panchal et al. Marsh et al reported comparative outcomes of 11 patients with sagittal synostosis who underwent craniectomy and 11 who underwent remodelling, and likewise Panchal et al compared 28 (extended) craniectomy patients with 12 who underwent remodelling. All patients in both of these studies had documented pre-operative cephalic index measurements and post-operative cephalic index measured one year after surgery with a reported mean change and standard deviation. In accordance with the review protocol this was regarded as “medium term”.

The other three studies did not present their data in a format that permitted meta-analysis. To be included in the meta-analysis a paper was required to provide the mean change and standard deviation for all patients in both the intervention and the comparator groups; while it is possible to calculate the mean change from the pre- and post-operative mean cephalic index values, to calculate standard deviation requires imputing a correlation between the initial and final values. To do this requires a sensitivity analysis, which could not be performed from the limited study numbers, and without this it was not appropriate to calculate standard deviation.

In the case of Brichtova et al it was unclear: (i) how they reached the mean values reported, as the authors only reported pre- and post-operative cephalic index values of a portion of their craniectomy population and (ii) why the mean change was only given for this select group. It was also unclear whether the authors provided the standard
Likewise Shah et al did not give information regarding mean change/change score, nor the standard deviation. In the case of Kohan et al, whilst providing appropriate comparison of craniectomy and remodelling, the study only had one patient in each group (reporting twin patients), making it inappropriate to include this data in the meta-analysis (there is no mean and no standard deviation). All three of these papers will be discussed in the next section as part of narrative synthesis.

3.3.2 Narrative synthesis

As mentioned earlier in this chapter, the narrative synthesis of those papers not appropriate for meta-analysis will be presented in parts in order of the strength of study design. The first part of narrative synthesis will present the results from papers that reported post-operative mean change in cephalic at short, medium and/or long term. The second part will present the lowest power evidence generated by review and present results of those papers that discussed post-operative mean cephalic index but did not provide mean change. The information has been presented in a descriptive format.

3.3.2a Mean change in cephalic index

The data for mean change in cephalic index was able to be extracted from 13 papers, including that by Brichtova et al, which had earlier been excluded from meta-analysis due to unclear methodology (Table 5).
Whilst some of the studies explicitly reported the mean change in cephalic index, others only provided the raw data of pre- and post-operative cephalic index for their patients. However it was possible to calculate mean change from this data by calculating the change in cephalic index for each patient individually then calculating the mean of these values. In a majority of papers, the mean change given was only for a subset of their patients who had post-operative data available; likewise in others it was unclear whether the mean change reported encapsulated the entire cohort (Table 5). Of the 12 papers, only Amm et al provided the standard deviation in addition to mean change.

Some authors have described mean change using the term “percentage”; it was assumed that this percentage equates mean change, rather than an actual percentage of the pre-operative cephalic index.

Only one of the papers reported the mean change at all three time points of interest and this was by Agrawal et al. Both this study and those by Kandasamy et al. and Massimi et al demonstrate that greater mean change in cephalic index can be observed at short-term follow-up compared with medium or long-term. This suggests that the peak improvement of cephalic index occurs early after surgery before tapering off over time (Table 5). Of note, all three of these papers studied patients who underwent remodelling procedures. Only one paper by Gociman et al reported mean change in cephalic index in a craniectomy population at more than one time point. Of note the results of that paper suggest that mean change increases over time i.e. cephalic index continues to improve.
The remaining papers only reported mean change at one time point so it is not possible to comment on the trend in mean change over time for the patients in these studies (Table 5). All that can be extracted from this is that patients who have undergone craniectomy appear to have greater mean change at early follow-up compared with those who underwent craniectomy.
Table 5. Mean change in cephalic index

<table>
<thead>
<tr>
<th>Study (citation)</th>
<th>No. remod.</th>
<th>No. cran.</th>
<th>Mean change (range) in CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Short term &lt;6 mth</td>
</tr>
<tr>
<td>Agrawal et al (2006)(44)*%</td>
<td>90</td>
<td></td>
<td>11.1%</td>
</tr>
<tr>
<td>Amm et al (2005)(46)*</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brichtova et al (2011)(47)*</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Engel et al (b)(50) (2012)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year Engel et al (b)(50) (2012)*</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gociman et al (2012)(54)</td>
<td></td>
<td>46</td>
<td>3.3</td>
</tr>
<tr>
<td>Greensmith et al (2008)(55)*%</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Massimi et al (2007)(63) control</td>
<td>94</td>
<td></td>
<td>12.0</td>
</tr>
<tr>
<td>Massimi et al (2007)(63) study</td>
<td></td>
<td></td>
<td>11.3</td>
</tr>
<tr>
<td>Murray et al (2007)(6)</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutchnick et al (2012)(64)*</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virtanen et al (1999)(69)</td>
<td>18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Indicates where either the whole cohort has not been measured at a particular follow-up timepoint, or where it is unclear how many of the patients have been examined and/or reported.
% Indicates where the authors have presented the mean change as a percentage.
3.3.2b Post-operative cephalic index

The second part of the narrative synthesis consists of those papers that reported post-operative cephalic index but did not give details regarding the mean change. It is not appropriate, statistically speaking, to calculate the mean change from simply subtracting the pre-operative mean cephalic index from the post-operative mean cephalic index. For this reason the results of these papers have been discussed separately to those above (Table 6).

Pre-operative mean cephalic index appears to be largely comparable across the different studies, regardless of the potential contribution of factors including age at the time of the first operation, the selected method of intervention (thought this may be a result of, rather than a contributing factor) and the geographic location of the study. The overall mean of these values (average of the mean pre-operative cephalic index for combined intervention and comparator cases), where given, was 66.3 (Table 6). Standard deviation was not provided for all pre-operative mean cephalic indices.

Short-term post-surgical cephalic index was only available for one paper by Jimenez et al, and even this was not clearly described (Table 6). Jimenez et al reported that in their patients who underwent remodelling ‘...after the 2nd postoperative month, the mean cephalic index reached a consistent plateau near 80.’ It was assumed from this information that the short-term mean cephalic index was 80.

Two papers reported on medium-term post-surgical cephalic index, reporting values of
73 and 74 (Table 6). One of these papers divided their results into patients who had undergone linear craniectomy and extended craniectomy, and these groups achieved mean post-operative cephalic indices of 73 and 74 respectively.\textsuperscript{58} This was also the only paper that reported mean post-operative cephalic index at more than one time point (medium and long term); its results appear to suggest that improvements in cephalic index are sustained over time. The second paper that also reported medium-term mean cephalic index studied patients undergoing remodelling procedure.\textsuperscript{23}

Eight papers reported long-term post-operative cephalic index (at a mean time of follow-up greater than one year after surgery), with two papers reporting values for subsets of their patient groups (Table 6). There was significant heterogeneity in the follow-up end points selected by authors, from one year to several, and not all papers stated the mean duration of their follow-up. Of these eight papers, values ranged from 71.1 at follow-up of 37 months in a study of 25 patients who underwent remodelling,\textsuperscript{52} to 77 at follow-up of 6 years in the child who underwent remodelling in the twin study.\textsuperscript{60}

The only comment that can be made from the result above is that both intervention and comparator procedures appear to improve cephalic index to varying degrees post-operatively. It remains to be seen whether these improvements are sustained over time; at the very least there is no evidence here to suggest that either intervention or comparator groups underwent regression of cephalic index at a later stage. It is important to remember that none of these studies measured cephalic index at all three
time points post-operatively. It is not possible to perform subgroup analysis based on
the available data to determine whether or not helmet contributes to the ongoing
improvement in cephalic index.
Table 6. Summary of post-operative mean cephalic index

<table>
<thead>
<tr>
<th>Study (citation)</th>
<th>No. remodeled</th>
<th>No. craniectomy</th>
<th>Pre-op CI</th>
<th>SD</th>
<th>Mean’</th>
<th>SD</th>
<th>Time (mth)</th>
<th>Mean</th>
<th>SD</th>
<th>Time (mth)</th>
<th>Mean</th>
<th>SD</th>
<th>Time (mth)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engel et al (2012)(49)</td>
<td>38</td>
<td>*65.1</td>
<td>72.7</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friede et al (1996)(52)</td>
<td>25</td>
<td>65.4</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guimarães-Ferreira et al (2001)(56)</td>
<td>110</td>
<td>*65</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Jimenez et al (2004)(57)</td>
<td>139</td>
<td>*67.4 (61-90)</td>
<td>*80f</td>
<td>2</td>
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<tr>
<td>Kaiser (1988) (linear)(58)</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td>73</td>
<td>5</td>
<td>8</td>
<td>72</td>
<td>5.5</td>
<td>19</td>
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<tr>
<td>Kaiser (1988) (extended)(58)</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
<td>74</td>
<td>7</td>
<td>7</td>
<td>73</td>
<td>5</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaufman et al (2004)(23)</td>
<td>12</td>
<td>*65 (58-70)</td>
<td>*73.4</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Kohan et al (2008)(60)</td>
<td>1</td>
<td>62</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Ridgway et al (2011)(66)</td>
<td>1</td>
<td>63</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Shah et al (2011)(67)</td>
<td>42</td>
<td>68.5</td>
<td>67.7</td>
<td></td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

Table does not include the results of the papers considered suitable for and included in previous meta-analysis. Where a box has been left blank indicates that this value was not reported by the study authors (excluding the no. remodeled and no. craniectomy which refers to sample size)

* Indicates where either the whole cohort has not been measured at a particular followup timepoint, or where it is unclear how many of the patients have been examined and/or reported.

a Including up to 6 months mean follow-up time of those patients for whom post-operative cephalic index was calculated. Range not included.
b Including up to 1 year
c Mean cephalic index and (range)
d Reported by the reaching a plateau by 2 months of an approximation around cephalic index 80.
? Unclear or unknown
3.4 SECONDARY OUTCOMES

3.4.1 Development and cognitive outcomes

Of the six papers that discussed one or both of the secondary outcomes, only one compared the intervention of interest to the comparator (60) (Table 7). As such it was not appropriate to conduct meta-analysis for either of the secondary outcomes, and all results for these outcomes have been subject to narrative synthesis alone. The majority of studies appropriately tested their patients at school age as suggested by previous studies (regarded as “long term” according to the review protocol); one study did not state their age of testing. A wide variety of scales and measures were used to examine development and cognition (Table 7). Of these the most frequently used was the Wechsler Intelligence Scale for Children (WISC). The WISC provides a measure of both overall intellectual ability and separate cognitive domains. The discrepancy between verbal and performance IQ has been regarded as one of the most interpreted results of the WISC.

The findings of the narrative synthesis suggest that there may be a discrepancy between the verbal IQ (VIQ) and performance IQ (PIQ) in patients who have previously undergone surgical correction of isolated sagittal synostosis, including patients who have undergone remodelling or craniectomy. This may indicate a potential risk for developing non-verbal learning disorders in patients who have undergone surgery to treat their synostosis. However, there is contradictory evidence to suggest that it is the opposite, verbal domain which suffers.
One of the challenges posed in systematic reviews is that studies do not always report on their methodology and how they reached particular conclusions. This is the case in one paper which commented on the secondary outcomes of development and neurological outcomes, but did not explicitly state their methodology, rendering their data practically redundant for this review. Five of the six papers reported on development separate to intelligence quotient, though each varied in their methodology and the way they chose to present their findings, making comparison and even narrative synthesis challenging (Table 7).
### Table 7. Summary of function (development) and neurological (cognitive) outcomes including the mean age of post-operative patients, methods used in the assessment and the outcomes quoted from the studies

<table>
<thead>
<tr>
<th>Study (Citation)</th>
<th>Remod.</th>
<th>Cran.</th>
<th>Mean age at testing (range)</th>
<th>Methods used</th>
<th>Function</th>
<th>Neurological (IQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chieffo et al (2010) (48)</td>
<td>35</td>
<td>13.4 years (9.2 – 16.10 years)</td>
<td>WISC-R Developmental Test of Visual-Motor and Perceptual Integration Purdue pegboard Reading and writing tests Rey Osterieth test Bell’s cancellation test Tower of London</td>
<td>“Seven percent of children with sagittal craniosynostosis showed visuospatial and constructional ability defects (Rey Complex Figure Test) with associated visual memory recall deficits” (p.234) “(6 of 35) exhibited selective and sustained attention deficits” (p.234) “Verbal planning, lexical tasks, visual motor integration, perceptual skills, and working memory were normal in all cases.” (p. 234) “Fourteen percent had mild writing difficulties. Speed in reading skills was below average in 2 cases (6%) and understanding was below average in 6 (17%).” (p.234)</td>
<td>“All the children with sagittal craniosynostosis had normal IQs, with 31% having above average VIQs, 43% average, 16% low average, and 10% low. Significant difference (&gt; 12 points) in the comparative evaluation of VIQ and PIQ… (mean VIQ = 111.14 and mean PIQ = 99).” (p. 234)</td>
<td></td>
</tr>
<tr>
<td>Engel et al (b) (2012) (50)</td>
<td>46</td>
<td>Unclear</td>
<td>BSID II (Bayley Scales of Infant Developmental Second Edition)</td>
<td>Griffiths’ Mental Development Scales (GMDS) Subscales: locomotor, personal social behavior, hearing and speech, eye–hand coordination, and performance. Results transformed into general development quotient (GDQ; mean,100; SD,15).</td>
<td>“3 patients &gt;12 months at time of procedure showed preoperative mental and/or motor developmental delays, compared to 5 patients &lt;12 months at time of procedure.” (p.1235)</td>
<td>Not measured</td>
</tr>
<tr>
<td>Gewalli et al (2000) (53)</td>
<td>26</td>
<td>16.33 months (9 – 40 months)</td>
<td>Griffiths’ Mental Development Scales (GMDS) Subscales: locomotor, personal social behavior, hearing and speech, eye–hand coordination, and performance. Results transformed into general development quotient (GDQ; mean,100; SD,15).</td>
<td>“Comparison of the mean GDQ for the whole group, using the paired Student’s t-test, showed no significant differences between pre- and post-operative scores (p = 0.33). (p. 418) “...no significant results for psychometric outcome measurements (GDQ) and age (p = 0.521) or surgical technique (shortening of the skull; p = 0.568)” (p. 418)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kohan et al (2008) (60)</td>
<td>1</td>
<td>1 (extended) (4 and 7 years)</td>
<td>Preschool receptive and expressive scales; IQ test at 4 years Global intelligence evaluations; IQ test at 7 years</td>
<td>“With the endoscopic patient, both preschool tests and global evaluations were lower compared with normative data (for the endoscopic patient preschool receptive scores = 89, pre-school expressive scores = 90; subtests were below normal for both attention and memory). With the CVR patient, both preschool tests (receptive score = 98, expressive score = 102) and global evaluations were similar to normative age-matched data.” (p.1456)</td>
<td>When comparing intelligence tests at 4 years of age (3 years postoperatively) and 7 years of age (6 years postoperatively), both children had similar IQ test scores (at 4 years: endoscopic IQ = 103, CVR IQ = 105; at 7 years: endoscopic IQ = 99, CVR IQ = 100).” (p. 1456)</td>
<td></td>
</tr>
<tr>
<td>Magge et al (2002) (61)</td>
<td>16</td>
<td>N/A (6 - 16 years)</td>
<td>WISC-III Developmental Test of Visual-Motor Integration Wide Range Achievement Test—Revised (WRAT) Conner’s Continuous Performance Test Wisconsin Card Sorting Test Vineland Adaptive Behavior Scales</td>
<td>“IQ scores (WISC-III) fell within the normal range for the general population, with an average full-scale IQ score of 110.6…there was a significant difference of 8.3 (P = 0.021) between the verbal IQ (VIQ) (mean = 113.8) and performance IQ (PIQ) (mean = 105.4) scores” (p. 100)</td>
<td>Etc</td>
<td></td>
</tr>
<tr>
<td>Virtanen et al (1999) (69)</td>
<td>18</td>
<td>N/A (7.8 - 16.3 years)</td>
<td>WISC-R Developmental Test of Visual-Motor Integration Purdue pegboard Reading comprehension test Visual Retention Test, Multiple Choice Form I by Benton et al</td>
<td>“On the tests of verbal conceptual thinking and reasoning and on the test of auditory short-term memory, the study group performed significantly less well than the control group…on tests of fine-motor skills, visual-motor skills, and visual-spatial skills, the study group and the control group did not differ.” (p. 793)</td>
<td>“All children were in the average or low-average range of general intelligence.” (p. 793)</td>
<td></td>
</tr>
</tbody>
</table>
3.4.2 Neurological and cognitive outcome

Four papers reported on the post-operative IQ measures of their patients who had undergone surgery for isolated sagittal synostosis, and suggested that these patients performed within a broadly normal range when looking purely at global IQ (Table 7). The twin patients in Kohan et al had comparable IQ at the different follow up times; however details regarding the measurement of their IQ and the different domains are not reported and it is not possible to comment whether or not there were any subtle discrepancies in their performance.\(^6\)
3.5 TERTIARY OUTCOMES

3.5.1 Mortality

Despite the highly invasive nature of the procedures there were no peri-operative deaths reported in any of the included studies, including those five papers that compared craniectomy with remodelling (Table 8). Therefore there is no apparent difference in mortality rate between the two treatments.

3.5.2 Infection

Many of the studies did not explicitly report infection as an outcome; those that did rarely identified the source of the infection, nor did they justify their use of antibiotics. None of the studies identified infection in accordance with the review’s criteria of treatment with antibiotic for surgical infection or confirmation on microbiology (Table 8). No comment can be made from the available data regarding the superiority of one procedure over another with regards to rates of peri-operative infection.
3.5.3 Transfusion

Fourteen of the studies reported peri-operative transfusion rates for their sample groups (Table 8); whilst some of the other papers discussed bleeding and transfusion, they did not give the data in the format required, choosing instead to report amount of bleeding, amount of transfusion required and red cell indices. Differentiation was not made between intra- and post-operative transfusion. There was a large variation in rates transfused from 3.6% in one study of craniectomy patients (66) to 100% in several other studies (Table 8). The narrative synthesis suggests that remodelling is associated with higher rates of transfusion, regardless of whether this is elective or unplanned/emergency transfusion.

3.5.4 Re-operation rate

Ten of the papers did not report on repeat operation (Table 8). One paper did not specify which initial procedure patients had received before re-operation.58 Patients undergoing either procedure as their primary intervention demonstrated low numbers of re-operation but there is insufficient evidence to comment on whether craniectomy has a higher or lower rate of reoperation compared with remodelling (Table 8). Meta-analysis has not been performed due to low numbers and because this was a tertiary outcome.
3.5.5 Intracranial hypertension

Only six of the papers measured and/or reported on intracranial hypertension; as all six of these papers concerned the comparator procedure remodelling (Table 8). In addition, none of these studies adequately defined their limits for intracranial hypertension, the method they have used to measure ICP and/or how they diagnosed the alleged intracranial hypertension.

No comment can be made from the available data regarding the superiority of one procedure over another with regards to preventing or relieving intracranial hypertension that may occur in sagittal synostosis.
<table>
<thead>
<tr>
<th>Study (Citation)</th>
<th>Remod. (no)</th>
<th>Cran. (no)</th>
<th>Mortality</th>
<th>Infection</th>
<th>Patients transfused</th>
<th>Re-operation</th>
<th>Raised ICP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agrawal et al (2006) (44)</td>
<td>90</td>
<td></td>
<td>None reported</td>
<td>No</td>
<td>90</td>
<td>Non reported</td>
<td></td>
</tr>
<tr>
<td>Amm et al (2005) (46)</td>
<td>22</td>
<td></td>
<td>None reported</td>
<td>No</td>
<td>1 patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brichová et al (2010) (47)</td>
<td>4 25</td>
<td></td>
<td>None reported</td>
<td>No</td>
<td>None reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chieffo et al (2010) (48)</td>
<td>35</td>
<td></td>
<td>None reported</td>
<td>No</td>
<td>Not applicable*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engel et al (2012) (49)</td>
<td>38</td>
<td></td>
<td>None reported; states there were no complications</td>
<td>No</td>
<td>38 of 38 (100%)</td>
<td>4 patients</td>
<td>3 patients with papilloedema; no raised ICP</td>
</tr>
<tr>
<td>Engel et al (b) (2012) (50)</td>
<td>46</td>
<td></td>
<td>0 both groups</td>
<td>No</td>
<td>4 patients</td>
<td></td>
<td>2 patients based on papilloedema; ICP not measured</td>
</tr>
<tr>
<td>Fata et al (2001) (51)</td>
<td>23</td>
<td></td>
<td>None reported; states there were no complications</td>
<td>No</td>
<td>23 of 23 (100%)</td>
<td>1 patient</td>
<td></td>
</tr>
<tr>
<td>Friede et al (1996) (52)</td>
<td>25</td>
<td></td>
<td>None reported</td>
<td>No</td>
<td>None reported</td>
<td></td>
<td>1/6 monitored, marginally raised</td>
</tr>
<tr>
<td>Gewalli et al (2000) (53)</td>
<td>26</td>
<td></td>
<td>0</td>
<td>No</td>
<td>26 of 26 (100%)</td>
<td>None reported</td>
<td></td>
</tr>
<tr>
<td>Gociman et al (2012) (54)</td>
<td>67 (+ Helmet)</td>
<td>0</td>
<td>No</td>
<td>11 of 67 (16.4%)</td>
<td>0 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greensmith et al (2008) (55)</td>
<td>30</td>
<td></td>
<td>0</td>
<td>No</td>
<td>30 of 30 (100%)</td>
<td>Not for reshaping surgery</td>
<td></td>
</tr>
<tr>
<td>Guimarães-Ferreira et al (2001) (56)</td>
<td>110</td>
<td></td>
<td>0</td>
<td>No</td>
<td>2 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jimenez et al (2004) (57)</td>
<td>139</td>
<td>39 (linear &amp; ext.)</td>
<td>None reported</td>
<td>No</td>
<td>12 of 139 (9%)</td>
<td>4 patients</td>
<td>3 patients, raised ICP, ventriculomegaly, requiring VP shunts</td>
</tr>
<tr>
<td>Kaiser (1988) (58)</td>
<td>66</td>
<td></td>
<td>None reported</td>
<td>No</td>
<td>2 patients (uncertain which group)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kandasamy et al (2011) (59)</td>
<td>12</td>
<td></td>
<td>None reported</td>
<td>No</td>
<td>4 patients</td>
<td></td>
<td>2 patients; reoperated</td>
</tr>
<tr>
<td>Kaufman et al (2004) (23)</td>
<td>1</td>
<td>1 (ext.)</td>
<td>0</td>
<td>No</td>
<td>12 of 12 (100%)</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Kohan et al (2008) (60)</td>
<td>1</td>
<td>1 (ext.)</td>
<td>0</td>
<td>No</td>
<td>1 of 1 (100%)</td>
<td>None reported</td>
<td></td>
</tr>
<tr>
<td>Magge et al (2002) (61)</td>
<td>16</td>
<td></td>
<td>Not applicable*</td>
<td>No</td>
<td>None reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marsh et al (1991) (62)</td>
<td>11</td>
<td>11 (ext.)</td>
<td>None reported</td>
<td>No</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Massimi et al (2007) (63)</td>
<td>94</td>
<td></td>
<td>0</td>
<td>No</td>
<td>34 of 94 (36%)</td>
<td>0 patients</td>
<td></td>
</tr>
<tr>
<td>Murray et al (2007) (6)</td>
<td>24</td>
<td></td>
<td>None reported; states there were no complications</td>
<td>No</td>
<td>4 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutchnick et al (2012) (64)</td>
<td>18</td>
<td></td>
<td>No mortality</td>
<td>No</td>
<td>16 of 18 (89%)</td>
<td>0 patients</td>
<td></td>
</tr>
<tr>
<td>Panchal et al (1999) (65)</td>
<td>12</td>
<td></td>
<td>None reported</td>
<td>No</td>
<td>1 patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ridgway et al (2011) (66)</td>
<td>42</td>
<td></td>
<td>None reported; states there were no complications</td>
<td>No</td>
<td>2 of 56 (3.6%)</td>
<td>3 patients</td>
<td></td>
</tr>
<tr>
<td>Shah et al (2011) (67)</td>
<td>47 (end. + Helmet)</td>
<td>0</td>
<td>No</td>
<td>42 of 42 (100%)</td>
<td>0 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sikorski et al (2007) (68)</td>
<td>21</td>
<td></td>
<td>0</td>
<td>No</td>
<td>18 of 21 (86%)</td>
<td>1 patient</td>
<td>1 patient; re-synostosis of the sagittal suture, raised ICP; re-operation</td>
</tr>
<tr>
<td>Virtanen et al (1999) (69)</td>
<td>18</td>
<td></td>
<td>Not applicable*</td>
<td>No</td>
<td>None reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* ‘Not applicable’ denotes where a study design precludes any patient not living and available for follow-up at the time of the study (mortality) or where study design precludes any patients who have undergone more than one procedure (re-operation). Where it states none reported, the study did not make any mention of patient deaths in their population. Where it is reported as a zero the paper explicitly stated that there were no patient deaths within their sample.
3.5.6 Aesthetic outcome

None of the included papers provided a clear and concise comparison of the aesthetic outcomes achieved by the intervention and the comparator (Table 9). Only half (14) of the papers report on aesthetic outcome in any way at all, and unfortunately there was little uniformity between papers in methodology or the manner with which the data were presented (Table 9).

Three of the papers utilised the Whitaker scoring system (Table 9). This scoring system focuses primarily on the need for secondary surgery based on the patient’s overall post-operative appearance. It was originally described by Whitaker et al in 1987 and was originally designed to be used by a panel of observers. Therefore, like any observational method, it is at risk of observer bias. The Whitaker score classifies the patient as one of four categories:

- Category 1. No revision required
- Category 2. Soft tissue or minor contouring of bone suggested
- Category 3. Major bony surgery needed
- Category 4. Repeat of original surgery or more extensive surgery required

Whilst two of the included papers compared craniectomy with the comparator procedure, only one gave a comparative Whitaker score between the intervention and comparator (Table 9). This was the head to head twin study comparing one craniectomy patient with one cranial vault-remodelling patient. The result in this case suggests that
the more extensive procedure (comparator) resulted in a lesser (and therefore “better”) Whitaker score i.e. the twin who underwent remodelling had an appearance that did not warrant further surgical intervention. Unfortunately this also happened to be the only paper that gave Whitaker score for craniectomy; the other papers that reported Whitaker scores were for single arm studies looking at the results of cranial vault remodelling (Table 9). Therefore no meta-analysis could not be performed using this scoring system.

The narrative synthesis suggests that generally patients, their families and the treating doctors reported favourable aesthetic outcomes across both procedures. Ideally, a study should report on both clinician assessment and the patient’s self-report of their aesthetic outcome. It is difficult, if not impossible, to comment on whether or not there is correlation between the clinician-derived Whitaker score and the self-assessment by patient and their family, as only one study comments on both of these aspects (Table 9).
<table>
<thead>
<tr>
<th>Study (Citation)</th>
<th>Remod.</th>
<th>Cranectomy</th>
<th>Whitaker score*</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brichtova et al (2010) (47)</td>
<td>4</td>
<td>25</td>
<td>-</td>
<td>&quot;Cosmetic postoperative effect was assessed largely visually by surgeons and parental assessment, and found to be better in patients in the remodelling surgery group, mainly due to early visible head shape improvement&quot; (p. 172)</td>
</tr>
<tr>
<td>Engel et al (2012) (49)</td>
<td>38</td>
<td></td>
<td>Class 1: 31 patients Class 2: 1 patient Class 3: 2 patients</td>
<td>&quot;Twenty nine children in this series experienced an excellent aesthetic correction of their deformities, as judged by both their families and the craniofacial team. In another 5 cases, the family was pleased with the outcome, although the craniofacial team still identified mild residual scaphocephaly (good outcome).&quot; (p. 366)</td>
</tr>
<tr>
<td>Engel et al (b) (2012) (50)</td>
<td>46</td>
<td></td>
<td>Class 1: 27 patients Class 2: 4 patients Class 3: 1 patient Class 4: 4 patients</td>
<td></td>
</tr>
<tr>
<td>Patients younger than 12 mth</td>
<td></td>
<td></td>
<td>Class 1: 8 patients Class 2: 4 patients Class 3: 1</td>
<td></td>
</tr>
<tr>
<td>Patients older than 12 mth</td>
<td></td>
<td></td>
<td>Class 1: 8 patients</td>
<td></td>
</tr>
<tr>
<td>Fata et al (2001) (51)</td>
<td>23</td>
<td></td>
<td>-</td>
<td>[In 17 of 23 patients] &quot;The results of the aesthetic rating were a score of 4 (normal appearance) in 12 patients and a score of 3 (mild residual deformity; no revision needed) in five patients. No patients received a score of less than 3, and 14 of 17 patients were given a score of 4 by at least one observer.&quot; (p. 826)</td>
</tr>
<tr>
<td>Gociman et al (2012) (54)</td>
<td>67 (+ Helmet)</td>
<td></td>
<td>-</td>
<td>&quot;Excellent preliminary aesthetic results, judged by physical examination and photograph comparison, were obtained in all patients at 1 year of follow-up (Figs. 1A-Y). The physical examination revealed excellent symmetry with no significant contour deformities and bony defects in any of the patients.&quot; (p. 223)</td>
</tr>
<tr>
<td>Guimaraes-Ferreira et al (2001) (56)</td>
<td>110</td>
<td></td>
<td>-</td>
<td>&quot;The change in the subjective aesthetic evaluation was significant for all inquired partial and global aspects of skull shape. This may be considered as a high degree of parental satisfaction with the surgical outcome.&quot; (p. 223)</td>
</tr>
<tr>
<td>Kaufman et al (2004) (23)</td>
<td>12 (+ ext.)</td>
<td>Cranectomy patient: 2.3 Remodelling patient: 1</td>
<td>-</td>
<td>&quot;Parental survey showed an equal overall high satisfaction in both cases; however, with regard to final head shape (aesthetic outcome) and ease of perioperative course, the CVR case had a higher satisfaction score (93% versus 77%)&quot; (p. 246)</td>
</tr>
<tr>
<td>Guimaraes-Ferreira et al (2001) (56)</td>
<td>110</td>
<td></td>
<td>-</td>
<td>&quot;The change in the subjective aesthetic evaluation was significant for all inquired partial and global aspects of skull shape. This may be considered as a high degree of parental satisfaction with the surgical outcome.&quot; (p. 223)</td>
</tr>
<tr>
<td>Kohan et al (2008) (60)</td>
<td>1</td>
<td>1 (exc.)</td>
<td>2.3 Remodelling patient: 1</td>
<td>&quot;The appearance of all patients improved (rated as good or excellent)&quot; (p. 246)</td>
</tr>
<tr>
<td>Massimi et al (2007) (63)</td>
<td>94</td>
<td></td>
<td>-</td>
<td>&quot;All the families declined their satisfaction about the cranial reshaping. All the patients are in the I (38 cases), II (six cases), or III (one case) Sloan’s class. However, near one third of them complained about the visibility of the surgical scar.&quot; -- regarding the control group (p. 1394)</td>
</tr>
<tr>
<td>Murray et al (2007) (6)</td>
<td>24</td>
<td></td>
<td>-</td>
<td>&quot;6% of patients assessed their head shapes as good to excellent, with the remainder saying fair (9%) or poor (one patient). In relation to the midline scar the zigzag scar produced a good to excellent result in 100% of cases compared to only 68% with the straight scar.&quot; (p. 992)</td>
</tr>
<tr>
<td>Mutchnick et al (2012) (64)</td>
<td>18</td>
<td></td>
<td>-</td>
<td>&quot;In the majority of cases the family members were: pleased with the cosmetic outcome (12 [86%] of 14 cases), happy to have avoided helmeting (13 [93%]), doubtful that helmeting would have provided more significant correction (10 [71%]), and doubtful that further surgery would be necessary (12 [86%]).&quot; (p. 225)</td>
</tr>
</tbody>
</table>

* This system, described by Whitaker et al (1987) classifies aesthetic outcome according to need for further surgery: Category I (no further treatment needed), II (minor revisions needed), III (alternative bony work required), IV (requires reduplication of work).

The aesthetic results table does not include those studies which based their post-operative outcome on cephalic index outcomes as this was not regarded as true aesthetic outcome assessment. Assessment has been conducted by surgeons/parents/both.
CHAPTER 4

DISCUSSION
CHAPTER 4

4.1 PRIMARY OUTCOME

We have identified that 24 of the 27 included studies discussed cephalic index as an outcome. However of these 24, only five compared the intervention of interest with the comparator procedure as desired by the review. Of these five, only two presented their data with enough detail and in such a format considered appropriate for meta-analysis. The scarcity of information is disappointing, if not entirely unexpected from the general quality of the included studies and indeed the literature in this area at large.

The results of the meta-analysis suggests that at one year post-operatively (medium term follow-up according to the review’s protocol), the comparator procedure (cranial vault remodelling) is associated with a greater mean change in cephalic index than craniectomy, the primary intervention of interest and is therefore superior to it. An earlier study by Boop et al found that remodelling was superior both objectively and subjectively to strip craniectomy in terms of aesthetic outcome, though their methodology in reaching this conclusion was not entirely clear, and did not include use of cephalic index. Mehta et al argue that whilst open techniques of cranial remodelling offers “excellent cosmetic results” it does so at the expense of increases in morbidity, limitations which the authors felt were the reason behind the move towards endoscopic techniques. No differentiation has been made in this review in that particular regard (endoscopic versus open).
The meta-analysis provides comparative results at one fixed time point only. It does not give us any information whether or not the mean improvement is over an extended time period after the follow-up one year post-procedure or if there is any regression of the initial improvement in cephalic index. Indeed it does not tell us whether the difference seen between intervention and comparator at 12 months is maintained over time or whether this difference becomes less significant in later follow-up.

The narrative synthesis does not entirely refute nor support the findings of the meta-analysis. The results of the first part of narrative synthesis suggest that the peak improvement in mean cephalic index change in patients who have undergone remodelling may be seen earlier than those who have undergone a craniectomy procedure. When comparing this to the results of the meta-analysis it may be implied that whilst the remodelling procedure achieves a greater change in cephalic index earlier in follow-up, at later follow-up patients who have undergone craniectomy may “catch-up” to their peers. Indeed this may explain why the authors of one review paper (of which some of the results have been used in this systematic review) found that extended craniectomy (with post-operative helmet therapy) was able to achieve outcomes that were comparable to cranial vault remodelling. Depending on the duration of follow-up, the peak effect of a procedure may not be adequately, if at all, captured in the data, as cephalic index may continue to increase/improve over time after surgery.
The remainder of the narrative synthesis is less clear as to which is the superior procedure in terms of primary outcome as there is insufficient evidence in these papers to comment on whether either procedure gives the patient an advantage over the other in terms of (i) achieving a greater improvement in cephalic index or (ii) sustaining the improvement and/or advantage over the other procedure over a longer period of time. Both the intervention and the comparator procedures appear to improve the cephalic index post-operatively, improvements that are generally seen to be sustained over time. As none of the studies in this second part measured cephalic index at all three time-points post-operatively, there is no evidence here to suggest that either intervention or comparator groups underwent regression of cephalic index at a later stage.

It is important to remember at this point that whilst surgery attempts to correct the reduced cephalic index seen in sagittal synostosis, the opposite, that is increased cephalic index, is just as undesirable. Increased cephalic index is called brachycephaly; this condition is usually associated with bi-coronal synostosis. Secondary coronal synostosis has been identified elsewhere as a potential complication after surgical repair of sagittal synostosis, with one study reporting an incidence of 10% in their patients who had undergone craniectomy for sagittal synostosis that did not involve the coronal sutures, and some of these patients required re-operation in order to resolve these complications. However it is also possible for this to be a radiological finding only without apparent clinical consequences.
There is no strong evidence in the current review to suggest that patients who have one or other procedure have significantly different pre-operative cephalic index values, regardless of the age at which they were operated upon – this would suggest that the pre-operative cephalic index did not influence which procedure was selected. There is contradictory evidence as to whether or not early/late surgery correlates with greater/lesser improvements in cephalic index, and any difference observed between the two may not be sustained in the long-term.

As subgroup analysis was not possible due to the limitations of the primary research we cannot comment on any potential influence that intra- or peri-operative adjuncts may have on the outcome of a procedure. This includes the use of helmet therapy. Helmets are generally designed to correct and minimise any further abnormal antero-posterior growth of the skull in the post-operative period while still permitting the desired expansion in the lateral direction.\textsuperscript{57} There is discrepancy in the duration of use, both on a daily basis and total duration, with some authors advocating use for one year after surgery and others arguing for use of helmets until the patient reaches one year of age. Some studies do not have such well-defined cut-offs, instead choosing to advocate use of the helmet until the “desired outcome” is achieved - an endpoint that is open to subjective interpretation. This variability in use, combined with the potential problems with patient and parent compliance, poses a significant challenge in analysis of the outcomes of helmet use across papers.
Studies have shown that patients with non-syndromic sagittal synostosis can have an increased intracranial volume. This is age-related and may be more pronounced in female patients. However it must be noted that the rate of intracranial volume growth (post-operatively) does not appear to be influenced by remodelling surgery.

It must be remembered that cephalic index alone is unable to account for the overall morphology of the skull. An infant may still display features such as fronto-occipital bossing or bony ridging even in the presence of an acceptably corrected cephalic index.

This review has not taken age groups of patients into consideration. Due to limitations of the data, no subgroup analysis was performed to determine the impact of patient age at time of surgery on outcome. Other authors have previously found that whilst craniectomy may be sufficient for younger infants, more extensive procedures are likely to be required for older infants and children.

There does appear to be genuine lack of high power evidence when it comes to which is the better procedure for single-suture synostosis, a point which other authors have agreed with in recent review articles. Longer periods of rigorous follow-up are needed to better understand the comparative efficacy of the two procedures in the long term.
4.2 SECONDARY OUTCOMES

Prevention of potential developmental and neurological deficits remains a key indicator for operative intervention with arguments being made that delayed surgery may result in raised ICP and subsequent developmental delay. Recent review articles agree that preventing cognitive impairment (which they have associated with raised ICP) is an important aim of surgical treatment, and go as far as to suggest this has overtaken aesthetic correction as the primary goal. Yet to date there is little to no proven benefit in the literature to advocate surgery for this reason. This review was unable to identify any studies in the published literature that provide head to head comparison of neurological outcomes for patients who undergo craniectomy versus those who undergo more extensive remodelling procedures for single suture sagittal synostosis.

Whilst the narrative synthesis suggests a generally satisfactory trend when it comes to neurological outcome, the comparative results remain inconclusive and there is no evidence to suggest either procedure is beneficial in terms of improved functional outcomes. We cannot deduce that any positive outcome is solely the result of surgery, as this would require a randomized controlled trial, discussed in the later section 5.3 Implications for Practice. As hypothesized in the introduction there was lesser emphasis placed in the literature on functional outcome. It is difficult to draw conclusions from the available data due to small numbers, incomplete reporting and a lack of comparative data sets. The only “comparative” paper that reported developmental and neurological function was the study comparing twin infants. The remaining papers examined single interventions with or without comparison to age-matched controls; these comparisons are redundant when the aim is to compare the outcome of one procedure with that of another for the purposes of this review. Those papers that reported on the primary
morphological outcome rarely, if at all, reported on functional outcome.

Some studies did not explain how they reached conclusions and findings regarding
development and neurological function; they did not detail the scales or measures they
used, or their markers/comparison for normality. A wide variety of scales and measures
were used as markers for function and cognition and in the majority of cases no
rationale was given for the author’s choice and why a scale was most appropriate for a
particular patient sample. Where the same scale has been used different elements of it
have been utilized e.g. subdomains of the WISC. Without uniformity it is not possible
within the scope of this review to combine the results from different studies. Larger
comparative studies with more rigorous methodology are required in order to do this.

While the narrative appears to demonstrate a general trend for global IQ scores to be
comparable to that of age-matched controls i.e. “normal”, there tended to be a
discrepancy between VIQ and PIQ scores in patients who had previously undergone
surgery (of either type) for sagittal synostosis. This discrepancy between verbal and
performance IQ has been noted elsewhere in the literature regarding neurocognitive
testing as one of the most interpreted results from the WISC.

There are conflicting reports in the literature dating as far back as the last century, that a
discrepancy between the VIQ and PIQ may represent a patient at risk of developing a
learning disorder. The clinical relevance of discordant IQ scores is subject to ongoing
debate, one that is outside the scope and objectives of this review and dissertation. All
we can infer from the limited evidence from the review is that post-operative sagittal
synostosis patients may be at increased risk of learning disorders.
Delaying surgery has been proposed elsewhere as a potential risk factor for developing raised ICP, which in turn is thought to contribute to developmental delays and/or cognitive impairment and neurological signs. It has been suggested that these symptoms may be improved by treating the raised ICP through corrective synostosis surgery, however, at this point there is limited data to support this hypothesis. No further comment can be drawn from this study as no standard scales or measures were used, and no comparison was made either between procedures, or between study populations to “normal” age-matched controls.

Clinicians who are involved in post-surgery follow-up should be aware of and screen for potential deficits in function and cognition. Previous authors have identified differences in neurodevelopment in patients with craniosynostosis along with potential for learning disorders. Simply testing general IQ may not sufficiently highlight problems in different subdomains. It is unknown from the available data whether these impairments are inherent to the condition and/or if the risk is altered by surgical intervention.

One previous study, presented in 1991, identified that out of 86 patients with non-syndromic craniosynostosis, 59 exhibited behavioural deficits with problems in fine motor skills and language acquisition. These problems were seen to resolve in all of the patients who went on to undergo surgical repair. These results contradict the findings of the narrative synthesis, which seem to indicate at the very least persistence, if not outright exacerbation, of what appears to be an underlying problem.
The concepts of development, cognition and neurological function are not mutually exclusive; to test one in isolation is inherently flawed if the aim is achieve a global perspective of the patient’s performance. It is not enough to test general IQ without testing domains separately. However the opposite also holds true; clinicians can be fooled into testing separate domains for statistical significance without taking the overall performance and behaviour of the child into consideration. To achieve this would require a combined qualitative and quantitative approach, something yet to be realized in this area of research. It has been contested elsewhere in the literature that craniosynostosis may not in fact be related to impaired neurological function, with at least one paper already failing to find clinical correlation between mental development and the type and severity of the synostosis condition.²⁴

Without comparison between patients who have undergone different procedures we cannot draw conclusions about the relationship between surgery and outcome. We do not know whether outcomes are inherent to the condition itself, regardless of whether or not the patient had surgery and likewise which procedure they had. We cannot comment on whether either surgery was able to alter a potentially inevitable outcome; we do not know whether or not these patients would still have the same neurological outcome regardless of whether or not they had surgical correction of their scaphocephaly. No studies in the present review adequately explore the potential association between delaying surgery and the theoretical risk of raised intracranial pressure, nor the effect of comparative procedures on relieving or preventing intracranial hypertension. It therefore remains unknown, at least from the available data, whether this mechanism plays a pivotal role in the development of any functional impairment.
Finally, we must remember that there are many potential factors involved in shaping a child’s development and function. Firstly, the patient may have underlying neurological impairments entirely separate to the craniosynostosis syndrome that for some reason have not been identified or diagnosed (although hopefully within a system of modern multidisciplinary care this is of low likelihood). Though the topic is too broad in the confines of this dissertation, there is ongoing debate whether cognitive performance is influenced by genetics or by the environment in which the child is raised. Therefore we may never have a “true” answer to this question, as any neurological outcome is unlikely to be the result of surgical intervention alone. Furthermore, differences may be subtle and their ramifications not readily apparent until later childhood or even adulthood. Therefore, follow-up duration may not be adequate to capture these differences. Unlike other easily measurable outcomes there are inherent difficulties in establishing the pre- and post-operative level of function of an infant. Research in this area of any type of any condition and intervention is likely to be fraught with the same methodological problems and we may never be able to completely eliminate all confounding factors.
4.3 TERTIARY OUTCOMES

4.3.1 Mortality

Despite the highly invasive nature of the interventions examined and their associated morbidity there were, perhaps surprisingly, no deaths reported in any of the included studies. This may be a true reflection of the series published. Another possibility for this is study design. Many of the included studies were retrospective in nature. Their methodology stated that to be included, patients had to be available for follow-up until a certain time point e.g. patients had to have their one-year post-operative cephalic index measurement available for analysis. Therefore in this example the patients included in the study would all, by definition, have to be alive at the time of reporting. Whilst some papers make an explicit statement that there were no deaths in their sample, others were less clear, alluding to this by stating there were no complications within their cohort. In this latter instance an assumption had to be made that complications also included death. Unfortunately many studies do not mention mortality as an outcome at all and no comparison could be made between the two procedures in terms of their safety profile from this point of view. The lack of mortality outcome may be a genuine reflection of the changing face of craniofacial surgery. A recent study of over 8000 patient undergoing major craniofacial procedures found that there has been a decline in morbidity and mortality associated with these operations as a combined result of improved peri-operative care and anaesthetic management. Of note this study was comprised of two parts; the first was a review of medical records of all craniofacial procedures performed at two large North American craniofacial centres, and the second was an internet based survey that was sent to the remaining centres on the American Cleft Palate-Craniofacial Association database. The first part included an 18-year
period in the two centres, and interestingly no strip craniectomies were performed in these centres over the study time period. As the authors acknowledge there is a potential reporting bias, as there was a low response rate (13%) to the survey component of their study. I propose that it is still possible there were unreported deaths in the centres who did not respond to their survey. The authors also identified that their survey may only have captured data from larger, more experienced centres, another reason which may explain their low mortality rate, as increased experience has been linked to low morbidity and mortality. In support of the results of this study, other authors have also previously reported low mortality rates amongst patients undergoing major intracranial procedures for craniofacial problems identified similarly low mortality rates of 0-2.2%. Other authors have also noted that there are no studies at present which compare mortality and morbidity outcomes for strip craniectomy and remodelling procedures.

4.3.2 Infection

In the included studies there was a noticeable lack of discussion regarding wound or surgical infection. Few studies reported explicitly on infection at all, many opting to say instead that there were “no complications”, but failing to expand on how they had reached this conclusion. None of the studies demonstrated evidence of actively seeking this outcome, as there was no evidence of routine wound swab collection post-operatively as part of follow-up procedure. Those few studies that do mention infection, either do not state the source (suspected or confirmed) or how they reached this particular diagnosis. Unfortunately none met the criteria of the review protocol, that is,
infection confirmed either by microbiological evidence or the justified use of antibiotics. While this may be a true reflection of low infection rates, it remains unknown, based on the results of this review, whether one procedure is associated with higher post-operative infection risk compared with the other.

Surgical infections after craniofacial surgery can be related with poor outcomes and can be difficult to treat, yet there are few published studies which have looked at this as an outcome after surgery. Certainly none have been found through this review comparing infection related outcomes of craniectomy and cranial vault remodelling. One previous study looking at surgical site infection after intracranial surgery for craniofacial problems was able to identify that there may be several specific factors associated with a higher rate of post-operative infection. These include longer duration of surgery and tension in the surgical wound. Whether or not these points are applicable to the comparator procedure remodelling remains to be seen.

4.3.3 Transfusion

As discussed in the introduction there is a significant degree of variation across the literature in terms of blood loss outcomes and transfusion, making comparison between studies difficult but not impossible. For this reason the absolute need for transfusion i.e. transfusion rate was used as the surrogate marker. This is a reasonable substitute indicator, as research has demonstrated that transfusion itself is associated with increased morbidity. Of course it does create potential for confounding results i.e.
whether an outcome is the result of blood loss and/or anaemia or due to the transfusion. In this review such subgroup analysis was not possible.

The general trend observed from the data is that with a few exceptions, most studies that involve cranial vault remodelling have a relatively high transfusion rate compared to those studies whose patients underwent craniectomy. No differentiation was made in the review between those patients who were transfused electively i.e. planned pre- or post-operative transfusion, and those who received emergency transfusion i.e. unplanned transfusion in the event of significant peri-operative haemorrhage and/or anaemia. Specific serum parameters were not taken into consideration. Whilst reporting a drop in mean haemoglobin from 12.1 to 9.4 pre and post-operatively, Engel et al did not specify whether their patients, all of whom received blood transfusion, did so electively or as an emergency. The remaining studies whose patients all received transfusion similarly reported on blood loss and reported a requirement for all patients to be transfused, yet did not elaborate on the rationale behind this and whether it was an elective decision or if there was a emergent clinical need. One study chose to electively transfuse all of their remodelling patients intra-operatively to avoid the potential complications of anaemia, but did not comment on the potential complications associated with transfusion and whether any of these were seen in their sample.

It may be assumed that were the transfusion requirement truly higher in patients undergoing remodelling, it is likely due to the more invasive and lengthier nature of the procedure when compared with craniectomy. The results of the review do not allow us to answer the question of whether the type of surgery determines a higher transfusion rate, nor does it tell us whether certain types of craniectomy or remodelling are related
to higher rates of transfusion, for which subgroup analysis would be required (and therefore further primary research). It also does not answer the question of whether there are confounding factors such as the patient’s serum and stored iron levels prior to surgery, or whether not the need for transfusion can be reduced through the use of erythropoietin pre-operatively. Those questions are beyond the scope of this review and need to be answered independently in future primary research.

4.3.4 Re-operation

There were no head-head comparison studies in the review to comment on whether the intervention or comparator procedure gave the patient a better chance at having their treatment completed in a single step without requiring further operative intervention. The study design of the primary studies prevented this, as some authors chose to include only those patients who had undergone one procedure at the time of study. It is unknown therefore whether any of those patients went on to later require a revision or re-do procedure to correct any persisting abnormalities. As per review protocol, return to theatre for reasons other than re-shaping or repair of persistent abnormalities was not regarded as a re-operation. It is possible that the studies have not adequately captured re-operation data. This may be either because the patients required reoperation after the study concluded, and therefore the re-operation was not documented in the current paper, or because they underwent reoperation in a different hospital to the one where they had their first procedure, and this data is either unknown or underreported.
4.3.5 Intracranial hypertension

All six of the papers which found raised ICP in a small portion of their cohort were studies which looked at a pure cranial vault remodelling population; this may be reflective of the fact that patients undergoing craniectomy are not routinely examined for raised ICP. There are currently no non-invasive methods for measuring intracranial pressure, and clinical assessment alone can only find features that raise suspicion for raised ICP, not diagnose the condition or quantify it.\textsuperscript{26} Where present, intracranial hypertension changes the primary objective of surgical intervention.\textsuperscript{28} Even so, only a minority of patients who underwent remodelling were found to have postoperatively raised ICP. The majority of these patients required reoperation in order to correct this. It is not clear whether or not there were confounding factors contributing to their raised intracranial pressure aside from the synostosis. It has been suggested that raised intracranial pressure in synostosis may be due to excessive brain growth in comparison to the growth of the skull; however it has also been proposed that patients with sagittal synostosis have larger than normal intracranial volume, in which case there may be another, yet to be discovered, explanation for why patients with synostosis develop raised intracranial pressure.

Other studies have found that whilst it is not common, recurrent synostosis with an associated increase in intracranial pressure can occur in patients who have undergone repair of isolated non-syndromic sagittal synostosis.\textsuperscript{82} Recent reviews continue to highlight prevention of raised intracranial hypertension as an important goal of synostosis surgery.\textsuperscript{77}

The exact relationship between these parameters remains to be seen and cannot be elucidated from the data available in this review. At present there are not even clear
guidelines when intracranial pressure should be measured to accommodate accurate
comparison. No direct assessment has been made for disease recurrence, though it
was hoped that this data could be captured by the tertiary outcome “re-operation” as a
surrogate marker of disease persistence or recurrence of primary disease. However it is
important to reiterate at this point that it may be possible to have recurrent synostotic
disease without associated phenotypic changes (and therefore in retrospect, re-operation
rate may not be entirely directly correlated with disease recurrence).

4.3.6 Aesthetic outcome

An ideal study in this area of research would seek to comment on both the subjective
and objective outcomes, and it would attempt to make association between the
subjective Whitaker score and actual rates of reoperation in those patients. As discussed
in the introduction the patient’s own self-perception may differ from objective testing.
However this was not the case amongst the included studies. For a condition that has
been defined by its morphology since its inception, there is little evidence in this review
to support either procedure as superior to its comparator. Reporting was so varied in
quality and nature across the various studies that any comparison becomes a challenge.

Certainly there are suggestions of a subjective nature that remodelling may offer a
superior aesthetic outcome in comparison to the intervention of interest, however, it is
unknown whether or not this difference becomes negligible later in time, as there are no
direct comparisons with craniectomy over any reasonable period of time.
It can of course be challenging to measure aesthetic outcome in a systematic and consistent fashion. Often the opinion must be obtained from a surrogate for the patient, such a parent, due to the inherent difficulties of obtaining perspective from the paediatric patient.\(^{30}\) This can be even more challenging where the child is too young or has cognitive impairments that may prevent them from forming or communicating their thoughts on their appearance.\(^{30}\) Unfortunately, others authors have reported that there is poor correlation between parent and child opinions.\(^{30}\)

Whilst there is no doubt surgery for a pure aesthetic rationale can and has drawn criticism in the past, as discussed in the introduction there is a body of evidence to suggest that a person’s appearances can impact on their experience and other people’s response to them. In one such study Pertschuk et al compared a group of craniofacial patients with facial anomalies to age-matched healthy peers, and found that the patients with the anomalies had ‘poorer self concept, greater anxiety…and more introversion.’\(^{83}(p.181)\) Parental reports found more negative social encounters and more hyperactive behaviour, whilst the teachers interviewed reported more problems with behaviour in the classroom.\(^{83}\) Therefore whilst it should not be considered the only reason or benefit to surgical repair, the importance of aesthetic correction should not be excluded entirely in practice and in research.
4.4 METHODOLOGY

The systematic review is designed to be just that; systematic in its approach. Its methodology calls for a prospectively designed protocol that provides clear and concise guidelines describing the steps involved in undertaking the review, along with the rationale to support these decisions. Despite best intentions, a systematic review protocol cannot cover all bases prospectively. In the case of this systematic review, it became apparent that despite best attempt at clearly describing inclusion and exclusion criteria prior to initial searching, more stringent criteria were required. This was primarily due to the significant heterogeneity of the primary studies on which the review would be founded, and the often open-ended interpretation of definitions used by authors. An example of this is the way authors would often interchangeably use the terms scaphocephaly and sagittal synostosis without clarifying that the former was secondary to the latter, even though prior knowledge tells us that the two are not immediately synonymous. It was identified during the search and appraisal process that there were many finer details regarding this population that had not been covered in the original protocol.

By using a strict systematic review methodology, it allows greater clarity around what was done and why. In situations where bias is a problem, this methodology allows for the use of broad inclusion criteria and subsequent analysis relating to suspected sources of bias and variability to minimize, although not necessarily eliminate, the impact of these on the overall findings. It is important to understand that the systematic review itself is an observational study, even when it is applied to randomized controlled trials. Therefore this review and the meta-analysis within have been performed with the
understanding that the same problems and biases that apply to observational studies also apply here.
4.5 LIMITATIONS

4.5.1 Limitations in methodology

Systematic reviews themselves are by nature both retrospective and observational. They are without a doubt reliant on the data sets of others, and their findings may be skewed not only by their own inclusion and exclusion criteria but also by the limitations of the available data from primary research. In some situations the full text of some articles could not be retrieved for this review, despite the perceived relevance of the article from the abstract to the review question. Where data sets were incomplete, attempts were made at contacting authors, however this was generally unsuccessful. Contact details were often unavailable or out of date; replies were not received from authors, or where contact was made, authors were unwilling to disclose their data.

Systematic reviews place a large amount of significance in published data and the statistics derived from these studies. In doing so, not only are they exposed to the same biases as these studies, they may also underestimate the clinical significance of those studies not included in the review. It must also be acknowledged that the statistical significance of an outcome seen in quantitative research may be a poor surrogate for clinical relevance. For example, while objective testing may show that a patient has neurological development in the “normal” range, this only provides a snapshot of their performance at the time of testing; a full assessment of a patient’s overall performance is likely to require teacher-derived school reports, behavioural charts and input from the patient’s family.
Retrospectively it became apparent that the heterogeneity of terminology and techniques used in the literature was an even greater obstacle than initially anticipated. For example, the protocol stated that the review would be looking at “craniectomy” as the intervention with “cranial vault remodelling” as the comparator. However whilst conducting the review it became obvious that the same terms were used throughout the literature to refer to a broad range of different techniques, and conversely different terms had been used to describe the same or at least very similar techniques. The rigid nature of protocol design did not allow for flexibility in this area.

Studies that did not readily fit in either category were excluded and therefore the results of these studies, whilst possibly relevant, were also excluded. Some papers did not explicitly state their selection criteria for cases nor the exact nature of their cohort; assumptions had to be made e.g. that the diagnosis of sagittal synostosis and eventual surgical repair implies that there was a degree of associated scaphocephaly, where the terms have been used interchangeably.

Another assumption that was commonly made throughout the review was that there were no other co-morbidities, and that all relevant measurements were made in the same way. None of the papers appropriately discussed confounding factors, nor did they seek to address them in their result analysis and interpretation, although through this review I have identified some potential confounding factors.
4.5.2 Study Quality

Study quality is a frequently encountered problem across many different areas in surgical research and craniofacial research is no exception. It may not be ethical to randomize patients into different surgical groups, nor is it possible to “blind” clinician and patient in the same way as for example a drug trial. Some of the included papers did not explicitly state their own selection criteria for cases, nor the exact nature of the cases. Brichtova et al included 29 patients with sagittal synostosis of whom four underwent remodelling and 25 underwent strip craniectomy. Of these patients, the data for all four remodelling patients was included but only 12 of the strip craniectomy patients. The study authors did not provide the reasons for this and further data could not be obtained through attempts at direct correspondence.

Many of the published studies of interest did not focus on the sagittal suture alone, furthermore the data were not separated into the different suture types; therefore these studies had to be excluded. Studies that looked at the outcome of interest but did not give details regarding the suture/s involved or what operation was performed were also excluded. As mentioned above, where there is a diagnosis of sagittal synostosis that has been treated it was assumed that the patient had at least some degree of the associated scaphocephalic morphology. This was also true in the opposite circumstance, where patients with scaphocephaly have been treated with an operation, unless there was another underlying cause explicitly given (and if so the paper was excluded from the review) it was assumed that the patient had underlying sagittal synostosis as their primary diagnosis. Likewise where it has not been expressed explicitly, it was assumed that the patient did not have any other existing co-morbidities which may also
contribute to their clinical condition and outcomes in follow-up.

Many papers, on full retrieval, were found to be a commentary on technique alone and did not report the outcomes of the procedure/s in an objective, transparent manner. Occasionally the same authors published results of the same cohort at different follow-up time points or in different journals. In some cases this was only clear after communicating directly with the authors. Comparisons were often made against age-matched controls that do not have sagittal synostosis; this does not allow comparison between procedures for the same condition. The following is a description of some of the biases the studies included in the review may be subject to.

- Selection bias: in some studies a particular procedure has been chosen over another as a result of the preference of an individual surgeon or surgical service. Infrequently, the decision for a procedure was made on the basis of the patient’s age e.g. older children received more invasive treatment. The review protocol attempted to eliminate or at least minimize this particular bias by limiting the age at time of surgery to a mean of less than 24 months. However it is acknowledged that because this was accepted as a mean, there were some exceptional patients who fell outside this timeframe within a study. It is hoped that because these patients were a minority, their results would not significantly influence the results of the majority. Likewise in some cases a particular procedure was chosen or not chosen because of the perceived severity of the case; more “severe” cases with more pronounced abnormalities were more likely to receive the more extensive comparator procedure.
• Time bias: depending on when a study was conducted and the results published sometimes determined which procedure was utilized i.e. as newer technologies come to light these are used instead of the more “traditional” methods. Even though the years for inclusion were left open it is noted that many of the included studies were published after 2000. There are several possibilities why this is the case: earlier papers may not have reported the outcomes of interest or else reported them in such a way that was not appropriate for inclusion. This may also reflect publishing bias and an explicit decision not to publish reports for reasons unknown. It may also be representative of inadequate post-operative data collection/documentation. In some cases the same study cohort was followed up over an extended period of time, and the results of an earlier operation are included in a later paper. As stated earlier, the earlier paper has been excluded to avoid repeated inclusion of the same cohort.

• Operator bias: Some papers did not comment on the identity nor the skill level of the primary operator, and/or whether or not the same surgeon had performed all operations or if there were multiple operators. In this situation it was unknown whether the skill level/experience of the primary operator is unknown whether the skill level and experience of the surgeon determined which technique. A bias may also exist where the operating surgeon was also one of the primary investigators in the study.

• Reporting bias: It is difficult to comment on the rigor of outcome reporting in surgical research in general. It is not known whether all complications and outcomes, positive or negative, have been reported in the published results. We are left to assume that where an outcome has not been reported in the published literature, that it did not happen. Unfortunately complications may be under-
reported through either omission or commission. They may not have been sought out or documented, or they may not be included in a paper’s published results. In one example of this, the patient with post-operative wound infection may be treated by their primary care provider or general practitioner, the specialist team may not be made aware unless they have sought this information out directly. Many papers also do not explicitly state what they mean by “infection”. Results did not take into account any re-operations and their potential effect on final outcome.

Measurement and analysis of single outcomes is unlikely to give adequate perspective of the overall impact on the patient.\textsuperscript{30} Simply reporting on functional or morphological outcomes may not correlate with the patient’s quality of life.\textsuperscript{30}

The overall impact of surgery is a dynamic process, evolving over time and not all studies are designed to adequately capture this. This is known as “response shift”.\textsuperscript{30} The patient’s own self-assessment of their outcome also changes, posing additional difficulties to those already highlighted in understanding aesthetic and subjective outcomes. Other authors have already identified that the concept of appearance and outcome change as their social environment change, particularly around school-age.(30)
CHAPTER 5

CONCLUSIONS
CHAPTER 5

This is the first systematic review to compare the post-operative outcome of local craniectomy and cranial vault remodelling in human infants with primary isolated sagittal synostosis. The review was able to identify 27 studies assessing the outcomes of craniectomy and/or remodelling in the areas of morphology (post-operative cephalic index), function and neurology. Through meta-analysis it was able to demonstrate that at one year after surgery, patients who have undergone cranial vault remodelling display greater mean change in cephalic index. This conclusion chapter will summarise the review findings of the review and explore how results may inform practice, whilst remaining of social and cultural influences. It will discuss implications for future research in the context of evidence-based surgery.
5.1 CONCLUSION OF FINDINGS

As already described above, meta-analysis demonstrated that at one year follow-up, the more aggressive comparator procedure is superior to craniectomy, the intervention of interest, in terms of mean change in cephalic index. However narrative analysis demonstrates that both patients undergoing remodelling, and those undergoing craniectomy, appear to achieve improvement of varying degrees in post-operative cephalic index; an argument made for remodelling based on the results at a fixed time point may be flawed. Results may peak early after remodelling surgery and continue to improve after craniectomy. Neither procedure offers distinct sustained advantage; likewise neither group appears to experience any regression of cephalic index with time. Longer post-operative follow-up is required to compare change in cephalic index at different time points. Morphology alone is inadequate as a marker of surgical success and other outcomes including function, mortality and morbidity must be taken into consideration.

Patients who have had surgical repair (any type) for isolated sagittal synostosis may have deficiencies in different subdomains at later school-age testing and be at risk of learning disorders, whilst maintaining an age-appropriate global IQ and school performance. It is unknown if either surgery imparts any restorative or protective benefit.

There is inadequate evidence to comment on which procedure is superior in terms of mortality and morbidity outcomes. The only observation that can be made is that transfusion rates appear higher in patients who undergo remodelling procedures; it is
unclear whether these patients received elective or emergency transfusions. Whilst there were no reported deaths in either group, it is possible that mortality has been underreported. It is possible that both mortality and re-operation rate were simply precluded by study design.

Where it was reported, aesthetic outcome was not measured uniformly. While the studies generally reported positive outcomes for both procedures, this outcome is subject to the greatest potential for bias and confounding factors. There is inadequate evidence to draw comparison between craniectomy and remodelling.
5.2 IMPLICATIONS FOR PRACTICE

In the infant with mild deformity and no evidence of intracranial hypertension, as may be the case in the very young patient with isolated single suture synostosis, the decision to undertake corrective surgery remains a contentious area. If postoperative change in cephalic index was the only outcome of interest in the patient with isolated non-syndromic sagittal synostosis then the results of this review indicate that cranial vault remodelling is superior to sagittal craniecctomy.

However as we have already identified, a single outcome alone is insufficient to determine the overall clinical picture and does not adequately reflect the patient’s overall quality of life. Therefore it would be prudent to comment that further primary and consequently higher-level research is needed before definitive recommendations can be made for clinical practice.
The review results indicate that the more aggressive procedure, cranial vault remodelling, is able to achieve a greater mean change in cephalic index, at least at one year after surgery. What it does not demonstrate is whether or not this is achieved at the cost of greater morbidity. Whilst this review cannot comment sufficiently on other clinical indicators of morbidity we have demonstrated that generally speaking cranial remodelling is associated with higher rates of transfusion. The ideal procedure would achieve maximal beneficial aesthetic and functional outcome with minimal morbidity; this ideal remains to be realised. Recent reviews suggest that the future may lie in endoscopic techniques, which may offer the benefits of cranial vault remodelling without the increased risk of an open technique.\textsuperscript{21}

Microbiological evidence of infection should be recorded where possible and patients should be swabbed for cultures prior to commencing antibiotic therapy in order to identify a primary source. It is widely understood that in this climate of high antibiotic resistance, the use of antibiotic agents should be rationalised. Likewise the use of blood products should be limited to those patients who have an evidence-based need; the reason/s for submitting the patient to transfusion of blood products should be clearly documented, as well as the nature of the transfusion i.e. whether it was a planned “prophylactic” or elective transfusion, or if it was in an emergency situation for haemorrhage. The total amount transfused should be clearly documented.

If the prevention and treatment of raised ICP to allow for restoration of cognitive function is considered a primary goal of surgery, as has been raised repeatedly in literature then there is a real need for clinicians to consider the role of routine ICP monitoring. Whilst it remains to be seen whether surgery is able to restore or prevent
further deterioration in neurological function, clinicians are advised to consider all cases as “potentially at risk” and at the very least arrange early referral to an appropriate centre with a multidisciplinary craniofacial care team.\textsuperscript{24}
5.3 IMPLICATIONS FOR RESEARCH

‘Outcome assessment is a critical tool in the evaluation of any surgical technique, and it is surprising to find that no long-term outcome studies have been published for any of the surgical procedures used in the treatment of sagittal craniosynostosis.’

This review attempted to answer the question of whether limited craniectomy could achieve superior results to cranial vault remodelling in cases of isolated sagittal synostosis. However results were limited by the quality of the available primary research. Future research should have clearly defined and clinically relevant goals. Many of the outcomes currently used in the literature represent surrogate markers for outcome instead of truly capturing the overall outcome for the patient in terms of quality of life.

For a clinical trial regarding any kind of treatment to be regarded ethical, there must be a sense of clinical equipoise. This is defined as the genuine uncertainty, shared by clinician and patient, regarding the risks and benefits of a treatment and the possible alternatives. Based on the findings of this systematic review, there is enough uncertainty in the area of synostosis management that this requirement of equipoise is satisfied.

However there are still many other factors that may hinder primary research in this area in terms of randomized controlled trials. One such problem is the issue of blinding; exactly who should be blinded and how remains to be seen. Whilst there has been some
discussion generated around introducing placebo or sham procedures in other areas of surgery,\textsuperscript{84} it is unlikely this will ever be an option in this area as a) it is not possible to do a “sham” intracranial procedure b) the very nature of the disease process and the population it affects (paediatric patients, a vulnerable population) would make this highly unethical. One possible solution for this would be to perform a head to head trial comparing the two procedures.

At least one author has previously suggested that carefully performed observational studies with appropriately defined measured and documented outcomes are appropriate to assess surgical intervention, and that new procedures should be assessed by systematic review of the problem and management, followed by prospective non-randomised trial.\textsuperscript{85} This may also be beneficial in existing procedures where there is uncertainty and therefore clinical equipoise.

Certainly there is a clearly a role for well-designed comparative studies with larger sample sizes, clear guidelines and rigorous, standardized follow-up. Studies should be designed in a prospective manner that allows for explicit declaration of re-operation and mortality, to ensure that patients who reach these unfortunate outcomes are not precluded from study by design. Cephalic index outcomes should be assessed in the immediate post-operative period and the medium and long-term to assess for peak and persisting improvement.
With regards to developmental and cognitive function, future research should not only look at procedure vs procedure outcomes but also comparison with age-matched controls and, if possible, un-operated cases. Ideally a trial is required comparing age-matched patients undergoing craniectomy or remodelling but logistically this is type of study would be fraught with the ethical implications of randomizing patients, and lacks the ability to blind participating clinicians.

Future research should take bleeding into consideration as well as transfusion, and should seek to determine elective vs emergency transfusion, other factors causing need for transfusion and the role of tranexamic acid and erythropoietin. There should be more robust reporting of all-cause mortality in the peri-operative setting and studies designed in such a prospective way that there is no selection bias to include only those alive and available for follow-up. Research should explore whether or not raised intracranial pressure can affect outcomes, and whether or not isolated sagittal synostosis results in raised intracranial pressure. It should ask the question whether or not children with raised intracranial pressure, with sagittal synostosis, should have more invasive surgery.

The review has not taken cost into consideration, as it was deemed beyond the scope of the original review question. However clinicians working within systems that have limited resources must be able to justify their decision to use a particular procedure; to do so requires evidence for the procedure’s relative efficacy compared to the cost of a procedure (cost/benefit ratio). Previous studies have found that operations using
minimally invasive (endoscopic) techniques attract lower in-hospital costs compared with operations that take an open or more invasive approach. While the costs of orthotics and costs to the family were higher compared to patients who underwent remodelling procedure, the overall cost was still lower.\cite{86} The concept of cost extends beyond in-hospital charges, including cost to the clinician, the patient and their families, as well as ongoing out-of-hospital or outpatient follow-up costs.\cite{86} Cost can be regarded as direct cost of treatment including equipment and personnel, costs generated during and after admission including ongoing treatment and postoperative care. Indirect costs include travel and accommodation while the patient is receiving treatment, attending any follow-up appointments and the cost of parental time taken off from work. Indirect costs can be difficult if not impossible to accurately measure.\cite{86}

Endoscopic methods have been found to not only result in lower overall financial cost but also shorter operative time, shorter length of admission and less use of resources including transfusion and ICU admission i.e. they are related to lesser morbidity as well as being cheaper.\cite{86,87} There are only a few studies that directly compare the cost-efficiency of one procedure with another. Unfortunately these studies, while exploring the associated morbidity and touching on issues of effectiveness, do not adequately explore the post-operative outcomes of interest in order to provide a definitive cost-effectiveness outcome. At present there is limited understanding of the total financial burden on the patient and the community at large in order to support one procedure over another; future reviews should take into consideration the financial burden of an intervention and weigh this against the expected benefit.
This review did not include qualitative outcomes (e.g. for patient and family, practitioner). While a result may not be statistically significant, it is likely to be of great significance to the individual patient and their family. Quantitative data, no matter how rigorous the study design, are unlikely to adequately capture the lived experience of the individual. The effect of associated craniosynostosis morphology on psychosocial function and development is difficult to assess due to lack of systematic psychometric data.\textsuperscript{24} Certainly longer term follow-up is required particularly for “mild” cases where the effects of appearance on psychosocial outcome may not be apparent until the patient is an older child or even into their adult years.\textsuperscript{24} Preliminary searching revealed very little information in terms of qualitative research in this aspect of patient care, despite the knowledge that patient-reported outcomes are an important endpoint of treatment.\textsuperscript{30}

Likewise the review has not placed the results into a social context and has not taken into consideration the effect of culture on concepts of a “normal” phenotype. Non-Anglo groups were poorly represented in the selected papers. Whilst this may be a reflection of the availability of the data from these countries, it is also likely to be related to the inclusion criteria of the review limiting to papers published in English. A significant number of studies were from the USA; it is unclear whether in this case culture has shaped local surgical practices. It almost certainly reflects the costs of treatment, at least in part.
It has been previously established that the evolution of our species through distinguishable, though gradual, changes in anatomy includes the size and shape of the cranium.\(^8\) There are also geographic and ethnic differences that are the subject of ongoing anthropologic debate, as was touched upon in the introduction.\(^{45}\) It is unclear whether the differences noted between different ethnic groups are a result of genetics and/or environment. Furthermore the practice of intentional cranial deformation is thought to predate recorded history.\(^{99}\) As part of this process the infant’s skull is deliberately moulded into a “desirable” shape through the application of various bindings and compressors to achieve an elongated shape (Figure 9). Clearly, the concept of so-called “normal” morphology is not a static one, and any research in this area should be conducted with an appreciation of this.
Figure 9. Mangbetu mother binding her baby's head in order to artificially elongate it. 90
5.4 EVIDENCE BASED MEDICINE AND SURGERY

Evidence based medicine (EBM) as a concept emerged in the 1980s and is defined as
‘the conscientious, explicit and judicious use of current best evidence in making
decisions about the care of individual patients’. 91

What this means in practice is integrating the best available evidence with individual
clinical expertise and experience in order to make decisions regarding optimum
treatment.92, 93 Best available evidence is defined as ‘clinically relevant research, often
from the basic sciences of medicine, but especially from patient centred clinical
research into the accuracy and precision of diagnostic tests (including the clinical
examination), the power of prognostic markers, and the efficacy and safety of
therapeutic, rehabilitative, and preventive regimens’. 93(p.71) Evidence can be obtained
from many different sources; part of assessing and interpreting a piece of research
within the EBM model involves applying a level of evidence to it. This level is based
on study design and allows an initial judgement to be made on study quality and rigour
even before reading the study (Table 10).94
Table 10. Joanna Briggs Institute levels of evidence

<table>
<thead>
<tr>
<th>Levels of Evidence - Effectiveness</th>
<th>Level 1.a – Systematic review of Randomized Controlled Trials (RCTs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1 – Experimental Designs</td>
<td>Level 1.b – Systematic review of RCTs and other study designs</td>
</tr>
<tr>
<td></td>
<td>Level 1.c – RCT</td>
</tr>
<tr>
<td></td>
<td>Level 1.d – Pseudo-RCTs</td>
</tr>
<tr>
<td>Level 2 – Quasi-experimental Designs</td>
<td>Level 2.a – Systematic review of quasi-experimental studies</td>
</tr>
<tr>
<td></td>
<td>Level 2.b – Systematic review of quasi-experimental and other lower study designs</td>
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<tr>
<td></td>
<td>Level 2.c – Quasi-experimental prospectively controlled study</td>
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<tr>
<td></td>
<td>Level 2.d – Pre-test – post-test or historic/retrospective control group study</td>
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<tr>
<td>Level 3 – Observational – Analytic Designs</td>
<td>Level 3.a – Systematic review of comparable cohort studies</td>
</tr>
<tr>
<td></td>
<td>Level 3.b – Systematic review of comparable cohort and other lower study designs</td>
</tr>
<tr>
<td></td>
<td>Level 3.c – Cohort study with control group</td>
</tr>
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<td></td>
<td>Level 3.d – Case – controlled study</td>
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<tr>
<td></td>
<td>Level 3.e – Observational study without a control group</td>
</tr>
<tr>
<td>Level 4 – Observational – Descriptive Studies</td>
<td>Level 4.a – Systematic review of descriptive studies</td>
</tr>
<tr>
<td></td>
<td>Level 4.b – Cross-sectional study</td>
</tr>
<tr>
<td></td>
<td>Level 4.c – Case series</td>
</tr>
<tr>
<td></td>
<td>Level 4.d – Case study</td>
</tr>
<tr>
<td>Level 5 – Expert Opinion and Bench Research</td>
<td>Level 5.a – Systematic review of expert opinion</td>
</tr>
<tr>
<td></td>
<td>Level 5.b – Expert consensus</td>
</tr>
<tr>
<td></td>
<td>Level 5.c – Bench research/ single expert opinion</td>
</tr>
</tbody>
</table>

In surgical practice this evidence can be used in conjunction with the surgeon’s personal experience and preferences to make a shared decision with the patient as to
what is the best treatment for them.\textsuperscript{92} However, the role of EBM is less well defined in surgery than it is in other healthcare disciplines and medical specialties. Surgical practice has long been based on experience and understanding of disease processes.\textsuperscript{84} This means that many new operations are introduced and performed without the rigorous scrutiny that would normally, for example, accompany a new medication, which has to pass clinical trials and be regarded as safe before it is approved for use.\textsuperscript{95} Other authors have similarly identified that the framework to evaluate new technical procedures and operations has not been well defined, and may well be different from the approach to assessing medical therapies.\textsuperscript{85}

There are a number of factors that have hindered the uptake of the evidence-based approach in surgery, unlike other disciplines, and the role of EBM in surgery is not without its critics. This includes the emphasis placed by evidence based medicine on randomised controlled trials (something often not feasible nor ethical in surgery).\textsuperscript{84} Another problem is the perceived notion by surgeons that it is not appropriate to apply the generalised evidence to the individual patient sitting in front of them in their rooms.\textsuperscript{84} Therein lies the central conflict that exists between the surgeon, whose primary concern is the individual patient they are treating, and the researcher, who perhaps has a ‘broader’ perspective and whose focus is on the community at large.\textsuperscript{84} The other reasons suggested in the literature are a perceived threat to the so-called “art of medicine” and concerns that EBM might be over simplifying matters.\textsuperscript{84} These factors threaten to reduce the impact that EBM and systematic reviews may have on clinical practice and individual behaviour. Any type of EBM approach in surgery must therefore be tempered with consideration for the individual patient and not the
potentially heterogenous sample at the heart of a systematic review. Evidence based medicine must be practiced in a contextually appropriate manner; it does not completely displace the role of experiential learning from one’s senior colleagues and teachers, and practice.\textsuperscript{84}

‘Good doctors use both individual clinical expertise and the best available external evidence, and neither alone is enough.’\textsuperscript{93(p.71)}

Whilst there is a large body of research in the area of craniofacial and craniosynostosis surgery, there are few if any clinical trials or systematic reviews, and often research is limited to descriptive studies including case series and cohort studies. While this may reflect certain qualities and characteristics of surgery in this field, the wide variation in techniques practiced and outcomes measured, and the apparent parochialism of various centres to different techniques, invite further critique and investigation around exactly what constitutes best practice in the surgical treatment of infants with sagittal synostosis.
APPENDICES
APPENDIX I. Search strategy

Embase:

(“craniofacial synostosis”:DE OR (Sagittal NEAR/4 Synostos*):TI,AB OR scaphocephal*TI,AB OR (“cranial suture” NEAR/4 synostos*):TI,AB OR cranial synostos*TI,AB OR (“cranial suture” NEAR/4 “premature closure”):TI,AB OR (“sagittal suture” NEAR/4 synostos*):TI,AB OR craniosynostos*:TI,AB) AND

(suturectom*:TI,AB OR (“cranial suture” NEAR/3 surg*):TI,AB OR (strip NEAR/4 craniectomy):TI,AB OR craniectom*:DE,TI,AB OR (“cranial sutures” NEAR/3 surg*):TI,AB OR “synostosis surgery”:TI,AB OR (“cranial vault” NEAR/3 remodel*:):TI,AB)

Embase .2

(“craniofacial synostosis”:DE OR (Sagittal NEAR/4 Synostos*):TI,AB OR scaphocephal*TI,AB OR (“cranial suture” NEAR/4 synostos*):TI,AB OR cranial synostos*TI,AB OR (“cranial suture” NEAR/4 “premature closure”):TI,AB OR (“sagittal suture” NEAR/4 synostos*):TI,AB OR craniosynostos*:TI,AB) AND

(cognition/syn OR intelligence/syn OR “developmental disorder”/syn OR esthetic*:TI,AB R aesthetic*:TI,AB OR morphology/exp OR morpholog*:TI,AB OR neuropsychology/syn OR neurology/syn)

exp = subject headings only

/syn = all and all for synonyms
Pubmed:


Pubmed .2


Web of knowledge:

(craniosynostos* OR “Sagittal Synostos*” OR scaphocephal* OR “cranial suture synostos*” OR “cranial synostos*” OR “premature cranial suture closure*” OR “sagittal suture synostos*”) AND (suturectom* OR “cranial sutures surgery” OR “strip craniectom*” OR craniectom* OR “synostosis surgery” OR “cranial vault remodel*”)
Web of knowledge.

(craniosynostos* OR “Sagittal Synostos*” OR scaphocephal* OR “cranial suture synostos*” OR “cranial synostos*” OR “premature cranial suture closure*” OR “sagittal suture synostos*”) AND (cogniti* OR intelligence developmental delay* OR developmental disabilit* OR aesthetic* OR esthetic* OR morpholog* OR neuropsycholog* OR neurolog*) AND (paediatric* OR pediatric* OR infant* OR child* OR baby OR babies*) AND (surg*) NOT (animal* NOT human*) NOT (gene* OR (trigonocephal* NOT scaphocephal*) OR (plagiocephal* NOT scaphocephal*) OR (syndromic NOT nonsyndromic))

Google scholar:

(craniosynostosis OR “Sagittal Synostosis” OR scaphocephaly OR “cranial suture synostosis” OR “cranial synostosis” OR “premature cranial suture closure” OR “sagittal suture synostosis”) AND (suturectomy)

(craniosynostosis OR “Sagittal Synostosis” OR scaphocephaly OR “cranial suture synostosis” OR “cranial synostosis” OR “premature cranial suture closure” OR “sagittal suture synostosis”) AND “cranial suture surgery”

OR “strip craniectomy” OR craniectomy OR “synostosis surgery” OR “cranial vault remodelling”)

Scirus

"sagittal synostosis" (surgery OR surgical OR craniectomy OR suturectomy OR remodelling OR remodelling) ("humans")
Mednar

“sagittal synostosis” AND surg*

("sagittal synostosis" OR craniosynostosis OR "cranial synostosis") AND (surgery OR surgical OR suturectomy OR craniectomy OR remodelling OR remodelling OR "cranial vault remodelling" OR "cranial vault remodelling")
APPENDIX II. Appraisal instruments

JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>Not Applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was the assignment to treatment groups truly random?</td>
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<tr>
<td>2. Were participants blinded to treatment allocation?</td>
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<tr>
<td>3. Was allocation to treatment groups concealed from the allocator?</td>
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<tr>
<td>4. Were the outcomes of people who withdrew described and included in the analysis?</td>
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<tr>
<td>5. Were those assessing outcomes blind to the treatment allocation?</td>
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<tr>
<td>6. Were the control and treatment groups comparable at entry?</td>
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<tr>
<td>7. Were groups treated identically other than for the named interventions</td>
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<tr>
<td>8. Were outcomes measured in the same way for all groups?</td>
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<tr>
<td>9. Were outcomes measured in a reliable way?</td>
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<tr>
<td>10. Was appropriate statistical analysis used?</td>
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</tbody>
</table>

Overall appraisal:  Include ☐  Exclude ☐  Seek further info. ☐

Comments (Including reason for exclusion)

________________________________________________________________________
________________________________________________________________________
## JBI Critical Appraisal Checklist for Descriptive / Case Series

**Reviewer**  
Date

**Author**  
Year  
Record Number

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

**Overall appraisal:**  
Include   
Exclude   
Seek further info

**Comments (Including reason for exclusion)**

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________
## JBI Critical Appraisal Checklist for Comparable Cohort/Case Control

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>Not Applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is sample representative of patients in the population as a whole?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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</tr>
<tr>
<td>2. Are the patients at a similar point in the course of their condition/illness?</td>
<td>☐</td>
<td></td>
<td>☐</td>
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<tr>
<td>3. Has bias been minimised in relation to selection of cases and of controls?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>4. Are confounding factors identified and strategies to deal with them stated?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>5. Are outcomes assessed using objective criteria?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>6. Was follow up carried out over a sufficient time period?</td>
<td>☐</td>
<td>☐</td>
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<td>☐</td>
</tr>
<tr>
<td>7. Were the outcomes of people who withdrew described and included in the analysis?</td>
<td>☐</td>
<td>☐</td>
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</tr>
<tr>
<td>8. Were outcomes measured in a reliable way?</td>
<td>☐</td>
<td>☐</td>
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<td>☐</td>
</tr>
<tr>
<td>9. Was appropriate statistical analysis used?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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</tbody>
</table>

**Overall appraisal:**  
- Include ☐  
- Exclude ☐  
- Seek further info. ☐  

**Comments (Including reason for exclusion):**

________________________________________________________________________

________________________________________________________________________
APPENDIX III. Data extraction instruments.

<table>
<thead>
<tr>
<th>Study results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dichotomous data</strong></td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Continuous data</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
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</tbody>
</table>
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:
REFERENCES

45. Ripley WZ. The racial geography of Europe: Head shape as a racial trait II. Popular Science Monthly. 1897; 50.


90. Cotlow L. In search of the primitive. Boston: Little, Brown & Company; 1966. Figure, Head-binding among Mangbetu. p231-2