DEFORMATIONAL PLAEGIOCEPHALY: PREVALENCE, QUANTIFICATION AND PREVENTION OF ACQUIRED CRANIAL ASYMMETRY IN INFANTS

Henri Aarnivala
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Abstract
The recommendation for infants to sleep supine has decreased the incidence of sudden infant death syndrome by more than a half, but as another consequence, a dramatic rise has been observed in the incidence of acquired cranial asymmetry (deformational plagiocephaly, DP). According to recent data, almost half of otherwise healthy infants are affected by some degree of DP at 7 to 12 weeks of age, and especially in the USA and some Central European countries, major effort is put into treatment of severe DP. However, little is known of the prognosis of DP in the absence of intervention, and although primary preventive strategies are often recommended, a lack of evidence on the effectiveness of such measures persists. Furthermore, although 3D imaging is nowadays frequently used on infants with DP, no data is available on the accuracy of the measurements used to quantify cranial asymmetry.

In the present study, the efficacy of a primary preventive program in reducing the incidence of DP was tested in a randomized, controlled trial. The course of DP in the absence of active treatment was studied throughout the first year of life, and factors impacting the prognosis of DP were investigated. The diagnostic accuracy of four 3D stereophotogrammetry-based measurements was also analyzed and compared, with a goal of determining their optimal cut-off values for DP.

DP was less prevalent and less severe in the intervention group infants at the end of the RCT (3 months). The point prevalence of DP peaked at 3 months, whereafter spontaneous improvement in DP was seen throughout the follow-up period until 12 months of age. A preferential infant head position at 3 months was the strongest predictor of a subsequently unfavorable course of DP. Cranial asymmetry seen at birth was transient, and none of the older infants with torticollis had presented neck imbalance at birth, but rather appeared to develop the condition postnatally concomitantly with DP. Although all studied asymmetry-related measurements performed well regarding diagnostic accuracy, OCLR produced the most accurate classification of DP.

In conclusion, primary preventive guidelines would likely aid in reducing the burden from both DP itself and associated healthcare costs, although substantial spontaneous improvement from DP can usually be expected. The cut-off values defined for the asymmetry-related measurements have clinical implication in both making the diagnosis of DP and determining the target outcomes for treatment.

Keywords: anthropometrics, cephalometry, cranial deformations, cranial growth, motor development, nonsynostotic plagiocephaly, positional asymmetry, positional plagiocephaly, prevention, skull, stereophotogrammetry, three-dimensional imaging, torticollis
Tiivistelmä

Imeväisten nukuttaminen selällään on vähentänyt kätkytkuolemien määrää alle puoleen aiemmasta, mutta käytäntö on myös huomattavasti lisännyt asentoperäisen, ei-synostoottisen vinokalloisuuden esiintyvyyttä; tuoreen tutkimustiedon mukaan jopa lähes joka toisella imeväisellä on nähtävissä jonkinasteista asentovinokalloisuutta 7–12 viikon iässä. Etenkin USA:ssa ja muutamissa Keski-Euroopan maissa vaikea-asteista asentovinokalloisuutta hoidetaan aktiivisesti kypäräortosein, mutta samanaikaisesti tietämystä tilan luonnollisesta kulusta on vähäistä. Vaikka riskitekijöitä tunnetaan ja ehkäiseviä toimenpiteitä usein suositellaan, ei niiden tehosta ole olemassa. Nykyään 3D-pintakuvantamista käytetään usein vinokalloisten imeväisten seurannassa, mutta epäsymmetrian mittaimiseen käytettyjen muuttujien osuvuudesta ei ole tietoa.


Yhteenvetona voidaan todeta, että ennaltaehkäiseviä ohjeistuksia on vähentänyt vinokalloisuutta ja sitä aiheutuvia hoitotarpeita kustannustehokkaasti, mutta vinokalloisuuden puhaltamista ja muiden seurantatöiden suorittamista voinut juutua myös merkittävää spontaania palautumista. Tutkimuksessa määritellyillä epäsymmetria ja muuttujien arviointi voinut tehtyäkin kehitettyä moeina ammis saroilla.

Asiasanat: antropometria, ehkäisy, ei-synostoottinen vinokalloisuus, epämuotoisuus, kefalometria, kierokaula, kolmiulotteinen, motorinen kehitys, plagiokefalia, pään kasvu, stereofotogrammetria
To Nina and Lilja
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Rovaniemi, April 2017

Henri Aarnivala
### Abbreviations

<table>
<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>2D</td>
<td>Two-dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>Three-dimensional</td>
</tr>
<tr>
<td>aOR</td>
<td>Adjusted odds ratio</td>
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<tr>
<td>AS</td>
<td>Asymmetry score</td>
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<tr>
<td>AUC</td>
<td>Area under the curve</td>
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<tr>
<td>BIC</td>
<td>Bayesian information criterion</td>
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<tr>
<td>CA</td>
<td>Corrected age</td>
</tr>
<tr>
<td>CI</td>
<td>Cephalic index</td>
</tr>
<tr>
<td>CMT</td>
<td>Congenital muscular torticollis</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CVAI</td>
<td>Cranial vault asymmetry index</td>
</tr>
<tr>
<td>DD</td>
<td>Diagonal difference</td>
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<tr>
<td>DP</td>
<td>Deformational plagiocephaly</td>
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<tr>
<td>FGFR</td>
<td>Fibroblast growth factor receptor</td>
</tr>
<tr>
<td>FS</td>
<td>Flatness score</td>
</tr>
<tr>
<td>GMDS</td>
<td>Griffiths mental development scale</td>
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<tr>
<td>KDE</td>
<td>Kernel density estimate</td>
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<tr>
<td>LMM</td>
<td>Linear mixed model</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>OCLR</td>
<td>Oblique cranial length ratio</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PCAI</td>
<td>Posterior cranial asymmetry index</td>
</tr>
<tr>
<td>PCM</td>
<td>Plagiocephalometry</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver operating characteristic</td>
</tr>
<tr>
<td>ROM</td>
<td>Range of motion</td>
</tr>
<tr>
<td>SIDS</td>
<td>Sudden infant death syndrome</td>
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<tr>
<td>TEA</td>
<td>Term equivalent age</td>
</tr>
<tr>
<td>ULC</td>
<td>Unilateral lambdoid craniosynostosis</td>
</tr>
<tr>
<td>wAS</td>
<td>Weighted asymmetry score</td>
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List of original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:


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1 Introduction

Mechanical forces play a significant role in both normal and abnormal morphogenesis. In contrast to malformations, which denote a problem in tissue morphogenesis, deformations represent anomalies resulting from a normal response of a tissue to unusual mechanical forces (1). One such anomaly is deformational plagiocephaly (DP); an asymmetrical head shape resulting from external pressure acting on the infant’s cranium. Typically, DP consists of unilateral occipital flattening, which can be accompanied with anterior displacement of the ipsilateral ear and malar complex, ipsilateral frontal bossing, and contralateral occipital bossing (2). Isolated anterior DP, on the other hand, is uncommon (3).

DP usually develops over the first months of life as a result of supine positioning combined with a preferential head orientation (4). The incidence of DP has risen substantially since the recommendations for infants to sleep supine were established in the early 1990s to prevent sudden infant death syndrome (SIDS), with recently reported point prevalences ranging up to 46.6% in otherwise healthy infants (5, 6).

Although the natural course of DP appears favorable, there is a risk of the deformation persisting or worsening, and occasionally even surgical intervention is undertaken to correct a severely deformed cranium (7). Fortunately, conservative interventions usually suffice; active repositioning therapy is often the first line of treatment, and if it yields no result, orthotic helmet therapy may be prescribed (8). However, the possibility of preventing DP from developing has gained little attention as a research subject, and pragmatic clinical trials on the efficacy of preventive strategies are lacking.

The diagnosis of DP has traditionally been made clinically, but the low reproducibility of the clinical diagnosis calls for objective quantification of cranial asymmetry (9). The past decade has seen digital 3D photogrammetry revolutionize the field of craniofacial imaging, and it has become an essential clinical tool. However, while variables related to cranial symmetry measured from 3D images have previously shown excellent reliability and reproducibility, studies determining or comparing the diagnostic accuracy of such variables are lacking (10, 11).

This research was designed to investigate the efficacy of parental counseling on reducing the incidence of DP, the natural course of DP in the absence of therapeutic intervention, and the accuracy of 3D stereophotogrammetry-based measurements in quantifying cranial asymmetry in DP.
2 Review of the literature

2.1 Historical aspects

Historical and archaeological descriptions show that different prehistoric civilizations around the world have routinely practiced several forms of intentional cranial deformation (12). As many as 90% of Mayan skeletal remains exhibit evidence of decorative or cosmetic cranial deformation practices, and evidence from Iraq on intentional head shaping dates back to 45,000 BC (13). Signs of intentional deformation have been documented even in fossilized remains of early Homo Sapiens from Australia (14). Devices used in the past to shape the infant’s head include cloth bindings, compression via boards or stones, and cradleboard attachments that compress the forehead. In some cultures, mothers reportedly molded the heads of their infants between their hands while nursing, changing them from breast to breast to achieve a desired symmetrical appearance (15). In several parts of the world, artificial cranial deformation was practiced well into the 20th century (16).

Unintentional cranial deformation is generally much less extreme than intentional deformation, but definite signs of unintentionally induced deformation have also been discovered in archaeological studies. Many historic and prehistoric Native American groups used cradleboards to contain an infant while sleeping and during daily routines, which caused the infant’s occiput to be flattened and, likely due to positional asymmetry, the deformation was often directed towards an asymmetrical shape. Consequently, DP is a common finding in prehistoric Southwestern skeletal samples (17). Investigations in a 13th to 18th century ossuary in the Czech Republic revealed as many as 12.5% of unearthed skulls to exhibit some form of DP, and the authors postulated whether the traditional supine infant sleeping position of the past local populations was behind the high prevalence (18).

In the modern era, neuroscientists have been intrigued by the possible impact of cranial deformation practices on brain development and cognition since the 19th century (15), whereas unintentional nonsynostotic cranial deformation in children started to become a subject of medical concern during the 20th century. The earliest case reports of DP in living subjects are from the 1920s concerning a tribe in Borneo, with 45% of the observed Sarawak adult males showing signs of DP (19). Discussions focusing on the treatment of plagiocephaly and other deformations of the cranium began to emerge at the Johns Hopkins Hospital in the late 1950s (12),
and the earliest prospective study on DP was published at that time, too, reporting cranial asymmetry seen in infancy persisting into 10 years of age in 90% of the studied children (20). The first descriptions of helmet therapy as a treatment for DP are from the late 1970s (21, 22).

2.2 Normal cranial development and growth

In the human embryo, skeletal elements are derived from embryonic mesoderm and cranial neural crest cells originating from the neural epithelium in the neural folds (23). Both types of cells possess a high degree of plasticity and can be patterned by the environment, which is significant considering the development and growth of the brain. In the embryonic skull, cartilage formation begins during the 7th week of gestation, ossification centers in the calvaria first beginning to appear during the 8th week in the frontal bone, and 8th to 9th week in the parietal, upper, and lower squamous parts of the occipital bone. Ossification is not complete, however, until well after birth (24).

At birth, the individual calvarial bones are separated by sutures of variable width and by fontanelles. These flexible membranous junctions between bones allow the sutures and fontanelles to be narrowed and the bones to overlap in the birth canal. Postnatally, sutures allow for brain growth, acting as the major growth sites of the skull for the first years of life (25). The patency and fusion of cranial sutures are mediated by an array of transcription factors, growth factor receptors, cytokines, and extracellular matrix molecules. Fibroblast growth factor receptor (FGFR)-1, FGFR-2, and FGFR-3, as well as transcription factors TWIST and MSX2 are of particular significance, as the majority of known craniosynostosis syndromes result from mutations in the genes encoding these proteins (26).

According to the functional matrix hypothesis, the expansion of the neural mass is the main event behind cranial growth, and the growth of the neurocranium is secondary to this primary driving force, with compensatory bone formation taking place at the cranial sutures to preserve the integrity of the neural skull (27). The precocious early development of the brain, which also gives rise to the predominance of the neurocranium over the facial portions in an infant’s skull, is reflected in the rapidly increasing head circumference in the prenatal and early postnatal periods (26). Head circumference nearly doubles from an average of 18 cm at the midgestational period to an average of 35 cm at birth, and continues to increase at a fast pace over the first months. The rate of head growth starts to slow down gradually after around 6 months of age, reaching an average of 46 cm at 12
Thereafter, head growth is much slower: mean head circumference is around 49 cm at 2 years, 50 cm at 3 years, and from 3 years of age to adulthood, the increase in head circumference is only around 6 cm. The still ongoing ossification process and the rapid rate of head growth also make the infant’s cranium susceptible to external deformational forces long after birth (29).

Over time, bone growth results in narrowing of the sutures, elimination of the fontanelles, and increasing of skull thickness. The posterior fontanelle closes two months after birth, the anterolateral ones three months after birth, and the anterior and posterolateral ones during the second year of life (26). According to a recent CT-based study, suture closure has occurred in the inferior region of the coronal suture, most squamosal suture, and in some portions of the sagittal suture near the frontal cranium in infants between 4 to 7 months of age; in all the squamosal sutures, a large portion of the coronal suture towards the superior region, the lambdoid suture under the occipital cranium, and the posterior suture between 8 to 12 months of age; in the whole lambdoid suture, coronal suture, and the sagittal suture near the occipital cranium between 12 to 18 months of age; and after 2 years of age, all sutures and fontanelles have closed (30). Another CT-based study reported skull thickness increasing rapidly over the first year of life, after which the rate of increase slowed. In turn, skull density increased with a fast but steady pace throughout the first 3 years of life, while both skull thickness and density continued to increase up to adulthood (31). Nevertheless, with the exception of the metopic suture, complete obliteration of cranial sutures does not normally occur before 20 to 40 years of age, while the occipitomastoid, sphenotemporal and squamous sutures may not be completely fused even at 70 years (26).

2.3 Clinical features of deformational plagiocephaly (DP)

DP refers to an asymmetrical head shape that is consequent of external pressure acting on the infant’s cranium. The clinical features present in an infant with DP depend on the severity of the deformation. Mild DP may consist only of isolated unilateral occipital flattening, but in its classical form DP presents as a “parallelogram head”, with anterior displacement of the ipsilateral ear, ipsilateral frontal bossing and contralateral occipital bossing. As the degree of deformation increases, facial and mandibular asymmetry may be observed. Occasionally, superior or lateral bulging, sometimes termed “occipital lift”, can be seen as an attempt of the brain to decompress vertically or temporally (2, 32).
The occipital flattening also often results in the skull being shortened, which gives the plagiocephalic head a wider, i.e., brachycephalic, appearance. If significant occipital flattening is present in the absence of visible cranial asymmetry, the condition is termed deformational brachycephaly, but it is a much rarer occurrence (2, 33). A bald spot and/or skin irritation may be observed occipitally in the flattened region as a sign of prolonged exposure to external pressure. Further common clinical findings in infants with DP include restrictions in the cervical range of motion (ROM), preferential head position, asymmetrical or delayed motor development, and abnormal tone, but they are mostly considered to be the cause for rather than the consequence of DP (34-39). The prevalence of different clinical characteristics in a series of 261 infants with DP are shown in Table 1.
Table 1. Prevalence of different clinical features in a sample of 261 infants with deformational plagiocephaly, aged ≤ 12 months. Adapted from Linz et al. (40).

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Unilateral occipital flattening</td>
<td>100%</td>
</tr>
<tr>
<td>Ipsilateral frontal bossing</td>
<td>89%</td>
</tr>
<tr>
<td>Contralateral occipital bossing</td>
<td>95%</td>
</tr>
<tr>
<td>Vertex view: parallelogram shape</td>
<td>89%</td>
</tr>
<tr>
<td>Posterior view: normal</td>
<td>99%</td>
</tr>
<tr>
<td>Ipsilateral anterior ear shift</td>
<td>93%</td>
</tr>
<tr>
<td>Facial asymmetry</td>
<td>8%</td>
</tr>
<tr>
<td>No skull deformation at birth</td>
<td>92%</td>
</tr>
<tr>
<td>Ultrasound: patent sutures</td>
<td>100%</td>
</tr>
<tr>
<td>Signs of sutural fusion in x-ray (if taken)</td>
<td>0%</td>
</tr>
<tr>
<td>Signs of sutural fusion in MRI (if performed)</td>
<td>0%</td>
</tr>
</tbody>
</table>

2.4 Epidemiology of DP

The first report on the incidence of DP in newborns, estimated at 1 to 300 live births based on a sample of 20,000 infants, was published in 1974 (41). No further reports on the incidence or prevalence rates were published and scientific interest over the subject was minor until a dramatic rise in the number of referrals for plagiocephaly was noted in three craniofacial centers in the USA in the early 1990s. Kane et al. reported of a six-fold increase in referrals between the years 1992 and 1994 in the Missouri area compared to the thirteen preceding years (42). Argenta et al. reported a similar finding in the North Carolina area (43) and Turk et al. in the New York area (44) over the same time period. All three studies recognized the newly adopted supine infant sleeping position as the main factor behind the rising incidence; following two pivotal case-control studies that convincingly demonstrated the increased risk of SIDS in prone sleeping infants, recommendations for infants to sleep supine had begun to emerge. In Scandinavia, the supine sleeping position was first recommended nationally in Norway in the beginning of 1990, and in the USA by the American Academy of Pediatrics in 1992 (5, 45). Despite the unforeseen consequences regarding cranial molding, the recommendations for supine sleeping have been tremendously successful, as the incidence of SIDS has subsequently decreased by more than a half (45, 46).

The rising incidence of DP called for input from the research community, and several reports on the prevalence of DP have been published since. The prevalence
of DP has been found to be age-dependent; a longitudinal cohort study of 200 Australian infants reported DP in 19.7% of 4-month-old infants, but the point prevalence decreased over time, being 3.3% in 2-year-olds at the end of the follow-up (47). Another longitudinal cohort study of 380 Dutch infants described an increase in the prevalence of DP from 6.3% at birth to 22.1% at 7 weeks (48). The authors of a cross-sectional study of 201 infants born in Boston reported 13% of newborns having “localized cranial flattening” (49). A more recent cross-sectional cohort study of 440 Canadian infants aged 7 to 12 weeks found as many as 46.6% to have some form of DP (6), while a cross-sectional study of 1,045 children described a 2.0% prevalence of positional skull deformations in youth aged 12 to 17 years (50).

DP has long been thought to occur more frequently in preterm infants, and a recent cross-sectional study of 195 German infants reported the prevalence of DP to be 38% in very preterm and 18% in late preterm infants at term equivalent age (TEA), compared to a 15% prevalence in newborn term infants (51). The same study group published a prospective follow-up of 56 infants born at less than 32 gestational weeks, reporting point prevalences of 34% at discharge, 46% at 3 months corrected age (CA), and 27% at 6 months CA (52). Another prospective study on 120 infants born at less than 30 gestational weeks reported a 30% prevalence at TEA, 50% at 3 months CA, and 23% at 6 months CA (37).

Based on the aforementioned literature, the prevalence of DP appears to increase from birth, peaking at around 2 to 3 months of age, whereafter it starts to decline, although the results from different studies are not necessarily directly comparable due to heterogeneity in the definition of DP and how the diagnosis is made (33, 53).

### 2.5 Pathogenesis and risk factors of DP

Contrary to synostotic plagiocephaly, which results from premature fusion of one or more cranial sutures, the pathomechanisms behind DP are related to the environment and surroundings of the infant or fetus (54). The rapidly growing head is malleable and susceptible to external forces, and if pressure directed on the cranium is distributed asymmetrically for a prolonged period of time, cranial growth may take on an asymmetrical course, ultimately resulting in noticeable, deformational asymmetry (1).
2.5.1 Pre- and perinatal deformation

Before the supine sleeping position became the norm in western countries, the general perception was that DP is a consequence of pre- or perinatal problems. In earlier studies, DP was mainly reported in infants with congenital muscular torticollis (CMT), and both conditions were considered different manifestations of intrauterine constraint and postural asymmetry (20, 21, 41, 55, 56). The elevated risk of DP and CMT in infants who had descended earlier or been fixed in the pelvic brim for a longer period before delivery was held suggestive of this causation, and the similar distributions of the left and right occiput anterior presentations at birth and the side of occipital flattening in infancy were considered indicative of skull deformation taking place in the birth canal (3, 20, 55, 56). Both DP and CMT could reportedly be diagnosed in newborns, and DP present in later childhood was considered a persisting congenital deformation (20).

Evidence accruing over the past two decades contradicts some of these notions. Although some level of cranial asymmetry has been reported in up to 61% of newborns (57), a prospective study by van Vlimmeren et al. found that presenting with DP as a newborn had no impact on the chance of having DP at 7 weeks of age, suggesting that cranial asymmetry seen at birth is, at least in most cases, transient (48). Furthermore, the occipital bone on the side of the flattening has been described to be thinner compared to the contralateral side in skulls of older subjects with DP, suggesting that external forces behind a persistent deformation continue to act for a longer time than just the perinatal period (32, 36). Additionally, most factors increasing the risk of DP at birth do not affect the risk of DP in later infancy, and in most cases parents first notice the deformation only a couple of weeks after birth (48, 49, 58, 59). Therefore, the current consensus is that the majority of children with DP develop the clinical condition postnatally, but in some cases, milder prenatal flattening might act as a precursor for further postnatal deformation, although there is no direct evidence of the latter (29, 58, 60).

2.5.2 Postnatal deformation

As soon as the newborn enters the extrauterine world, he is faced with the gravitational force and has much less control over his own position than in utero (55). Before the infant gains proper control over head position, he will predominantly remain in the position placed in. If long periods of time are spent in the same position, the pressure from the surface below may distract the growth of
the cranium, and if the infant tends to keep the head turned to one side, the process can ultimately result in DP (29, 33).

Fig. 2. Unevenly distributed external forces on the occiput may cause cranial growth to take on an asymmetrical direction.

The time frame in which the deformation process generally takes place is between birth and when the infant learns to crawl and sit; thereafter, time spent with the occiput against the underlying surface is greatly reduced. Therefore, the time at risk differs between infants, and those born preterm or with slower motor development are found to be more prone to developing DP (60). On the other hand, the supine sleeping position itself has been shown to hinder some aspects of infant motor development, with milestones such as rolling prone to supine, tripod sitting, creeping, crawling, and pulling to stand attained later, which in part elucidates the etiology of the dramatic rise in the incidence of DP after the supine sleeping position became a norm (61, 62).

**Positional asymmetry, torticollis and DP**

In accordance with exposure to unevenly distributed external forces on the occiput serving as the pattern of deformation (1), several studies have recognized a predominantly asymmetrical head position as the greatest risk factor for DP (47, 48,
Although positional asymmetry is usually idiopathic, it may sometimes be a symptom of an underlying disorder such as CMT, ocular pathology, a clavicular fracture, an obstetric brachial plexus palsy, or a central nervous system disorder (59, 65-71). A unilaterally restricted passive neck ROM with persistent head tilt and/or a sternocleidomastoid tumor is categorized as CMT, which directly results in a predominantly asymmetrical head position (72, 73). Respectively, a brachial plexus palsy or a central nervous system disorder may restrict active neck rotation to one side, which can be followed by a limited passive ROM secondary to muscle imbalance; this condition is also known as positional torticollis. Although positional torticollis is often present in idiopathic positional asymmetry, too, it is unclear whether positional asymmetry of the head secondarily causes the active neck ROM to be restricted over time, or whether an initially subtle restriction of the neck ROM is the primary cause behind evident, “idiopathic” positional asymmetry (71). It has also been postulated that the localized occipital flattening observed in some newborns might induce a position of comfort with the flat part against the underlying surface (49). With no regard to the etiology, Boere-Boonekamp and van der Linden-Kuiper found positional preference in 8.2% of Dutch infants (n = 623) under 6 months of age, with a right-sided preference in 72% (63). A preference of right-handed laterality in head position, assumed to be intrinsic, has also been observed in neonates (74). In a recent prospective study, Leung et al. described a progressive change in the head position of healthy infants over the first nine weeks, with a trend from symmetrical lateral head orientation towards midline orientation, and noted a clear association between asymmetrical head orientation duration and strength and the risk of DP. They also noted a significant shift from evenly distributed left-right orientations at 3 weeks to a more consistent and prevalent right-sided orientations at 9 weeks, possibly hinting at an environmental influence. However, neck ROM was not assessed, precluding any conclusions on the etiology of asymmetrical head orientation (75).

### 2.5.3 Risk factors for DP

As mentioned earlier, different causes for positional asymmetry, such as limited active or passive neck ROM, infant positional preference, or parents not altering the infant’s head position regularly, have been presented as major risk factors for DP in infancy (47, 48, 63, 64). Other factors associated with an increased risk of DP in infancy also appear to contribute to the development of DP through increasing the likelihood of positional asymmetry and/or slower motor
development (48, 58, 64, 76-78). Existing studies have investigated the effect of different factors on the risk of DP at or before 4 months of age, but no data is available on the effect of environmental factors on the subsequent risk or course of DP. In Table 2, risk factors reported in case-control and cohort studies are summarized.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Reference (author, year)</th>
<th>Male sex</th>
<th>Primiparity</th>
<th>Assisted delivery (vacuum/forceps)</th>
<th>Prematurity</th>
<th>Twin</th>
<th>Small for gestational age</th>
<th>Birth trauma</th>
<th>Congenital anomaly</th>
<th>Torticollis (any)</th>
<th>Limited passive neck rotation at birth</th>
<th>Limited active rotation at 4 months of age</th>
<th>Early established positional preference</th>
<th>Always sleeps head turned to same side</th>
<th>Infant only bottle-fed on same arm</th>
<th>&lt;1 hour/day upright</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>Hutchison et al. 2003 (64)</td>
<td>2.5 (1.2––6.2)</td>
<td>NS</td>
<td>NS</td>
<td>3.3 (1.0–10.5)</td>
<td>3.0 (1.0–10.5)</td>
<td>NS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20.4 (5.8–71.4)</td>
<td>-</td>
<td>NS</td>
<td>37.5 (8.4–166.3)</td>
<td>7.1 (2.6–18.4)</td>
<td>-</td>
</tr>
<tr>
<td>Primiparity</td>
<td>Hutchison et al. 2004 (47)</td>
<td>2.0 (1.8–2.2)</td>
<td>NS</td>
<td>NS</td>
<td>2.2 (2.0–2.5)</td>
<td>1.4 (1.1–1.8)</td>
<td>NS</td>
<td>-</td>
<td>NS</td>
<td>-</td>
<td>9.5 (2.6–34.9) at 6W; 6.5 (1.9–22.3) at 4M</td>
<td>-</td>
<td>NS</td>
<td>-</td>
<td>-</td>
<td>3.1 (1.2–8.1) at 4M</td>
</tr>
<tr>
<td>Assisted delivery (vacuum/forceps)</td>
<td>McKinney et al. 2009 (78)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>-</td>
<td>-</td>
<td>1.6 (1.3–1.9)</td>
<td>1.4 (1.2–1.7)</td>
<td>2.0 (1.8–2.3)</td>
<td>-</td>
<td>57.7 (16.5–202.1)</td>
<td>-</td>
<td>-</td>
<td>5.0 (3.4–7.1)</td>
<td>4.3 (1.6–11.6) at 4M</td>
<td>4.0 (1.4–11.2) at 6W</td>
</tr>
<tr>
<td>Prematurity</td>
<td>van Vlimmeren et al. 2007 (48)</td>
<td>5.4 (1.9–15.3) at 0W; 2.0 (1.1–3.4) at 7W</td>
<td>2.4 (1.4–4.2) at 7W</td>
<td>NS</td>
<td>-</td>
<td>NS</td>
<td>-</td>
<td>9.5 (5.3–17.0) at 7W</td>
<td>NS</td>
<td>-</td>
<td>NS</td>
<td>-</td>
<td>NS</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Risk factors for deformational plagiocephaly in infancy and their respective adjusted Odds Ratios (aOR) from previous publications. If risk for deformational plagiocephaly at a particular age was investigated, it is reported after the respective aOR.
<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Reference (author, year)</th>
<th>aOR (95% CI)</th>
<th>aOR (95% CI)</th>
<th>aOR (95% CI)</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placed prone &lt;3 times per day</td>
<td>Hutchison et al. 2003</td>
<td>2.3 (1.0–5.0)</td>
<td>NS</td>
<td>-</td>
<td>2.4 (1.1–6.2)</td>
</tr>
<tr>
<td></td>
<td>et al. 2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine sleeping</td>
<td>Hutchison et al. 2004</td>
<td>7.0 (3.0–16.5)</td>
<td>5.3 (1.8–15.4)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>et al. 2009</td>
<td></td>
<td>6W</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive infant</td>
<td>McKinney et al. 2009</td>
<td>3.2 (1.4–7.6)</td>
<td>3.3 (1.2–9.3)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>van Vlimmeren et al. 2007</td>
<td></td>
<td></td>
<td>0.6 (0.4–0.9)</td>
<td></td>
</tr>
<tr>
<td>Motor development ahead of average</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant temperament average to difficult</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal educational level:</td>
<td></td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td>5.6 (2.0–15.6)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0W = birth; 6W = six weeks of age; 7W = seven weeks of age; 4M = four months of age; NS = factor not statistically significant; dash (-) = factor not assessed in the study.

### 2.5.4 The role of cranial sutures in DP

Back in the early 1990s, before a better understanding was gained over the differences between DP and unilateral lambdoid craniosynostosis (ULC), some researchers considered DP and ULC to be parts of the same continuum. True DP was thought to always self-improve, while a persisting or worsening deformity was considered a sign of a “functional” ULC that would not respond to conservative treatment (79, 80). Many children who actually very likely had DP were operated on as craniosynostoses, because the decision to operate was based principally on the degree of deformation, as clinical and radiological diagnostic criteria for DP and ULC were lacking. The lambdoid suture was found to be patent in many operated infants, but researchers described the suture as “sticky”, implying a role of cranial suture pathology in the development of DP (81, 82). However, several subsequent studies have shown DP and ULC to be two distinct conditions, both with their own typical clinical and radiographic features, which will be discussed later (32, 83-86).

In DP, cranial sutures are patent and, in the light of current evidence, there is no increased risk of synostosis even with the deformation persisting. Experimental studies on animal models have investigated the effect of compression and restriction on the patency of cranial sutures. A study with fetal lambs showed that
even rigid metal plate fixation over the coronal suture in utero did not cause the suture to fuse prematurely──instead, the authors observed deformational changes in craniofacial morphology (87). Similarly, a study using head-gear appliances in macaques reported narrowing of the sutures, but instead of the sutures fusing, some osteogenic fronts actually became resorptive, and only deformational morphological changes were observed (88). One study on children with persistent DP described elevated levels of transforming growth factor beta 3 (TGF-β3)──a growth factor implicated in preserving cranial suture patency──in the affected lambdoid sutures (89, 90). Then again, intrauterine constraint has been associated with occasional synostotic bridging of the sagittal suture in humans (91). These findings suggest that while intrauterine constraint might lead to craniosynostosis by altering the immature sutural tissue and initiating mineralization of the sutural ligament in the fetus, compensational mechanisms postnatally suffice to preserve suture patency under external compression (26).

2.6 Diagnosis of DP: distinguishing DP from craniosynostosis

2.6.1 Clinical differentiation

Generally, it is possible to clinically differentiate whether the distorted cranial shape is caused by external deformation or craniosynostosis (84). ULC is the only type of craniosynostosis causing unilateral occipital flattening, and the typical clinical features mentioned help to distinguish DP from isolated ULC (40, 54). In craniosynostoses, arrested bone growth occurs at right angles to the fused suture (92), and hence cranial growth is restricted on the affected side in ULC, resulting in occipital bossing on the contralateral side. Therefore, the shape of the skull with ULC is typically trapezoidal from the vertex point of view, as opposed to the parallelogram shape seen in DP, and the ear on the side of occipital flattening is displaced posteriorly in ULC. From the posterior point of view, a parallelogram shape and an inferior cant to the ipsilateral skull base are seen in ULC, as opposed to the roughly normal shape from the posterior view usually seen in DP (40, 86). There is also often a thick, palpable ridge over the fused cranial suture in ULC, whereas in DP no ridges are palpable along the major cranial sutures, and the anterior fontanelle is open and soft (3). Additionally, asymmetry caused by craniosynostosis is often, or has already been present at birth, whereas DP usually develops to its full extent over the first months of life (40). Furthermore, the
incidence of lambdoid synostosis—the rarest form of craniosynostosis—has been estimated at only around 1–2 per 100,000 live births (93).

2.6.2 Radiographic differentiation

Occasionally, radiological imaging is needed to confirm the patency of cranial sutures, mainly when the deformation is severe and the infant presents with other clinical features hinting at a possible synostosis. Plain radiographs were used in the past, but their specificity was not optimal due to the lambdoid suture on the flattened side occasionally appearing blurred as a result of the left and right sutures occupying different planes in the anteroposterior radiograph (94). Studies using CT scans have revealed changes in the endocranial morphology of patients with DP different to those in patients with ULC, and they accord with the typical clinical findings of DP. There is only minimal midline deviation of the endocranial fossa in DP, as opposed to a significant deviation seen in ULC. The anterior and posterior hemifossae on the side of the occipital flattening are displaced ventrally, and the contralateral hemifossae are displaced dorsally (83, 95). The thickness of the occipital bone may be decreased on the side of the flattening compared to the contralateral side, and in severe cases of persistent DP, severe unilateral erosions and even true perforations of the calvarial bone have been described (24, 83). Anterior mandibular deviation on the side of occipital flattening has also been observed (96). In DP, lambdoid sutures have demonstrated areas of focal fusion, endocranial ridging, narrowing, sclerosis, and changes from overlapping to end-to-end orientation, but never ectocranial ridging, which is considered indicative of craniosynostosis (85). One study using MRI reported that brain volume is not affected in DP, while there are differences in brain shape coinciding with the endocranial patterns of deformation (97). After the description of the distinct clinical features of both DP and ULC in a CT scan, CT has gained foothold as a diagnostic procedure and is still primarily used in many craniofacial centers. Although it provides virtually perfect sensitivity and specificity, it subjects the infant to a high amount of ionizing radiation (83, 98, 99). While no reports on the accuracy of MRI exist, some consider it to be as accurate as CT, but the infant still needs to be sedated to facilitate the procedure (40).

The reliability of ultrasonography as a screening test was first investigated by Sze et al. in a study involving 41 infants (two had lambdoid synostosis, 39 had DP) referred to a tertiary center because of skull deformation, and they reported the sensitivity and specificity of sonography to be 100% and 89%, respectively, in
distinguishing a patent suture from a fused suture (100). In a slightly larger study, researchers using high-frequency sonography managed to identify patent sutures in 99 out of 100 infants with skull deformation, but they missed a single partially fused suture (94). Recently, Linz et al. reported that sonography was sufficient to determine the patency of cranial sutures in all of the 261 infants with DP included in their sample, and to recognize the prematurely fused lambdoid suture in all of the 8 participants with true ULC. However, they did not perform MRI on all of the subjects, and hence could not exclude the possibility that some of the 261 infants with sutures appearing patent on sonography might in fact have had a partial or complete synostosis. Nevertheless, to decrease radiation exposure and avoid unnecessary sedation, the authors advocate the use of sonography as the primary screening tool for suture pathology, and additional plain skull radiographs if necessary to further confirm the diagnosis (40).

2.6.3 Genetics

Craniosynostosis can either occur sporadically or be a part of a collection of various syndromes. Most of the known craniosynostosis syndromes, such as Crouzon, Apert, and Pfeiffer, are caused by mutations in the gene family encoding FGFR-1, -2, and -3 (101). Alterations in the function of the transcription factors TWIST and MSX2 are also frequently implicated in craniosynostosis syndromes (24). Recently, exome and whole genome sequencing have been used as well to seek novel genetic causes for craniosynostoses of previously unknown etiology: a newly published study of 40 patients described new likely associated mutations in 14 different genes, at least some of which will probably add to the previously known mutations in at least 57 genes associated with craniosynostosis (102). Infants with syndromic craniosynostosis often present with multiple synostoses, as well as additional dysmorphic features characteristic to the particular syndrome (24). In these cases, genetic testing enables determining the exact etiology of craniosynostosis, providing invaluable aid in treatment-related decision-making, and assessing for potential comorbidities. However, to our knowledge, no underlying genetic cause has yet been identified for unilateral synostosis of the lambdoid suture. DP has not been associated with a specific genetic cause, either, although DP is frequently present in various syndromes with associated neurological problems (e.g., hypotonia, paresis) or developmental delays (38, 103-105). Therefore, at present, genetics do not play a significant role in differentiating between DP and ULC in particular.
2.7 Diagnosis of DP: quantifying cranial asymmetry

To both understand the natural course of DP and to evaluate the effect of therapeutic intervention, there is a need for a reliable standardized method for measuring positional cranial asymmetry. Several approaches from visual classification to photogrammetry and even sonography-based methods have been proposed, and while no universal agreement on a gold standard exists, 3D surface imaging has become the method of choice among many craniofacial specialists (2, 36, 106, 107).

2.7.1 Visual assessment

In clinical practice, the initial need for quantifying cranial shape always stems from either parental or expert concern—in other words, visual assessment—of the cranial shape. The Argenta classification system, presented in Fig. 3, is a diagnostic tool used to categorize the type of DP based on the presence (or absence) of different clinical findings characteristic to DP (occipital asymmetry, ear deviation, frontal asymmetry, facial asymmetry, and occipital lift). The purpose of such classification is to standardize clinical judgment, to avoid classifying negligibly small differences in asymmetry-related anthropometric measurements as abnormal, and to facilitate the follow-up of the course of DP (2).
Fig. 3. Argenta classification system. Type I deformation consists of only occipital asymmetry, type II adds malposition of the affected ear, type III adds forehead deformity, type IV adds malar deformity, and type V adds either occipital lift or temporal bulging.

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The classification has been widely implemented into clinical use, and retrospective studies have found the classification to correlate with the length of required treatment and time to recovery (108, 109). However, concerns have arisen about the reproducibility of the diagnosis based on the classification. In one reliability study, 20 participants referred to a tertiary center because of cranial deformation were assessed twice by several experts from different professions, and while the authors reported substantial intra-rater reliability, inter-rater reliability was only moderate. However, some of the experts had only received a single training session regarding the diagnostics of DP, which may have influenced their results (110). While no further reliability studies regarding the Argenta classification have been conducted, Atmosukarto et al. have reported of a slightly higher inter-rater reliability for a custom three-point severity scale than what has been reported for the Argenta scale (11). Studies using a nine-point severity scale for cranial deformation and a three-point scale combining the type of cranial deformation and
the supposed underlying neck muscle pathology have also been published, but no data on the accuracy or reproducibility of these methods is given (66, 111).

2.7.2 Direct two-dimensional measurements

Because of the inherent subjectivity of a visual diagnosis, there is a risk of bias, for instance, due to the clinician's knowledge of the infants' referral status, or whether the assessment is made pre- or post-treatment (11, 110). Hence, several objective methods to quantify cranial asymmetry have been developed. Calipers have been used in measuring craniofacial dimensions since historical times, initially presenting as the obvious choice for converting cranial asymmetry into numbers. With calipers, two transcranial diagonal measurements are usually taken, and their difference is either reported in millimeters, or an asymmetry index is derived from the diagonals (9).

![Fig. 4. Transcranial diagonal measurements. Adapted from (112) under the terms of the Creative Commons Attribution Non-Commercial License.](image)

Two of the most commonly used indices are termed oblique cranial length ratio (OCLR) and cranial vault asymmetry index (CVAI), but in fact the two indices are virtually equivalent: OCLR is the ratio between the longer and shorter diagonal multiplied by 100%, while CVAI is the difference between the longer and shorter diagonals divided by the shorter diagonal, usually multiplied by 100% (36, 113,
Therefore, for the sake of simplicity, numeric CVAI scores reported in the discussed literature are converted into and presented as OCLR scores in the present work. There is variation in how the transcranial diagonals themselves are measured: some authors have measured them at a fixed angle to the anteroposterior midline while others either use specific craniofacial landmarks (e.g. frontozygomaticus and euryon) to define the measurement points, or simply just measure the diagonals at the greatest deformity (54, 115-117). Glasgow et al. have reported of a good correlation between the caliper measurements and visual perception of asymmetry (118).

The main disadvantages of direct measurements are the subjective identification of the points of measurement and the inaccuracy caused by the infant resisting (119). There is also wide variance in the reported inter-rater reliability of direct anthropometric measurements. Mortenson and Steinbok performed caliper measurements on 71 infants, and while they achieved virtually perfect intra-rater reliability (κ = 0.98–0.99), inter-rater reliability was only moderate (κ = 0.42) (9). Skolnick et al., on the other hand, achieved an excellent inter-rater reliability of > 0.94 in a sample of 51 infants (119). In another study of 30 infants, Wilbrand et al. reported very low mean intra-observer variability and low mean inter-observer variability for the diagonal measurements, both being negligible in terms of clinical significance (120). However, with inexperienced assessors, a potential source of error with direct measurements lies in the identification of craniofacial landmarks (9), while Skolnick et al. assumed that their observation of a significant bias in one, but not the other of the measured transcranial diagonals was a result of the different measurement positions and handedness of their experts (119).

### 2.7.3 Indirect two-dimensional measurements

Concerns on the repeatability of caliper measurements have led researchers to develop indirect quantification methods, aiming to minimize the impact of human error. Loveday and de Chalain used an artist’s flexicurve to obtain a circumferential head tracing, which was subsequently traced on paper from where the two transcranial diagonals were measured. The paper images could also be stored and reassessed afterwards to allow for a more reliable assessment of the changes in cranial shape (121). A study of 21 infants found both intra- and inter-rater reliability to be excellent (κ = 0.87) for the flexicurve method (122).

Van Vlimmeren et al. developed a similar technique further, describing a method using a thermoplastic band called plagiocephalometry (PCM). The band is
positioned around the infant’s head at the level of the maximum head circumference, and after the ring has hardened, locations of both ears, nose, and midpoint in the posterior region are marked. The ring is then copied with a regular scanner onto a transparent sheet, from which the transcranial diagonals and further indices measuring ear malposition, localized flattening, and cranial proportions can be obtained (123). In a sample of 50 infants, the intra-rater reliability of PCM was found to be > 0.92 and inter-rater reliability > 0.90, while the transcranial measurements were found to show a difference less than 1 mm compared to measurements taken from a 3D CT-scan (123, 124). Another study of 75 infants found OCLR values obtained with PCM to correlate with a numeric severity score given by the experts, but not at all with a severity score given by the parents (125).

Multiple methods based on digital photography have also been described. Hutchison et al. used a computer-based method called HeadsUp™, which automatically analyzes a standardized digital photograph and measures the transcranial diagonals, ear deviation angles, and the cephalic index (CI), the latter being the ratio between maximal cranial width and maximal cranial length. The photograph is taken with the infant wearing a headband, with the locations of both ears and nose marked beforehand. The authors reported of a better repeatability and compliance with the photographic method compared to the flexicurve method, both methods yielding similar values (113). Zonenshayn et al. also used a headband with pre-identified landmarks, but measured overall hemispheric asymmetry instead of the commonly used transcranial diagonals, which eventually proved to be inferior to the diagonal measurements (126). Schaaf et al. took digital photographs without a headband, and manually measured the transcranial diagonals in relation to the anteroposterior midline by using the tip of the nose and ears as landmarks. Despite not using a headband, they reported of an excellent ($\kappa = 0.95$) inter-rater agreement for the method. However, likely due to the calipers compressing the skin, the photographic method yielded slightly lower CVAI values compared to caliper measurements, resulting in a slight underestimation of the asymmetry (127).

### 2.7.4 Three-dimensional measurements

New 3D imaging techniques have emerged over the last decade. The advantages of 3D imaging lie in the recording of the entire craniofacial complex, which enables the measurement (and re-measurement) of angles, surfaces, and volumes, in addition to the traditional point-to-point measurements. Initially, the cost of the required hardware restricted the clinical use of 3D imaging, but this has changed
over the past few years. Many craniofacial centers now use 3D imaging not only in quantifying craniofacial asymmetry, but also in recording the pre- and postoperative appearance of patients undergoing cranial or orthognathic surgery (10, 128).

The most common method for capturing 3D images is digital stereophotogrammetry, in which images of the head are captured simultaneously from different angles by multiple synchronized cameras and a 3D surface mesh of the craniofacial complex is automatically generated by computer software. Owing to a capture speed of around 1.5 milliseconds, infant movement does not cause any artifact in the images. However, to achieve a proper image of the whole craniofacial complex, the infant is required to support the head in an upright position, making stereophotogrammetry unsuitable for newborns (129). A laser scanning method has been developed to facilitate 3D imaging in newborns, but the crib-like scanner requires the subject to stay still for at least 3 seconds, and is only big enough for infants. This limits its potential for clinical use, but both methods produce essentially similar 3D images (130).

Measurements can be taken from the 3D images either manually or by using a specifically designed computer software. In the latter case, the image position must be standardized and the measurement planes or areas defined before any measurements can be extracted. This is usually done by first identifying certain craniofacial landmarks on the 3D image manually, whereafter a custom software is used to align the image (131). In addition to the common transcranial diagonals, which are relatively simple to measure manually from the images, symmetry-related measurements used in literature include variables based on the distribution on cranial surface normal vectors and ratios of volumes within different quadrants of the cranium (11, 132-134). Other described measures of symmetry include a statistical model that calculates an asymmetry score by comparing each point on the cranial surface relative to its contralateral counterpart, as well as a method using the root mean square of the mean difference between each point on the cranial surface within the occipital region (135-137). Intracranial volume has also been measured from 3D surface images in infants with craniosynostosis, with an excellent correlation (> 0.91) reported between the volume measured from 3D images and the volume measured from a CT scan (138).

Transcranial diagonals measured manually from 3D images have shown better repeatability and reliability compared to both direct and indirect 2D measurements. In a study of 100 infants and five assessors, inter-rater reliability of the transcranial diagonals was almost perfect, as were reproducibility and repeatability (10). A
study of 51 infants found an excellent correlation (> 0.90) between transcranial diagonals measured with calipers and diagonals measured manually from 3D images (119). Measurements taken from a 3D image reportedly slightly overestimate the diagonal lengths (and underestimate the OCLR) compared to manual caliper measurements, just like the 2D photographic method (10, 119). In a study of 10 infants, with measurements performed 10 times on each infant, no significant difference was found between transcranial measurements taken with PCM, measurements taken from CT scans, and measurements taken manually from 3D surface images (139). Transcranial diagonals measured from a 3D image with a specifically written software have shown even better reproducibility than the manually measured ones (132). This stems from the good reproducibility (< 1 mm in adults) of the craniofacial landmarks used to standardize the image position, as the need for visually recognizing the points of measurement for the diagonals is eliminated by using the landmarks and a co-ordinate system to define the planes and points of measurement (140).

2.7.5 Radiological modalities

Kim et al. described a sonography-based method, in which the transducer is placed perpendicular to the lambdoid suture, and an occipital angle is subsequently measured between lines projecting along the lambdoid sutures of the skull. The angle measurement had a strong correlation with the OCLR, and the values were later found to decrease over a helmet treatment period similarly to OCLR values measured with calipers. However, the authors present no clear justification for using the sonographic method instead of regular caliper measurements (107, 141). CT and MRI have been compared against direct and indirect surface measurements in validation studies as they are considered diagnostic and accurate, but due to the associated risks and limited accessibility, they are not recommended for assessing cranial asymmetry in clinical practice unless additional indications for using such modalities are present (124, 139). There is no advantage of plain skull radiographs in quantifying cranial asymmetry (142). Some professionals have routinely ordered cervical spine radiographs for infants with DP to exclude possible segmentation and fusion anomalies behind the associated torticollis, but due to the extremely low incidence of such anomalies, radiographs are of low diagnostic value and such routine screening is discouraged (143).
2.7.6 Correlation between objective measurements and visual appearance

There is little data on how the objective measurements discussed in chapters 2.7.2, 2.7.3, and 2.7.4 correspond with the clinical diagnosis of DP (e.g., sensitivity, specificity), although all of the asymmetry-related measurements are assumed to correlate with the visual perception of asymmetry at some level: each measurement has either yielded higher values in infants that have been prescribed orthotic helmet therapy as opposed to infants not receiving helmet therapy, or the values of the measurements have decreased over a period of helmet therapy, according with the visual perception of improvement in cranial shape (114, 132, 133, 135-137, 141).

Nevertheless, proposed cut-off values for DP exist chiefly for indices based on transcranial diagonals, but even these are mainly based on expert opinion, and no information on their sensitivity or specificity can be found. Suggested cut-off values for OCLR found in literature range from 103.5% to 106.0% (113, 114, 123, 124), but even the probably most commonly used cut-off of 104.0% was deemed premature by the authors of the work in which it was established, and no subsequent studies on its validity have been conducted (123). Wilbrand et al. did propose age- and sex-specific cut-offs oscillating between 103.5% and 104.0%, based on percentile curves of 401 normal infants and pre-treatment OCLR values of more than 2,500 infants subsequently treated with orthotic helmets, but with no reference to how the cut-offs match the visual perception of asymmetry (114). Glasgow et al. reported that all infants with a diagonal difference (DD; difference of the transcranial diagonals in millimeters) of more than 0.6 cm had visually apparent, significant deformation, but the authors did not report the sensitivity of the cut-off (118).

The only paper providing a candidate cut-off value for DP based on receiver operating characteristic (ROC) curve analysis is a study of 140 infants conducted by Atmosukarto et al. They described 96% sensitivity and 80% specificity for a cut-off value of 0.035 for their ‘absolute asymmetry score’, computed with a method based on normal vector distributions represented as fixed-bin 2D histograms. The authors also reported of a lower diagnostic accuracy for OCLR (78.6%, as opposed to 90.9% for their absolute asymmetry score), but did not report the sensitivity, specificity, or the cut-off value itself for OCLR (11). Vuollo et al. developed the normal vector distribution-based method further, using a smooth kernel density estimate (KDE) of the directional data defined by the normal vectors instead of fixed-bin histograms defined on the spherical coordinate plane,
achieving a significantly better correlation with clinical assessment compared to the histogram-based method. They also reported of a good correlation between a posterior cranial asymmetry index (PCAI; ratio of the volumes measured from the posterior quadrants of the head) and clinical assessment (144).

2.8 Long-term outcomes

2.8.1 Natural course of DP

Due to the small number of follow-up studies, there is little evidence on the long-term consequences and persistence of DP in the absence of intervention; only two cohort studies on the course of DP can be found. Using the HeadsUp™ method and OCLR \( \geq 106.0\% \) as the cut-off for DP, Hutchison et al. found the point prevalences to be 19.7% in 4-month-olds and 3.3% in 2-year-olds, indicating spontaneous resolution in five out of six infants (47). Using the PCM method and OCLR \( \geq 104.0\% \) as the cut-off for mild DP and \( \geq 108.0\% \) for moderate DP, van Vlimmeren et al. recently reported that out of infants presenting with DP at 7 weeks of age, 19% still had mild DP and 1% moderate or severe DP at the end of the follow-up, yielding a 4.4% point prevalence for DP at 5.5 years. In their study, OCLR values improved until 24 months of age, whereafter improvement stagnated, suggesting that the window for spontaneous improvement of cranial asymmetry closes before 2 years of age (145). This at least partly contradicts the traditional understanding of the improvement potential being directly proportional to the remaining head growth potential (146).

Estimates on the prevalence of DP in adolescence and adults rely on cross-sectional studies with variable methodology. Roby et al. performed caliper measurements on 1,045 teenagers between 12 and 17 years of age, and found DP in 1.1% of the subjects. However, their results might underestimate the true prevalence, as they used DD \( \geq 1.0 \) cm as the cut-off for DP, which is higher than the commonly used cut-offs, and also not indexed to head size (50). Feijen et al. reported a prevalence of 10.3% in 87 randomly selected teenagers (mean age 13.2 years), with DP defined as OCLR \( \geq 106.0\% \); a much higher prevalence than subject or parent concern would have led to expect, again possibly reflecting an unsuitable cut-off value (147).
2.8.2 Developmental delays

Retrospective studies by Miller & Clarren and Steinbok et al. found that 33.0–39.7% of children with a history of DP in infancy had required some form of special assistance in primary school as opposed to only 7.7–10.5% of unaffected controls (148, 149). Hutchison et al. found that 36% of infants referred to an outpatient clinic because of DP had developmental delay in at least one area studied at the time of referral (150). Prospective studies have reported developmental delays in infancy most evident in the area of gross motor development, but also in the areas of fine motor development and mental development (69, 151, 152). Defective language development has also been reported by Korpilahti et al. in 51% of 3-year-olds with a history of DP, 21% having severe disorders in speech-language-related skills (153). Decreased auditory event-related potential amplitudes, considered a predictor of impaired long-term cognitive functioning in infants, were reported in seven out of 10 examined infants with DP by Balan et al. (154), while Hashim et al. found the event-related potentials to be normal in all of their 16 subjects with DP (155). Collett et al. reported children with a history of DP still receiving lower scores in all of the studied areas of development at 3 years of age, with the largest differences in cognition, language, and parent-reported adaptive behavior (156), whereas Hutchison et al. found that developmental delays in infants with DP had reduced to approach the expected level at a mean age of 17 months (157).

As no dose-response effect between the severity of DP and developmental delay can be seen, and because the increased risk of developmental delay in infants with DP has generally lost significance after adjustment to additional risk factors for developmental delay, DP is more likely to be a sign of than rather a cause for the delays (69, 152, 156). It has therefore been suggested that infants presenting with DP should be screened for developmental delays to facilitate earlier diagnosis, intervention, and other supportive measures (158).

2.8.3 Facial asymmetry and malocclusion

Asymmetry of the viscerocranium is present in more severe forms of DP, and cross-sectional studies have described such asymmetry persisting into later childhood. In a case-control study of 112 Finnish children aged 5 to 10 years (mean 8 years) by Hanis et al. the authors observed a chin-point deviation to the right, a more prominent left orbital ridge, and a more protrusive nose and upper lip in the 56 children with a history of Von Rosen splint treatment for developmental dysplasia.
of the hip, compared to 56 age- and sex-matched controls. Such facial asymmetry was hypothesized to be secondary to cranial deformation induced by immobilization in the supine position, as none of the treated infants had had DP when splint treatment was initiated (159, 160). In a cross-sectional study of 100 children aged 2 to 5.7 years, Kluba et al. found class II malocclusion (36% vs. 14%), edge-to-edge bite (28% vs. 12%), and deviations of the midline (38% vs. 16%) to be more prevalent in children with a history of helmet treatment compared to unaffected controls (161). In a prospective study of 27 infants, St John et al. found a significant correlation between the degree of cranial asymmetry and the degree of temporomandibular joint displacement, but no effect from helmet treatment in correcting the displacement (162). Siatkowski et al. found visual field defects, more specifically hemifield asymmetry of at least 20 degrees, in 17.5% of 6-month-old infants with DP, but there is no further evidence on whether such defects are persistent (163).

2.8.4 Parental concern, patient concern and quality of life

In general, parental concern about the misshapen head tends to decrease when the infant starts growing more hair and spend less time on the parents’ lap, where the deformation appears more obvious to the parents. In a cohort study of 129 infants aged between 3.3 and 4.8 years (mean 4 years) diagnosed with DP in infancy, 35% of the children still had mild to moderate asymmetry and 4% severe asymmetry, but only 13% of the parents remained concerned about it, compared to 85% being concerned in the first months (68). In a questionnaire study including the parents of 65 children aged more than 5 years and with a history of DP in infancy, parents perceived the cosmetic appearance of their child as “very abnormal” in two and “mildly abnormal” in 25 cases, but only 21% of the parents remained concerned. 7.7% of the children themselves had commented about the asymmetry of head, and 4.6% had been teased because of it over the past year (149). Past studies have found no decrease in the quality of life of children aged 1–5 years with DP (149, 164). Furthermore, in a cross-sectional study of 87 teenagers, measured absolute cranial asymmetry (OCLR ≥ 106.0%) did not correlate with the subjects’ own perception of cranial shape, and no impact on the quality of life was seen (147).
2.9 Treatment of DP

Concerns of the deformation worsening and ultimately resulting in problems with appearance in later life are the primary motivator for commencing active treatment in infants with DP. However, due to the lack of evidence on the natural course of DP, the long-term benefit of active treatment remains uncertain (36, 53). Depending on the severity of the deformation at the time of diagnosis and associated neck pathology, the treatment usually consists of repositioning therapy, physiotherapy and/or helmet therapy, but occasionally even surgical intervention has been undertaken to correct severely deformed skulls (7, 36, 165).

2.9.1 Repositioning therapy and physiotherapy

Repositioning (counterpositioning) therapy, conducted by the parents or caregivers, involves active repositioning of the child during sleep, play and feeding. The aim is to reduce pressure on the flattened side of the occiput and to alleviate possible neck muscle tightness by encouraging the infant to turn his head predominantly to the less preferred side, allowing the flattened areas of the skull to remodel (166). Physiotherapy may be considered if the infant presents with positional preference, neck muscle imbalance, or asymmetrical motor performance; it usually consists of stretching and strengthening of the cervical muscles, and promoting symmetrical motor development through a variety of methods related to play and care (167). Repositioning therapy, with or without physiotherapy, is usually recommended as the first line of treatment especially in young infants (< 4–6 months), and medical reimbursement systems and companies have generally required that repositioning and/or physiotherapy is attempted before covering the costs of helmet therapy (36).

Nevertheless, evidence on the effectiveness of repositioning therapy and physiotherapy is limited. A randomized controlled trial (RCT) by van Vlimmeren et al. (n = 65) found that in 7-week-old infants with positional preference, regular physiotherapy over a 4-month period decreased the risk of DP (OCLR ≥ 104.0%) by 46% at 6 months and 54% at 12 months of age, compared to the natural course (167). Another RCT (n = 50) by Wilbrand et al. found that cervical stretching exercises (without repositioning) over a short follow-up period of 6 weeks resulted in a significant improvement in OCLR scores, albeit the improvement was slightly greater in a group using a positioning pillow (168). In a small retrospective case series (n = 28), a 3-month course of repositioning therapy led to a subjectively satisfactory result in 88% of cases (169). In another small retrospective series (n =
34), repositioning and physiotherapy until the infants were 12 months old resulted in a significant improvement in parents’ perception of the severity of DP (170). An RCT (n = 126) by Hutchison et al. found repositioning therapy alone to be equally effective to repositioning therapy combined with the use of a positioning wrap, with 80% of the subjects showing good improvement in the severity of DP (determined by OCLR) in a 12-month follow-up (171). A long-term prospective follow-up by the same study group found that out of 129 infants diagnosed with DP before 12 months of age and treated with repositioning therapy, 61% had OCLR in the normal range at 4 years of age (68). Prospective studies comparing helmet therapy to repositioning therapy have also, in most cases, demonstrated improvement in asymmetry-related outcome measurements with repositioning therapy (8, 121, 137). However, studies comparing repositioning therapy to the natural course of DP are lacking altogether.

2.9.2 Orthotic (helmet) therapy

The concept of using an orthotic helmet to correct the distorted cranial shape was introduced by Clarren in 1979 (22). The helmet intends to allow for cranial growth in the flattened areas of the skull and simultaneously restrict growth in the prominent areas, aiming to direct cranial growth in a more symmetrical direction. Helmets are to be worn around 23 hours per day, and treatment duration varies depending on the severity of DP and infant age at onset, usually from 3 to 6 months (53). Demand for such treatment has increased over the current century, and a recent systematic review listed 37 different devices on the market approved by the Food and Drug Administration in the USA (146). Nevertheless, the level of evidence on the effectiveness of helmet therapy has been low to moderate according to past reviews (146, 172, 173), and no RCTs on the subject had been conducted until recently. An RCT (n = 84) by van Wijk et al. published in 2014 found no benefit from helmet therapy and a relatively high incidence of adverse effects, leading the authors to discourage the use of helmets (174). Subsequently, many hospitals have changed their protocols and now refrain entirely from prescribing helmet therapy, while the research community has become even more polarized regarding the use of helmets (36, 175).

In the most recent systematic review published in 2013, Goh et al. found 21 primary research articles on orthotic therapy (146). At the time of writing of the present work, 13 primary research articles published after the previously mentioned review article, as well as one full research article and one abstract of a case-control
study published before, but not included in the aforementioned review, were available. Using the same classification for the level of evidence as Goh et al., found in the footnote of Table 3, for the total of 36 currently available primary research articles on orthotic therapy; one is a Class I study (174), 12 are Class II studies (8, 115, 121, 137, 176-183), two are Class III studies (175, 184), and 21 are Class IV studies (109, 134, 135, 146, 185-189). In Table 3, class I–III studies (studies with a control group) concerning helmet therapy for DP in particular are summarized. All 21 published Class IV studies have described improvement in either perceived or measured cranial asymmetry over a period of orthotic therapy.

Table 3. An overview of studies conducted on orthotic treatment for deformational plagiocephaly. HT = Helmet therapy, RT = Repositioning therapy, PT = Physiotherapy. Primary outcomes were measured at the end of the treatment period, unless stated otherwise in the table.

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Study Design, n</th>
<th>Treatment</th>
<th>Main Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Wijk et al. 2014 (174)</td>
<td>RCT, n = 84</td>
<td>HT for 6 months (n = 42) vs. natural course (n = 42)</td>
<td>No difference in the prevalence of DP at 2 years</td>
<td>HT not effective for moderate to severe DP</td>
</tr>
<tr>
<td>Freudlsperger et al. 2016 (183)</td>
<td>Cohort, n = 213</td>
<td>HT for 18 weeks, started at &lt;24 (n = 82), 24–32 (n = 75), or &gt;32 (n = 56) weeks of age</td>
<td>Better improvement in CVAI with earlier HT, but no improvement in mild DP</td>
<td>HT is more effective the earlier it is started</td>
</tr>
<tr>
<td>Graham et al. 2005 (8)</td>
<td>Cohort, n = 298</td>
<td>HT (n = 159) vs. RT (n = 139) for mean 4.3 months</td>
<td>61% reduction in DD with HT vs. 52% with RT</td>
<td>HT is more effective than RT</td>
</tr>
<tr>
<td>Ho et al. 2016 (176)</td>
<td>Cohort, n = 171</td>
<td>HT (n = 84) vs. natural course (n = 87) for mean 7.8 and 3.9 months</td>
<td>No difference in perceived DP, greater reduction in DD with HT</td>
<td>HT may be effective in correcting severe DP</td>
</tr>
<tr>
<td>Jalaluddin et al. 2001 (182)</td>
<td>Case-control, n = 303</td>
<td>HT (n = 137) vs. RT + PT (n = 166), duration not reported</td>
<td>No difference in DD at 3 to 5 years</td>
<td>RT + PT is as effective as HT in the long term</td>
</tr>
<tr>
<td>Kluba et al. 2011 (115)</td>
<td>Cohort, n = 62</td>
<td>HT started before (n = 24) vs. after 6 months of age (n = 38), mean 16 weeks</td>
<td>75% vs. 60% relative improvement in OCLR favoring early HT</td>
<td>Response to HT is better in younger infants</td>
</tr>
<tr>
<td>Authors, year</td>
<td>Study Design, n</td>
<td>Treatment</td>
<td>Main Results</td>
<td>Conclusion</td>
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<tr>
<td>Class II studies</td>
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<tr>
<td>Lipira et al. 2010 (137)</td>
<td>Case-control, n = 70</td>
<td>HT (n = 35) vs. RT (n = 35) for mean 3.1 and 5.2 months</td>
<td>26% vs. 14% reduction in a 3D hemispheric asymmetry score favoring HT</td>
<td>HT is superior in terms of statistical significance, clinical significance remains debatable</td>
</tr>
<tr>
<td>Loveday &amp; de Chalain 2001 (121)</td>
<td>Case-control, n = 74</td>
<td>HT (n = 29) vs. RT (n = 45) for mean 22 and 64 weeks</td>
<td>No difference in OCLR improvement</td>
<td>HT may correct DP faster, but not better than RT</td>
</tr>
<tr>
<td>Naidoo et al. 2015 (177)</td>
<td>Case-control, n = 100</td>
<td>HT (n = 50) vs. RT (n = 50) for mean 3 months</td>
<td>61% vs. 39% relative improvement in OCLR at 4.5 years favoring HT</td>
<td>Long-term results of HT are superior to RT</td>
</tr>
<tr>
<td>Plank et al. 2006 (179)</td>
<td>Case-control, n = 224</td>
<td>HT (n = 207) vs. natural course (n = 17) for mean 4 months</td>
<td>All 25 outcome measurements improved in 96% receiving HT, but in none of the controls</td>
<td>Better improvement in head shape is achieved with HT compared to no treatment</td>
</tr>
<tr>
<td>Seruya et al. 2013 (180)</td>
<td>Cohort, n = 346</td>
<td>HT in 7 groups stratified by age, treatment length between 8 to 13 weeks</td>
<td>Duration of HT positively correlated with age at initiation</td>
<td>Correction rate of asymmetry with HT decreases with age</td>
</tr>
<tr>
<td>Wilbrand et al. 2014 (178)</td>
<td>Case-control, n = 80</td>
<td>HT (n = 40) vs. RT (n = 40) for 6 months</td>
<td>No statistically significant difference in OCLR improvement</td>
<td>Despite no difference in terms of statistical significance, HT may be more effective</td>
</tr>
<tr>
<td>Class III studies</td>
<td></td>
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<tr>
<td>Wilbrand et al. 2016 (175)</td>
<td>Cohort with historical controls, n = 81</td>
<td>HT (n = 40) vs. natural course (n = 41) for 6 months</td>
<td>OCLR 102% vs. 106% and DD 3.9mm vs. 9.4mm at 5 years favoring HT</td>
<td>HT is effective in correcting DP; no spontaneous correction is seen</td>
</tr>
</tbody>
</table>

Class I: evidence from a randomized controlled trial; Class II: evidence from a prospective trial comparing treatments in a nonrandomized manner; Class III: evidence from a case series with historical controls; Class IV: evidence from a prospective or retrospective case series with no control group.

As seen in the table, most studies have used a continuous measurement as the primary outcome, with no regard to changes in subjective perception of severity, or whether the infants were still plagiocephalic after the treatment. Despite the lack of effect described by van Wijk et al. in their trial (174) and discordance between
results from Class II studies, a recently published review comes to the conclusion that helmet therapy is recommended over repositioning and physical therapy in severe cases of DP, while mild to moderate cases should be assigned the treatment preferred by the parents (36).

Complications associated with helmet therapy

Minor complications are a relatively frequent event during helmet therapy. In a series of 205 infants treated with helmet therapy, 13.7% experienced pressure sores, 2.9% experienced ethanol erythema, and 4.3% experienced skin erosions or infections (190). In another patient series, pressure sores were observed in 10.5%, ethanol erythema in 6.3%, skin infection in 1.2%, and a subcutaneous abscess in one of the 410 infants treated with helmet therapy (191).

2.9.3 Operative treatment

DP does not restrict brain growth and there is no known risk of associated increased intracranial pressure (97, 158); surgery is thus very rarely used in correcting DP. If considered appropriate, surgery is usually performed after 15 to 18 months of age. A long-term follow-up of 30 children by Marchac et al. described the morphological results of operative treatment to be good or excellent, depending on the used technique, but also reported dural tears or sinus venosus breaches occurring during 28–36% of the operations. Therefore, as a potentially life-threatening procedure, surgery is recommended to be considered only in very severe cases, after exhaustion of all nonsurgical methods (7). Even then, whether such a massive operation is justified to treat an essentially cosmetic condition is a subject of controversy (53).

2.9.4 Age and response to treatment

Several studies have documented the risk of treatment failure increasing the older the infant gets before treatment is initiated. With repositioning and physiotherapy, not much effect can be expected after the infant has developed control over his own sleeping position and no longer spends long periods of time lying supine. Thus, they are usually not considered after 6 months of age (63, 171). Helmet therapy has also yielded better results in terms of OCLR and DD when commenced before 6 months of age (115, 183), and a positive correlation between age at treatment onset
and required treatment duration has been reported (180). However, a recent retrospective cohort study of 4,378 infants with DP found that starting with a trial of mean 4.1 months of repositioning therapy before shifting to helmet therapy had no adverse effect on the final treatment outcomes compared to starting helmet therapy immediately, and as 77% of the infants achieved satisfactory correction with repositioning therapy alone, the authors recommend repositioning therapy as the first line of treatment for most cases (187). After 12 months of age helmet therapy is seldom prescribed, because the required treatment period may exceed a year and the treatment may still be unsuccessful due to a massive increase in the amount of compliance issues (192).

2.10 Prevention of DP

After the pathomechanisms behind DP began to unravel, guidelines for preventing DP from developing started to emerge. As supine positioning appears to increase the risk of DP both directly and through delaying the achievement of certain motor milestones (61), a daily dose of supervised prone time (“tummy time”) starting from birth has long been recommended to improve motor development and reduce the risk of DP (193). At the same time, spending prolonged periods in bouncers, carriers, and car safety seats has been discouraged as passivating. Alternating the supine head position from side to side during sleep, and periodically changing the orientation of the infant to outside activity has been encouraged to allow for even distribution of external forces on the occiput (29). However, the evidence on the effectiveness of such measures is mainly obtained from studies investigating risk factors for DP (48, 64). Additionally, one prospective case-control study reported promising results for a preventive program directed to parents of newborns, reducing the relative risk of DP at 4 months of age by 67%. Regrettably, DP was diagnosed by multiple assessors, all clearly aware of subject allocation, which acts as a major limitation of the study (194). A Swedish pilot study also reported that a lower prevalence of DP was observed in 6-month-olds who had regularly attended a primary healthcare nurse who followed preventative guidelines and provided the families with such advice, but no conclusions on nursing actions de facto impacting infant head shape could be drawn due to an insufficient sample size (195). Nevertheless, the high prevalence of DP and the amount of effort put into its treatment do call for a primary preventive approach, but a need for pragmatic clinical trials to determine whether such measures truly are effective in reducing this burden persists.
3 Aims of the study

This study was designed to investigate the course of cranial asymmetry over the first year of life and to test the efficacy of a primary preventive program in reducing the incidence of DP. Another objective was to assess the suitability of 3D stereophotogrammetry in quantifying cranial asymmetry by testing and comparing the diagnostic accuracy of several stereophotogrammetry-based measurement variables.

More specifically, the aims of the present work were as follows:

- To determine the prevalence of deformational plagiocephaly (DP) and the course of cranial asymmetry from birth to 12 months of age in an unselected population (I, III)
- To test, whether a preventive program directed to the parents of newborns reduces the prevalence of DP at 3 months of age (II)
- To investigate the impact of limited neck range of motion, positional preference, and other infant- and environment-related factors on the development and persistence of DP in infancy (I, II, III)
- To compare the diagnostic accuracy of stereophotogrammetry-based variables and determine their optimal cut-off values for DP in different age-groups (IV)
4 Subjects and methods

4.1 Subjects and study design

The study was carried out in the Clinic for Children and Adolescents, Oulu University Hospital, and the Unit of Oral Health Sciences, University of Oulu. All neonates born at Oulu University Hospital on pre-selected dates between February 2012 and December 2013 were asked to participate as long as they were born after \( \geq 35 \) weeks of gestation, managed without intensive care during the initial hospitalization, and resided within a 30-min driving distance from Oulu University Hospital. However, newborns with craniosynostosis, cleft lip and/or palate, or clearly dysmorphic features were excluded. All participants were of Finnish origin.

After enrolment and an initial clinical examination, subjects participating in the follow-up study were randomized into two groups. Allocation was performed in permuted blocks of four according to a computer-generated randomization plan. Before discharge from the maternity ward, parents of newborns in the intervention group received detailed recommendations regarding their infant’s environment, positioning, and handling, provided by an experienced neonatologist in a private 15-min guidance session as well as in printed form. Parents of control group infants received the usual guidance on infant positioning and caring from the midwife. The randomized part of the study terminated after a follow-up visit held when the infants were 3 months of age, but long-term follow-up continued with visits at 6 and 12 months. Some participants have also already attended a 3-year follow-up visit, and the follow-up will continue in the future with visits taking place at 6 and 9 years. Researchers responsible for the processing of the craniofacial images and data analysis were blinded to group allocation until study II was complete. The study flow (I–III) is shown in Fig. 5.

For study IV, the material consisted of a pool of 407 de-identified 3D craniofacial images of infants between 3 to 36 months of age. 347 of the images were of cohort infants and 60 of the images of moderately to extremely preterm infants not included in the cohort. The preterm infants had originally been recruited by convenience sampling in the neonatal intensive care unit at the Oulu University Hospital for a separate study not included in the present work.
Fig. 5. Study flow for sub-studies I-III.

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4.2 Methods

4.2.1 Clinical examinations and background data (I–III)

Background data regarding pregnancy, delivery, and subsequent hospitalizations were collected from maternal and infant medical records. Clinical examinations were performed in the maternity ward at birth, and in an outpatient study clinic at each follow-up visit. During the initial examination at 36 to 72 hours of age (0 months), the subjects were screened for clavicular fractures, sternocleidomastoidal masses, and other malformations, deformations, or injuries that could account for the supposed cervical imbalances. At every examination, anthropometric measurements of the head, height, and weight were obtained, and the neck ROM was measured with a digital goniometer. At 0 months, passive rotation was assessed in the supine position by supporting the head from below, allowing it to turn as far as possible. At 3, 6, and 12 months, active rotation was measured by encouraging the rotation of the head as far as possible, using either a musical toy or a parent. Lateral flexion was always assessed by applying very gentle pressure until resistance was noted. All measurements were always performed three times. CMT was defined as persistent head tilt or a sternocleidomastoid tumor associated with a limited neck ROM, while an imbalance of $\geq 15^\circ$ in head rotation or lateral flexion without persistent head tilt or a sternocleidomastoid tumor was defined as positional torticollis (72). At 3 and 6 months, the subjects were screened for positional preference in the supine position, defined as keeping the head turned to the same side for more than three quarters of the examination (63). Motor development was evaluated with the Griffiths Mental Development Scale (GMDS; Hogrefe, Göttingen, Germany), specifically the parts assessing gross motor development, eye-hand coordination and performance, converting the sum of calculated sub-quotients into Z-scores. Prior to each follow-up visit, the parents filled out a questionnaire inquiring about caring habits and the infant’s environment (daily time spent in carriers/bouncers/car seats, prone on the floor, and supine on the floor), pacifier use, sleeping position, diet, and illness history, as well as parents’ perception of the cranial shape and possible positional preference.
4.2.2 Preventive program (II)

A preventive program was designed based on known risk factors for DP, previous recommendations on preventing DP, and a previous study on physical therapy to treat positional preference (29, 167, 194, 196). Following the American Academy of Pediatrics’ recommendations, the parents were instructed to put their infant to sleep on the back, alternating the position of the head evenly between left and right. Additionally, the parents were encouraged to prepare the infant’s environment so as not to restrict the infant’s spontaneous movement. Because the infant should receive stimuli equally from all directions, toys and other interesting objects were instructed to be spread out on the floor evenly, and their positions changed regularly. The bed/cot was to be placed with the infant’s head or feet towards the window or other major source of light, if possible. Alternatively, parents could regularly alternate the infant’s sleeping position in relation to the source of light. Parents were encouraged to alternate sides when handling the infant (e.g., right or left hand when holding the infant). The infant was recommended to spend time in the prone position when awake and under supervision, starting at birth with shorter periods of time, aiming to provide more than 30 minutes of daily prone time as early as possible. In general, the aim was to provide the infant with as much time freely on the floor as possible, and to minimize the time spent immobilized (e.g. in car seats, bouncers, and carriers). In the case of the parents noticing the infant showing a positional preference, they were instructed to place interesting objects predominantly on the opposite side, as well as to favor the opposite side in handling, bottle-feeding, sleeping position, and other activities. Finally, parents were informed about neck stretching exercises, which were recommended to be started and performed regularly if the infant showed or began to show signs of cervical imbalance (i.e., inability to fully rotate and/or flex the head to one direction, or a persistent head tilt).

4.2.3 Acquisition of craniofacial images

At 0 and 3 months, a standard digital photograph of the head was taken from the vertex point of view with a Canon® EOS 600D DSLR camera. Head position was standardized for the photograph by having the infant lie supine on the edge of the examination table and extending the head slightly, until an imaginary line through the otobasion superius and exocanthion was perpendicular to the examination table.
The facial midline was parallel to a straight line in the floor, and the camera was situated 80 cm from the head on the level of the examination table.

At 3 months and every subsequent visit, a 3D image of the head was obtained using the 3dMDhead 5-pod camera system (3dMD, Atlanta, Georgia, USA) in a standardized manner. First, a tight nylon cap was fitted on the infant’s head to avoid hair artifacts. Next, the infant was seated on a chair, centered in the 3D scanner, and lured to look through a small window in the panel in front of him, whereafter five synchronized cameras captured a 360° image of the head. Lighting and surroundings remained consistent throughout the study.

Fig. 6. The 3D scanner has enough room for an adult to be holding the infant in position.

4.2.4 Processing of 3D images (II–IV)

The 3D images were processed and analyzed with RapidForm® 2006 (Geomagic, Rock Hill, South Carolina) 3D software using custom macros written with Visual Basic for Applications (VBA). More complex mathematical analyses regarding the outcome measurements were performed with Matlab R2014b (MathWorks, Natick, Massachusetts, USA). First, ready-made software tools were used to remove shoulders and other excess data from the images and to level out possible bumps
caused by cap seams. Next, the craniofacial landmarks endocanthion left, endocanthion right, tragion left, and tragion right were manually identified on the image. The 3D image position was standardized by using a custom macro that creates a co-ordinate system based on the aforementioned landmarks and the sagittal reference plane (yz), which it constructs with the mirror face method (131). In the mirror face method, the original facial shell and a mirror shell are registered together using the best fit technique, and the symmetry plane of the resulting structure is treated as the sagittal plane for the original face and head. The origo of the co-ordinate system was set at the intersection of the sagittal plane and a line connecting the tragions. The transverse reference plane (xz) was defined to run through the point right in the middle of the two endocanthsions and origo perpendicular to the sagittal plane, and the coronal reference plane (xy) perpendicular to the other two planes. At this point, the x-, y-, and z-axes have also been defined. After the aligning process, two planes used in measuring the outcome variables were defined. With the transverse plane serving as the base plane, the measurement plane for point-to-point variables was the plane parallel to the base plane at the maximum curvature in the occipital region (i.e., maximum head circumference). The measurement plane for the remaining variables was defined as running parallel to the base plane, immediately above the highest part of the helix of the higher set ear.
4.2.5 Outcome measures

From the standard digital photographs, the variables oblique cranial length ratio (OCLR) and cephalic index (CI) were measured using custom-written computer software. From the 3D images, the 2D variables OCLR, diagonal difference (DD), ear offset (EO), and CI were calculated as indicated in Fig. 8. The 3D volumetric variables anterior cranial asymmetry index (ACAI) and posterior cranial asymmetry index (PCAI) were calculated from volumes within the quadrants shown in Fig. 7 using the formula: (larger cuboid volume – smaller cuboid volume) / smaller cuboid volume x 100%. Finally, three 3D surface variables based on normal vector distribution were calculated: asymmetry score (AS), weighted asymmetry score (wAS), and flatness score (FS). AS, wAS, and FS scores are calculated from the surface area within the posterior quadrants by integrating the KDE function. The square of KDE function is integrand in FS, while the square of difference between the KDE function and its reflection against the sagittal plane is
The transcranial diagonals for OCLR and DD were measured at a 40° angle to the anteroposterior midline from both standard digital photographs and 3D images. In studies I–III, OCLR ≥ 104% was used as the cut-off for DP in the univariate and logistic regression analyses, as described by van Vlimmeren et al. in (48). Cut-offs for moderate and severe DP were set at OCLR ≥ 108% and OCLR ≥ 112%, respectively, as described by van Wijk et al. in (174).

Fig. 8. OCLR = ratio of the longer and shorter oblique transcranial diagonal (a, b) x 100%. DD = difference between the transcranial diagonals. Ear offset = distance between the tragion landmarks (TrL, TrR) in the anteroposterior direction (c). CI = maximum cranial width (d) divided by maximum cranial length (e) x 100%.
Fig. 9. On a flat area the surface normal vectors have similar directions (left), leading to a local maximum in the density function of direction angles (middle). Contour plot (right): a KDE function of the surface unit normal vectors on the occipital region projected onto a 2D unit disk.

4.2.6 Visual classification of DP (IV)

In order to study the correlation between the subjective perception of cranial asymmetry and objective asymmetry-related measurements, visual ratings were given to 407 3D craniofacial images of infants between 3 and 36 months of age. An independent investigator first created files with the images de-identified and randomized into different orders. The images were then consecutively assessed by two experts blinded to case status. The assessment was performed twice by both assessors with a two-week interval, with the images in a different order for each assessment. The assessors rated the heads as symmetrical or deformed using the five-stage scale described by Argenta shown in Fig. 3 (2).

4.3 Statistics

For the RCT, the calculated sample size was 86 (43 in each group) using a 5% significance level, a power of 80% and an expected decrease in the prevalence of DP by 75% (approximately from 31% to 8%) at 3 months of age, which were based on previous publications. The final sample size was determined by taking into account an estimated dropout rate of 20%. The groups in study II were compared on an intention-to-treat basis with the $\chi^2$ test, Fisher’s exact test, and the Mann-
Whitney U test. One set of twins was excluded from the randomized part of the study (II) prior to statistical analyses, as twins are known to naturally be at a higher risk of DP, and equivalent compliance with the preventive instructions could not be expected from the parents of twins (76). In studies I–III, univariate analyses (χ², Independent Samples and Paired Samples t tests) were carried out to investigate potential risk factors for DP, and in studies I and III, factors with p < 0.2 in the univariate analyses were included in additional multivariate logistic regression analyses. In study III, linear mixed models (LMM) were used to study the impact of time and different infant and environment-related factors on cranial asymmetry between 3 and 12 months of age; LMM was used instead of standard linear regression, as the study had a repeated measures design with two time points (6 and 12 months), and thus correlation occurred between the residual errors within the subjects. OCLR, PCAI, and wAS were used as dependent variables in the models, and a backward stepwise strategy to select the explanatory variables in the final models by first entering all putative variables into the models, and then removing one at a time until the best possible models were reached. In order to ensure finding the best possible models, the stepwise process was performed multiple times in different orders for each of the outcome variables, and several interactions between the putative predictive factors were considered. The Bayesian information criterion (BIC) was used to test model adequacy and the models with the lowest BIC values were selected as the final models. The BIC values also indicated that the Compound Symmetry covariance structure was to be used for all of the models. In study IV, ROC curves were created, from which area under the curve (AUC) values and Youden's indices were calculated to test and compare the accuracy of OCLR, DD, PCAI, and wAS, and to determine cut-off values for different classes of DP. The ROC curves were compared visually and the significance of difference between the AUC values was tested according to Hanley and McNeil (198). Cohen’s Kappa coefficient was used to study intra- and inter-rater reliability of the visual classification. Results are expressed as means unless stated otherwise, with p < 0.05 considered statistically significant. All statistical work was carried out with SPSS v. 22.0 (IBM®, Armonk, New York, USA).

4.4 Ethical considerations

The study was approved by the Ethics Committee of the Northern Ostrobothnia Hospital District and it was carried out according to the Declaration of Helsinki. Written, informed consent was obtained from all of the parents, prospectively. The
RCT (study II) was registered with ClinicalTrials.gov under the identifier NCT02283229. Due to ethical reasons, the follow-up in the RCT setting was terminated when the infants were 3 months of age, and advice on repositioning and physiotherapy was provided if the parents were concerned about their infant’s head shape and DP was present.
5 Results

5.1 Demographics (I–III)

Table 4 shows details regarding gestation, delivery, and neonatal examination for the 155 newborns included in study I and the 99 infants participating study III. In Table 5, background characteristics and anthropometric measurements at birth are presented separately for the intervention and control group infants attending the 3-month visit in study II. There were no differences in the background characteristics between participants and non-participants, or between those who completed follow-up and those who were lost to follow-up. All in all, 57% of eligible infants participated in study I, and 41% in the RCT (II) and long-term follow-up (III). No infants were diagnosed with CMT at any point of the study; all cases of torticollis were positional.
Table 4. Characteristics of the participants in studies I and III regarding infant details, delivery and gestation presented as mean ± SD or n (%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study I (n = 155)</th>
<th>Study III (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>76 (49)</td>
<td>52 (53)</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3548 ± 483</td>
<td>3542 ± 506</td>
</tr>
<tr>
<td>Birth length, cm</td>
<td>50.2 ± 2.0</td>
<td>50.2 ± 1.4</td>
</tr>
<tr>
<td>Head circumference at birth, cm</td>
<td>35.0 ± 1.5</td>
<td>35.3 ± 1.4</td>
</tr>
<tr>
<td>Gestational age, days</td>
<td>279 ± 11</td>
<td>279 ± 11</td>
</tr>
<tr>
<td>Primiparous mother</td>
<td>68 (44)</td>
<td>47 (48)</td>
</tr>
<tr>
<td>Maternal age, years</td>
<td>30.0 ± 5.8</td>
<td>30.9 ± 5.6</td>
</tr>
<tr>
<td>Presentation at delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occiput anterior</td>
<td>125 (81)</td>
<td>85 (86)</td>
</tr>
<tr>
<td>Occiput posterior</td>
<td>20 (13)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Compound (arm-head)</td>
<td>3 (2)</td>
<td>-</td>
</tr>
<tr>
<td>Breech</td>
<td>7 (5)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>118 (76)</td>
<td>82 (83)</td>
</tr>
<tr>
<td>Vacuum-assisted</td>
<td>13 (9)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Elective caesarean section</td>
<td>12 (8)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Non-elective caesarean section</td>
<td>12 (8)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Length of 2nd stage of labor, min1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-10</td>
<td>44 (34)</td>
<td>33 (40)</td>
</tr>
<tr>
<td>11-30</td>
<td>44 (34)</td>
<td>26 (32)</td>
</tr>
<tr>
<td>31-60</td>
<td>34 (28)</td>
<td>16 (20)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>9 (7)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Problems with pregnancy or delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green amniotic fluid</td>
<td>23 (15)</td>
<td>16 (16)</td>
</tr>
<tr>
<td>Gestational diabetes mellitus</td>
<td>13 (8)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Toxemia</td>
<td>9 (6)</td>
<td>6 (6)</td>
</tr>
</tbody>
</table>

1Excluding cesarean sections.
Table 5. Background characteristics and anthropometric measurements at birth for the intervention and control group infants included in the final analyses in study II. Means ± SDs or n (%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention group (n=45)</th>
<th>Control group (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>25 (56)</td>
<td>25 (49)</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3660 ± 528</td>
<td>3485 ± 430</td>
</tr>
<tr>
<td>Birth length, cm</td>
<td>50.5 ± 2.0</td>
<td>50.0 ± 1.9</td>
</tr>
<tr>
<td>Head circumference at birth, cm</td>
<td>35.1 ± 1.4</td>
<td>34.8 ± 1.4</td>
</tr>
<tr>
<td>Gestational age, days</td>
<td>280 ± 9.3</td>
<td>279 ± 11.9</td>
</tr>
<tr>
<td>Primiparous mother</td>
<td>21 (47)</td>
<td>25 (49)</td>
</tr>
<tr>
<td>Maternal age, years</td>
<td>31 ± 6.2</td>
<td>31 ± 5.0</td>
</tr>
<tr>
<td>Presentation at delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occiput anterior</td>
<td>41 (91)</td>
<td>43 (84)</td>
</tr>
<tr>
<td>Occiput posterior</td>
<td>2 (4)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Breech</td>
<td>2 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>37 (82)</td>
<td>42 (82)</td>
</tr>
<tr>
<td>Vacuum assisted delivery</td>
<td>4 (8)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Problems with pregnancy&lt;sup&gt;1&lt;/sup&gt;</td>
<td>12 (27)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Cephalic Index, %</td>
<td>79.2 ± 3.8</td>
<td>80.5 ± 4.1</td>
</tr>
<tr>
<td>Oblique Cranial Length Ratio, %</td>
<td>101.7 ± 1.3</td>
<td>101.6 ± 1.3</td>
</tr>
<tr>
<td>Imbalance in head rotation, °</td>
<td>4.0 ± 3.1</td>
<td>3.9 ± 2.7</td>
</tr>
<tr>
<td>Imbalance in lateral flexion, °</td>
<td>4.1 ± 3.3</td>
<td>4.2 ± 5.0</td>
</tr>
</tbody>
</table>

<sup>1</sup>Gestational diabetes, pre-eclampsia, cervical insufficiency, polyhydramnion or oligohydramnion 

5.2 Prevalence of DP and course of cranial asymmetry during the first year of life (I, III)

The prevalence of DP in infants completing the 12-month follow-up was 8% at birth, 28% at 3 months, 24% at 6 months, and 19% at 12 months, with DP determined as OCLR ≥ 104% in the 2D image at birth and in the 3D image at 3, 6, and 12 months. Fig. 10 shows the prevalence of DP at each visit grouped by whether the family received preventive counseling at birth. For OCLR, the means and ranges were 101.8% (100.0–105.3%) at birth, 103.1% (100.0–113.5%) at 3 months, 102.6% (100.0–109.3%) at 6 months, and 102.3% (100.0–107.7%) at 12 months. Out of the infants diagnosed with DP at the 3-month visit, only two had had DP at birth. Respectively, only three infants with OCLR in the normal range at 3 months presented with DP at a subsequent visit: two were plagiocephalic at 6 months, of whom one had OCLR again in the normal range at 12 months, while one infant with OCLR in the normal range at 3 and 6 months exceeded the cut-off at 12 months.
However, the OCLR values for the three infants were only slightly over the cut-off for DP (104.0–104.7%). 18 out of the 26 (69%) infants with DP at 3 months saw a decrease in their OCLR from 3 to 6 months, while 20 out of the 22 (91%) with DP at 6 months saw a decrease in their OCLR from 6 to 12 months.

Table 6 shows descriptive statistics of anthropometric measurements and outcome variables at 3, 6, and 12 months. Although the mean head circumference increased just as much from 6 to 12 months as from 3 to 6 months, the change in the means of asymmetry-related measurements OCLR, DD, PCAI, AS, and wAS from 6 to 12 months was only 17–55% of what it was from 3 to 6 months. Whereas the overall mean scores for all five measurements showed statistically significant improvement from 3 to 6 months (p < 0.05), only OCLR continued to improve significantly (p < 0.05) from 6 to 12 months regarding all participants. However, in infants with DP at 6 months, all four measurements showed statistically significant improvement (p < 0.05) from 6 to 12 months as well.
Table 6a. Anthropometric measurements and obtained at the 3, 6, and 12 month follow-up visits.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Means ± SDs of anthropometric measurements, CI, and FS.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 months (n=99)</td>
</tr>
<tr>
<td>Age, mo</td>
<td>3.0 ± 0.6</td>
</tr>
<tr>
<td>Weight, g</td>
<td>6213 ± 954</td>
</tr>
<tr>
<td>Length, cm</td>
<td>61.0 ± 3.0</td>
</tr>
<tr>
<td>Head circumference, cm</td>
<td>41.2 ± 1.6</td>
</tr>
<tr>
<td>Full ROM in neck rotation, °</td>
<td>180.0 ± 11.0</td>
</tr>
<tr>
<td>Imbalance in neck rotation, °</td>
<td>4.7 ± 4.3</td>
</tr>
<tr>
<td>CI, %</td>
<td>77.5 ± 3.5</td>
</tr>
<tr>
<td>FS</td>
<td>0.203 ± 0.016</td>
</tr>
</tbody>
</table>

Table 6b. Asymmetry-related measurements and obtained at the 3, 6, and 12 month follow-up visits.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Means ± SDs and 95th percentiles of asymmetry-related measurements.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 months (n=99)</td>
</tr>
<tr>
<td>ACAI, %</td>
<td>3.2 ± 2.7</td>
</tr>
<tr>
<td>95th percentile</td>
<td>9.4</td>
</tr>
<tr>
<td>PCAI, %</td>
<td>9.3 ± 8.8</td>
</tr>
<tr>
<td>95th percentile</td>
<td>30.4</td>
</tr>
<tr>
<td>DD, mm</td>
<td>4.0 ± 3.5</td>
</tr>
<tr>
<td>95th percentile</td>
<td>12.8</td>
</tr>
<tr>
<td>EO, mm</td>
<td>1.5 ± 1.2</td>
</tr>
<tr>
<td>95th percentile</td>
<td>3.4</td>
</tr>
<tr>
<td>OCLR, %</td>
<td>103.1 ± 2.8</td>
</tr>
<tr>
<td>95th percentile</td>
<td>109.5</td>
</tr>
<tr>
<td>AS</td>
<td>7.4 ± 5.5</td>
</tr>
<tr>
<td>95th percentile</td>
<td>16.9</td>
</tr>
<tr>
<td>wAS</td>
<td>27.1 ± 47.8</td>
</tr>
<tr>
<td>95th percentile</td>
<td>94.8</td>
</tr>
</tbody>
</table>

5.3 Prevention of DP through parent guidance (II)

At the end of the prevention trial at 3 months of age, five infants (11%) in the intervention group and 16 infants (31%) in the control group had DP in the 2D image analysis, yielding a risk ratio of 0.35 (95% confidence interval 0.14–0.89; p < 0.05). Changes in the mean OCLR scores from birth to follow-up were +0.2% in
the intervention group and +1.5% in the control group (p < 0.01). In the 3D image analysis, seven infants (15%) in the intervention group and 17 infants (33%) in the control group had DP, resulting in a risk ratio of 0.48 (95% confidence interval 0.22–1.04; p = 0.05). Two infants in the intervention group and four infants in the control group had moderate DP, while none in the intervention group and two in the control group had severe DP. Including the degree of asymmetry in the analysis yielded a significant difference between the groups (p < 0.05). Secondary outcome variables grouped by therapy allocation appear in Table 7.

Table 7. Secondary outcomes of study II at the 3 month visit grouped by allocation. Means ± SDs.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention group (n=45)</th>
<th>Control group (n=51)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mo</td>
<td>3.0 ± 0.6</td>
<td>3.1 ± 0.6</td>
<td>1.000</td>
</tr>
<tr>
<td>ACAI, %</td>
<td>3.3 ± 2.91</td>
<td>3.1 ± 2.6</td>
<td>0.844</td>
</tr>
<tr>
<td>PCAI, %</td>
<td>6.9 ± 6.81</td>
<td>9.5 ± 8.4</td>
<td>0.308</td>
</tr>
<tr>
<td>DD, mm</td>
<td>2.8 ± 2.51</td>
<td>4.2 ± 3.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>EO, mm</td>
<td>1.3 ± 1.01</td>
<td>1.5 ± 1.3</td>
<td>0.120</td>
</tr>
<tr>
<td>CI, %</td>
<td>79.5 ± 4.41</td>
<td>78.8 ± 3.9</td>
<td>0.749</td>
</tr>
<tr>
<td>Full ROM in neck rotation, °</td>
<td>179 ± 12</td>
<td>178 ± 13</td>
<td>0.295</td>
</tr>
<tr>
<td>Full ROM in lateral flexion °</td>
<td>103 ± 15</td>
<td>96 ± 13</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Imbalance in neck rotation, °</td>
<td>4.0 ± 3.9</td>
<td>5.3 ± 4.7</td>
<td>0.154</td>
</tr>
<tr>
<td>Imbalance in lateral flexion, °</td>
<td>4.5 ± 4.3</td>
<td>5.8 ± 4.5</td>
<td>0.980</td>
</tr>
<tr>
<td>Z-score from GMDS</td>
<td>0.02 ± 0.96</td>
<td>-0.10 ± 0.94</td>
<td>0.590</td>
</tr>
</tbody>
</table>

GMDS = Griffiths Mental Development Scale. *3D data missing for one infant

Although there was no significant difference in the CI between the groups at birth or at 3 months, the change in the CI from birth to follow-up differed significantly between the intervention and control group (+0.3% vs. −1.6%; p < 0.05). Sleeping position had a clear effect on the CI: despite a lack of difference at birth (80.1% vs. 79.7%; p = 0.61), infants who slept exclusively in the supine position had a greater CI at follow-up than did infants whose sleeping positions alternated (80.8% vs. 78.3%; p < 0.01). However, a trend towards a smaller increase in the OCLR of supine-sleeping infants was observed (+0.4% vs. +1.3%; p = 0.09).

According to the parents’ own evaluation, therapy compliance was good in the intervention group. Based on parents’ estimate of daily activity, on average the intervention group infants spent more time on the floor (3.7h vs. 3.0h) and less time in carriers, car seats, and bouncers (2.9h vs. 3.8h). They were also more likely to sleep exclusively in the supine position (67% vs. 53%) and spent more time in the
supine position when awake (2.8h vs. 2.4h). Control group infants had more often hanging toys (61% vs. 73%) and were more likely to have their toys spread asymmetrically in relation to the infant’s position (7% vs. 22%). None of the aforementioned differences were statistically significant, however. In addition, the groups showed no differences in the type or frequency of feeding or pacifier use.

5.4 Risk factors for DP developing or persisting (I–III)

For DP at birth, significant risk factors identified in the univariate analyses were prolonged second stage of labor (p < 0.05), cesarean section (p < 0.05), vacuum-assisted delivery (p < 0.01), and gestational diabetes (p < 0.01). In the logistic regression analysis, only vacuum-assisted delivery (aOR 6.8; 95% confidence interval 1.31–35.1) and gestational diabetes (aOR 5.6; 95% confidence interval 1.17–27.4) were statistically significant. There was no association between DP and unilaterally restricted neck ROM at birth. However, there was a linear correlation between the CI and the full ROM for neck rotation (r = −.368) and lateral flexion (r = −.288), more brachycephalic infants having smaller ranges of motion, and infants with DP at 3 months did have a higher mean CI at birth (81.5% vs. 79.5%; p < 0.05). Infants with DP at 3 months were also more often born preterm (p < 0.05), had lower Z-scores for motor development, (−0.39 vs. 0.10; p < 0.05), showed a higher mean imbalance in head rotation (6.7° vs. 3.9°; p < 0.01), and more frequently had torticollis (16.7% vs. 2.8%; p < 0.05) at 3 months. Neither DP nor cervical imbalance at birth was associated with DP or cervical imbalance at 3 months, however. Univariate analyses for potential risk factors for DP at 3 months were also carried out separately within the intervention and control groups, and while infants in the control group who were born preterm (p < 0.01), spent more time supine (p < 0.05), or had a lower motor Z-score (p < 0.01) were more likely to have DP, the only factor associated with DP in the intervention group was preterm birth (p < 0.05).

Infants with DP at 6 months had more positional preference (35% vs. 5%; p < 0.001) at 3 months, had more imbalance in head rotation at 3 months (6.6° vs. 4.1°; p < 0.01), were more often first born (65% vs. 42%; p < 0.05), had a higher CI at all time-points (overall means 79.0% vs. 77.4%; p < 0.01), and had reached fewer motor milestones by 6 months (−0.45 vs. 0.14; p < 0.05). Infants with DP at 12 months showed more frequently positional preference at 3 months (44% vs. 5%; p < 0.001), had more imbalance in head rotation at 3 months (7.0° vs. 3.9°; p < 0.01) and 6 months (6.8° vs. 4.1°; p < 0.01), had a higher CI at all time-points (overall
means 78.7% vs. 77.5%; p < 0.05), had reached fewer motor milestones by 6 months (−0.40 vs. 0.11; p < 0.05), and spent more time supine on the floor at 6 months (1.7h vs. 0.9h; p < 0.05). Positional preference at 6 months was not associated with DP at 6 or 12 months. Analysis of potential risk factors for DP developing after 3 months was omitted because the number of new DP cases emerging after 3 months was very low. Infants with DP persisting from 3 to 12 months had a higher mean gestational age (265 vs. 279 days; p < 0.05), were more frequently first born (36% vs. 74%; p < 0.05), and showed more frequently positional preference at 3 months (9% vs. 53%; p < 0.05). Apart from supine time spent on the floor, none of the investigated environment-, caring-, diet-, or illness-related factors (Table 8) were associated with DP in the univariate analyses.

Table 8a. Characteristics regarding diet and illness history.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Means ± SDs or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of breastfeeding</td>
<td></td>
</tr>
<tr>
<td>&gt;6 months</td>
<td>74 (75)</td>
</tr>
<tr>
<td>2-6 months</td>
<td>17 (17)</td>
</tr>
<tr>
<td>&lt;2 months</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Acute otitis media (1 or more)</td>
<td>29 (29)</td>
</tr>
<tr>
<td>Conditions requiring prolonged hospitalization¹</td>
<td>5 (5)</td>
</tr>
</tbody>
</table>

¹Pyelonephritis (2), RSV-infection (2), and hemophilia (1)

Table 8b. Characteristics regarding parent caring habits and infant’s environment.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>At 3 months</th>
<th>At 6 months</th>
<th>At 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant positional preference</td>
<td>12 (12)</td>
<td>6 (6)</td>
<td>N/A</td>
</tr>
<tr>
<td>Primarily sleeping supine</td>
<td>64 (65)</td>
<td>62 (64)</td>
<td>20 (22)</td>
</tr>
<tr>
<td>Time in carriers/bouncers/car seats, h/day</td>
<td>1.7 ± 1.1</td>
<td>1.4 ± 0.9</td>
<td>0.2 ± 0.4</td>
</tr>
<tr>
<td>Time supine on the floor, h/day</td>
<td>2.6 ± 1.4</td>
<td>1.0 ± 1.2</td>
<td>N/A</td>
</tr>
<tr>
<td>Time prone on the floor, h/day</td>
<td>0.6 ± 0.5</td>
<td>2.7 ± 2.2</td>
<td>N/A</td>
</tr>
<tr>
<td>Pacifier use, h/day</td>
<td>2.2 ± 2.9</td>
<td>1.8 ± 1.9</td>
<td>1.4 ± 1.6</td>
</tr>
</tbody>
</table>

Positional preference, supine time, and prone time were not assessed at 12 months.

In the multivariate logistic regression analysis, significant risk factors for DP at 6 months were positional preference at 3 months (aOR 5.67; 95% confidence interval 1.15–27.81) and fewer motor milestones reached by 6 months (aOR 2.35; 95% confidence interval 1.25–4.42). For DP at 12 months, the only statistically significant risk factor was positional preference at 3 months (aOR 22.15; 95%
confidence interval 3.31–148.17). Group allocation in the prevention study was included in both models, but it had no significant effect. The Nagelkerke $R^2$ values for the models varied between 0.39 and 0.44.

The LMM describe the effect of infant and environment-related factors on cranial asymmetry and shape after 3 months of age. Putative explanatory variables included in the LMM are shown in Table 9, and results from the LMM in Table 10.

**Table 9. Factors included in the initial linear mixed models for all outcome variables.**

<table>
<thead>
<tr>
<th>Putative explanatory variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time$^{1,2,3}$</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Gestational age</td>
</tr>
<tr>
<td>Maternal Age</td>
</tr>
<tr>
<td>Mode of delivery</td>
</tr>
<tr>
<td>Presentation at delivery</td>
</tr>
<tr>
<td>Weight$^4$</td>
</tr>
<tr>
<td>Length$^2,4$</td>
</tr>
<tr>
<td>Head circumference$^{3,4,5}$</td>
</tr>
<tr>
<td>Cephalic index$^5$</td>
</tr>
<tr>
<td>Pacifier use</td>
</tr>
<tr>
<td>Duration of full breastfeeding</td>
</tr>
<tr>
<td>Value of dependent variable at 3 months</td>
</tr>
<tr>
<td>Preventive counselling received at birth</td>
</tr>
<tr>
<td>Repositioning instructions received at 3 months</td>
</tr>
<tr>
<td>Positional preference at 3 months$^{6,7}$</td>
</tr>
<tr>
<td>Positional preference at 6 months$^{5,8}$</td>
</tr>
<tr>
<td>Imbalance in neck rotation$^{7,8}$</td>
</tr>
<tr>
<td>Daily time spent in carriers/bouncers/car seats$^9,10$</td>
</tr>
<tr>
<td>Daily time spent supine on the floor$^{10,11}$</td>
</tr>
<tr>
<td>Daily time spent prone on the floor$^{9,11}$</td>
</tr>
<tr>
<td>Primary sleeping position$^{12}$</td>
</tr>
<tr>
<td>Sleeping only supine until 3 months$^{12}$</td>
</tr>
<tr>
<td>GDMS Z-score</td>
</tr>
<tr>
<td>Acute otitis media (1 or more)</td>
</tr>
</tbody>
</table>

Same superscript numbers indicate a considered two-way interaction.
Table 10. The final linear mixed models, estimating the effect of different factors on three variables measuring cranial asymmetry (OCLR, PCAI, and wAS) after 3 months of age.

<table>
<thead>
<tr>
<th>Fixed effects</th>
<th>OCLR Coefficient estimate (95% CI)</th>
<th>PCAI Coefficient estimate (95% CI)</th>
<th>wAS Coefficient estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>39.73 (25.84–53.62)^3</td>
<td>44.53 (13.14–75.92)^2</td>
<td>-67.10 (-150.69–(-16.48))</td>
</tr>
<tr>
<td>Value of dependent variable at 3 months</td>
<td>0.60 (0.50–0.71)^3</td>
<td>0.59 (0.49–0.69)^3</td>
<td>0.35 (0.28–0.42)^3</td>
</tr>
<tr>
<td>Received preventive advice at birth</td>
<td>0.17 (-0.35–0.70)</td>
<td>0.11 (-1.45–1.68)</td>
<td>-2.65 (-8.87–3.56)</td>
</tr>
<tr>
<td>Time</td>
<td>-12.80 (-20.80–(-4.81))^2</td>
<td>1.29 (-0.80–3.39)</td>
<td>-3.09 (-10.00–3.81)</td>
</tr>
<tr>
<td>Head circumference</td>
<td>0.044 (-0.14–0.23)</td>
<td>-0.73 (-1.26–(-0.21))^2</td>
<td>0.34 (0.05–0.64)</td>
</tr>
<tr>
<td>Gestational age</td>
<td>-0.01 (-0.09–0.07)</td>
<td>0.34 (0.05–0.64)</td>
<td></td>
</tr>
<tr>
<td>Positional preference at 3 months</td>
<td>1.39 (0.43–2.36)^2</td>
<td>5.68 (-2.80–8.57)^2</td>
<td>14.60 (2.53–26.67)^3</td>
</tr>
<tr>
<td>Imbalance in neck rotation</td>
<td></td>
<td>2.42 (1.20–3.64)^3</td>
<td></td>
</tr>
<tr>
<td>Time spent in carriers/bouncers/car seats</td>
<td>-0.014 (-0.55–0.52)</td>
<td>-0.06 (-2.03–1.91)</td>
<td></td>
</tr>
<tr>
<td>Time spent prone on the floor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otitis media</td>
<td>0.40 (-0.15–0.96)</td>
<td>0.74 (-0.91–2.38)</td>
<td></td>
</tr>
<tr>
<td>Slept exclusively supine at 3 months</td>
<td>-0.15 (-0.68–0.37)</td>
<td>0.16 (-1.46–1.79)</td>
<td>-6.99 (-13.81–(-0.16))^1</td>
</tr>
<tr>
<td>Primary sleeping position:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td></td>
<td>-6.24 (-13.43–0.96)</td>
<td></td>
</tr>
<tr>
<td>Side</td>
<td></td>
<td>-4.59 (-11.52–2.33)</td>
<td></td>
</tr>
<tr>
<td>Prone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction term: Time x Head circumference</td>
<td>0.28 (0.11–0.45)^2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction term: Positional preference at 3 months x imbalance in neck rotation</td>
<td>2.53 (1.15–3.91)^3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^1p < 0.05, ^2p < 0.01, ^3p < 0.001. Fixed effects include measurements at 6 and 12 months, unless stated otherwise.
A significant association between positional preference and cervical imbalance was also observed. Infants with positional preference at 3 months were more likely to have torticollis at 3 (50% vs. 3%; p < 0.001) and 6 months (33% vs. 3%; p < 0.01). Similarly, infants with positional preference at 6 months had more torticollis at 3 (43% vs. 6%; p < 0.05) and 6 months (43% vs. 4%; p < 0.01). However, there was no difference in the mean imbalance of passive neck rotation at birth between infants with and without positional preference at 3 months. Furthermore, there was no correlation between cervical imbalance at birth and imbalance at 3 months or positional preference at 3 months. Positional preference at 3 months was associated with positional preference at 6 months (p < 0.001), and only two infants with positional preference at 6 months had not shown positional preference at 3 months. Cervical imbalance at 12 months showed no association or correlation whatsoever with previous imbalance or positional preference.

5.5 Accuracy of measurements used to quantify cranial asymmetry in DP (IV)

Out of the 407 3D craniofacial images assessed, 123 were of 3-month-olds, 117 were of 6-month-olds, 110 were of 12-month-olds, and 57 were of 36-month-olds. 84 (21%) of the images were rated as asymmetrical and 277 (68%) as symmetrical by both assessors. 46 (11%) heads received discrepant ratings. Out of the heads rated as asymmetrical by both assessors, one head was rated as type IV, 10 were rated as type III, 29 as type II, and 44 as type I deformation on the Argenta scale. Out of the heads with discrepant ratings, one was rated as type III, nine were rated as type II, and 36 as type I by the other assessor. The assessors achieved decent intra-rater reliability for the visual classification (κ = 0.680–0.714), and the inter-rater reliability was also good (κ = 0.677). Means for the measured variables were nearly equal across all age groups in the no deformation group. Means in other groups showed more fluctuation, especially in the groups with Argenta class > 1. Descriptive statistics for the measured variables appear in Table 11.
Table 11. Descriptive statistics (means ± SDs) for the outcome variables in study IV grouped by subject age and Argenta score.

<table>
<thead>
<tr>
<th>Group</th>
<th>OCLR, %</th>
<th>DD, mm</th>
<th>PCAI, %</th>
<th>wAS</th>
<th>Cl, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>102.6 ± 2.3</td>
<td>3.6 ± 3.0</td>
<td>7.9 ± 7.1</td>
<td>22.3 ± 32.5</td>
<td>77.5 ± 4.2</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>103.0 ± 2.7</td>
<td>3.9 ± 3.4</td>
<td>9.0 ± 8.3</td>
<td>25.9 ± 28.3</td>
<td>76.9 ± 4.3</td>
</tr>
<tr>
<td>6 months</td>
<td>102.5 ± 2.7</td>
<td>3.5 ± 3.1</td>
<td>8.0 ± 7.0</td>
<td>20.3 ± 27.2</td>
<td>78.3 ± 4.4</td>
</tr>
<tr>
<td>12 months</td>
<td>102.3 ± 1.9</td>
<td>3.4 ± 2.8</td>
<td>7.3 ± 6.4</td>
<td>19.5 ± 24.8</td>
<td>77.5 ± 4.1</td>
</tr>
<tr>
<td>3 years</td>
<td>102.2 ± 1.5</td>
<td>3.5 ± 2.4</td>
<td>6.5 ± 5.6</td>
<td>24.0 ± 26.1</td>
<td>77.0 ± 3.3</td>
</tr>
<tr>
<td>Argenta score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No deformation</td>
<td>101.6 ± 1.2</td>
<td>2.3 ± 1.7</td>
<td>5.1 ± 3.8</td>
<td>11.2 ± 11.2</td>
<td>77.0 ± 3.6</td>
</tr>
<tr>
<td>Any deformation</td>
<td>105.2 ± 2.3</td>
<td>7.1 ± 3.0</td>
<td>15.6 ± 8.2</td>
<td>52.3 ± 48.4</td>
<td>78.9 ± 5.1</td>
</tr>
<tr>
<td>Type I</td>
<td>104.2 ± 1.8</td>
<td>5.8 ± 2.5</td>
<td>12.8 ± 6.6</td>
<td>37.2 ± 27.1</td>
<td>77.9 ± 5.3</td>
</tr>
<tr>
<td>Type II</td>
<td>105.9 ± 1.8</td>
<td>8.1 ± 2.4</td>
<td>17.6 ± 6.6</td>
<td>60.4 ± 42.1</td>
<td>80.8 ± 4.8</td>
</tr>
<tr>
<td>Type III</td>
<td>108.1 ± 1.6</td>
<td>10.6 ± 1.9</td>
<td>23.7 ± 10.2</td>
<td>88.6 ± 7.9</td>
<td>79.4 ± 3.2</td>
</tr>
<tr>
<td>Type IV</td>
<td>113.6</td>
<td>16.6</td>
<td>44.9</td>
<td>120</td>
<td>80</td>
</tr>
</tbody>
</table>

To determine and compare the optimal thresholds for differentiating children with DP (Argenta class ≥ 1) from children without DP, ROC curves for the outcome variables were first created for each age group separately. The differences between the AUC values of the ROC curves for different age groups were not statistically significant. Moreover, the Youden's indices and visual interpretation of the curves showed that the optimal thresholds for OCLR, PCAI, and wAS were similar in all age groups, whereas the threshold for DD increased monotonically with age, as seen in Table 12. Hence, the final ROC curves for OCLR, PCAI, and wAS were created with all of the images pooled together, and further analysis of DD was omitted. In Fig. 11–13 separate ROC curves are provided for Argenta classes 1–3, both excluding and including images with discrepant expert ratings. The cut-off values for OCLR, PCAI, and wAS producing the most accurate classification and their respective Youden's J values are shown in Table 13.
Table 12. Cut-off values for deformational plagiocephaly (Argenta score ≥ 1) and their respective (Youden’s J values) in different age-groups.

<table>
<thead>
<tr>
<th>Age</th>
<th>OCLR, %</th>
<th>DD, mm</th>
<th>PCAI, %</th>
<th>wAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>103,5 (0,71)</td>
<td>4,3 (0,71)</td>
<td>10,5 (0,66)</td>
<td>24,1 (0,76)</td>
</tr>
<tr>
<td>6 months</td>
<td>103,4 (0,75)</td>
<td>4,5 (0,75)</td>
<td>11,1 (0,67)</td>
<td>28,5 (0,67)</td>
</tr>
<tr>
<td>12 months</td>
<td>103,6 (0,85)</td>
<td>5,1 (0,84)</td>
<td>10,4 (0,82)</td>
<td>28,0 (0,79)</td>
</tr>
<tr>
<td>3 years</td>
<td>103,7 (0,99)</td>
<td>6,2 (0,99)</td>
<td>10,8 (0,87)</td>
<td>30,7 (0,94)</td>
</tr>
</tbody>
</table>

Fig. 11. Youden’s J are marked with a black dot, and the corresponding sensitivity (sens.), specificity (spec.), and AUC values for each curve are as follows: (a) OCLR: sens. 90%, spec. 92%, AUC 0.97; PCAI: sens. 90%, spec. 90%, AUC 0.96; wAS: sens. 88%, spec. 90%, AUC 0.93; (b) OCLR: sens. 79%, spec. 91%, AUC 0.92; PCAI: sens. 76%, spec. 90%, AUC 0.89; wAS: sens. 78%, spec. 90%, AUC 0.89.
Fig. 12. (c) OCLR: sens. 93%, spec. 95%, AUC 0.97; PCAI: sens. 90%, spec. 93%, AUC 0.96; wAS: sens. 85%, spec. 93%, AUC 0.94; (d) OCLR: sens. 89%, spec. 89%, AUC 0.95; PCAI: sens. 87%, spec. 87%, AUC 0.92; wAS: sens. 82%, spec. 91%, AUC 0.92.

Fig. 13. (e) OCLR: sens. 100%, spec. 93%, AUC 0.98; PCAI: sens. 91%, spec. 92%, AUC 0.96; wAS: sens. 100%, spec. 95%, AUC 0.98; (f) OCLR: sens. 100%, spec. 91%, AUC 0.98; PCAI: sens. 91%, spec. 88%, AUC 0.94; wAS: sens. 100%, spec. 94%, AUC 0.97.
Table 13. Cut-off values for deformational plagiocephaly and respective (Youden's J values) from the final ROC curves.

<table>
<thead>
<tr>
<th>Argenta score</th>
<th>OCLR, %</th>
<th>PCAI, %</th>
<th>wAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Images with discrepant ratings excluded</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1</td>
<td>103.5 (0.82)</td>
<td>10.5 (0.80)</td>
<td>24.5 (0.78)</td>
</tr>
<tr>
<td>≥ 2</td>
<td>104.5 (0.87)</td>
<td>13.0 (0.82)</td>
<td>38.9 (0.79)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>105.7 (0.93)</td>
<td>15.2 (0.83)</td>
<td>58.7 (0.96)</td>
</tr>
<tr>
<td>Images with discrepant ratings included</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1</td>
<td>103.5 (0.71)</td>
<td>10.5 (0.65)</td>
<td>24.5 (0.68)</td>
</tr>
<tr>
<td>≥ 2</td>
<td>104.5 (0.78)</td>
<td>13.0 (0.73)</td>
<td>38.9 (0.73)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>105.7 (0.91)</td>
<td>15.2 (0.78)</td>
<td>58.7 (0.95)</td>
</tr>
</tbody>
</table>

OCLR and DD showed a virtually perfect bivariate correlation (Pearson’s r = 0.99), as they are calculated from the same transcranial diagonals. The correlation was slightly lower between OCLR and PCAI (r = 0.89) and considerably lower between wAS and OCLR (r = 0.69). Fig. 14 shows that, although neither OCLR nor wAS produced perfect classification, they may complement each other, as only three heads (4%) with consistent expert ratings simultaneously fell under the proposed cut-off values for both outcome variables.
Fig. 14. Argenta scores for the participants, with wAS plotted against OCLR. Discrepant expert ratings not shown. The colored lines represent the candidate cut-off values from the ROC curves for wAS and OCLR: black for Argenta score ≥ 1, red for ≥ 2, and blue for ≥ 3.

There was a significant difference between the mean CI values (79.5% vs. 76.9%, p < 0.001) of the heads rated as symmetrical and asymmetrical. It is noteworthy that with all outcome variables, subjects receiving false negative results had a significantly higher mean CI than subjects receiving false positive results when using the cut-off values reported in Table 12. The mean CI values were 82.3% vs. 75.7% (p < 0.01) using OCLR 103.5%; 80.4% vs. 76.4% (p < 0.05) using PCAI 10.5%; and 79.4% vs. 76.2% (p < 0.05) using wAS 24.5.
6 Discussion

6.1 The course of cranial asymmetry over the first year of life (I, III)

The incidence of DP in Finnish infants during the first year of life was found to be in the range of the rates reported in literature (6, 47). 37% of the infants completing the 12-month follow-up met the criteria for DP at some point. Cranial asymmetry seen at birth was transient, as DP at birth was not associated with subsequent DP; only 29% of the subjects with DP at birth had DP at 3 months, a proportion nearly identical to the total point prevalence of 28% at that point. It can therefore be concluded that in most cases, DP develops between birth and 3 months of age. From 3 to 12 months the prevalence of DP steadily decreased, and only two subjects with DP first diagnosed after 3 months of age, both very mild cases, saw the condition persist to 12 months of age, indicating a favorable natural course for DP. Furthermore, although the point prevalence of DP was still as high as 19% at 12 months, the asymmetry was significantly milder than at 6 months in terms of the outcome measurements. Nevertheless, there was still a considerable amount of absolute anthropometric cranial asymmetry present in the 12-month-old infants. All in all, the point prevalence of DP behaved similarly in this study compared to earlier studies conducted in other populations (47, 48, 145).

The mean CI values for Finnish infants were lower throughout the first year of life than in recent reports from Australia and the Netherlands (47, 48); they were closer to the mean CIs of American infants published in 1977 before the supine sleeping position was the norm (199). This is likely due to ethnic traits, although methodological differences may account for some of the variation. Both CI and FS values increased from 3 to 6 months, and decreased again from 6 to 12 months, while there was also a fair correlation between CI and FS; another likely indication of the association between the supine position and cranial shape.

With the exception of EO, mean values of all asymmetry-related measurements obtained from the 3D images decreased throughout the observation period, and aside from the value of the outcome variable at 3 months, time was the strongest factor influencing the course of cranial asymmetry in the LMMs, too. Contrary to a recently published case-control study reporting no decrease in the DD scores of untreated infants followed from 7 months to 5.9 years of age, the present results indicate a significant decrease in the DD of infants with DP from 3 to 6 and from 6 to 12 months as well (175). However, most of the correction in asymmetry-related
variables occurred between 3 and 6 months of life, after which the rate of correction was considerably slower. The finding also held true in relation to the rate of head growth, thus implying a role on the maturation of the cranial sutures and bones (26). Hence, the older the infant with DP is, the smaller appears to be the likelihood for DP to resolve spontaneously. The fact that DP was less likely to persist to 12 months in infants born at a lower gestational age provides additional support to the hypothesis, as their skull development is behind their chronological age, denoting a higher remaining potential for spontaneous resolution of asymmetry. Based on the present data and previous literature, the window for spontaneous improvement of cranial asymmetry likely extends closer to two years of age, but no further (145). The aforementioned findings also fit with the common observation of the effectiveness of DP treatment strongly depending on the age at which it is started (134, 183).

6.2 Prevention of DP (II)

The RCT (II) provides evidence that promoting spontaneous, unhindered physical movement in infants through instructions provided in the maternity ward reduces the prevalence and severity of DP in early infancy. The results suggest that the instructions may also lead to an improvement in the neck ROM. To our knowledge, this is the first study to evaluate the effectiveness of a preventive strategy aimed to reduce the incidence of DP in an RCT. While the study groups showed no differences at birth, analysis of the 2D images revealed a significant difference in both the prevalence of DP at 3 months and the change in OCLR from birth to 3 months. Analysis of the 3D images revealed a significant difference in the severity of cranial asymmetry at 3 months as well as in DD, whereas the difference in the prevalence of DP as a dichotomous variable was statistically borderline insignificant. Because the measurement plane for the transcranial diagonals is bound to differ a little between the 3D and 2D methods, a slight difference between the two OCLR values is inevitable, which is the likely cause behind the discrepancy.

The lack of exclusively prone-sleeping infants in the present study precludes comparison between the effect of supine and prone sleeping positions, but interestingly, sleeping exclusively in the supine position did not increase the risk for DP in this study. In fact, despite the fact that CI increased significantly more in infants who only slept supine, they simultaneously developed less cranial asymmetry. However, univariate analysis showed that control group infants who spent more time in the supine position were at a greater risk for DP at follow-up,
as were those with slower motor development. This suggests that the preventive program reduces the risk for cranial deformation especially in these ‘at risk’ subgroups. Moreover, it leads one to contemplate whether an environment that lacks stimuli and is passivating de facto is the cause for both delayed motor development and DP, although no difference in motor development was found between the study groups in the present trial.

All of the study outcomes thus far adhere to the findings of a previous case-control study on preventing DP by Cavalier et al. (194). However, unlike their study, there was no significant difference in time spent freely on the floor and time spent immobilized in carriers, bouncers, or car seats between the groups in the present study. Furthermore, infants in the present study spent more time freely on the floor and less time immobilized in both groups compared to the previously mentioned study. This difference may stem from differences in caring practices between different countries, while the public child healthcare system in Finland includes monthly visits, starting at birth, where infants presenting with slow or asymmetrical motor development can be referred early to physiotherapy. These factors may have diminished the differences between the groups in the present study.

Based on existing data, it is impossible to tell whether the infants not benefiting from the preventive program have a greater risk for DP persisting or worsening, or whether the lack of benefit was due to infant-related factors or to parental compliance issues. Then again, the difference between the study groups was found to decrease over time, as seen in Fig. 10; this may partly stem from the fact that, due to ethical considerations, advice on repositioning therapy was provided at and after 3 months of age if necessary, regardless of original group allocation.

Nevertheless, the results at hand indicate that the prevalence of DP at 3 months of age can effectively be reduced by providing the parents of newborns with information on positioning, handling, and environmental measures. We feel that the most important aspects of the preventive program were informing the parents about the importance of floor time and prone time; during the study it became increasingly evident that many parents had interpreted the guidelines for supine sleeping to prevent SIDS as “never keep the infant in the prone position to prevent SIDS.” While DP itself may cause major anxiety in the parents—and sometimes in the child if the deformation persists—it has also been associated with a higher incidence of facial and mandibular asymmetry in childhood, and it may theoretically increase the risk for subsequent occlusal defects (161, 162). Considering the possible sequelae, and the fact that some experts justify even surgical intervention to correct the severely deformed cranium (7, 200), a primary
A preventive approach is called for. In the light of these facts, routinely providing such education in, for example, antenatal clinics, maternity wards, and child healthcare centers would benefit the infants in a cost-effective manner. Infants undergoing splint or harness treatment for developmental dysplasia of the hip deserve to be mentioned separately as a high-risk group, and providing advice to the parents on prevention of DP at the initiation of treatment would be advisable. Finally, to determine whether the beneficial effect of the preventive measures extends to later childhood requires additional research; hypothetically, preventing DP from developing altogether might decrease the burden of associated facial asymmetry and possible subsequent occlusal defects (161).

6.3 Factors influencing the course of cranial asymmetry (I–III)

6.3.1 Risk factors for DP developing or persisting

For DP at birth, gestational diabetes mellitus and vacuum assisted delivery were identified as significant, independent risk factors. In literature, only male gender, first-born rank, and brachycephaly have previously been associated with an increased risk of DP at birth (48). Additionally, multiple pregnancy, assisted delivery, prolonged labor, and unusual birth position have been associated with “localized cranial flattening” and “other anomalous head shapes” in newborns (49). Both birth trauma and forceps delivery have been associated with “moderate vertex asymmetry” at birth (57), but variability in the diagnostic criteria precludes direct comparison. Although the risk of DP at birth in males, firstborns, or brachycephalic infants was not elevated in the present study, the results are not necessarily contradictory to those of van Vlimmeren et al. (48). In this study, as many boys as girls had DP at birth, but there also was no difference in the birth weight between boys and girls, and it is known that intrauterine constraint—a potential risk factor for DP—is associated with fetal size (1). All plagiocephalic subjects born to mothers with gestational diabetes were girls, which is another potential confounding factor. Furthermore, past studies have not included gestational diabetes as a factor in their models at all (57, 60). On the other hand, the fact that DP seen at birth appears to resolve quickly in most cases reduces the clinical significance of these findings.

A correlation between CI and neck ROM in all directions at birth was observed in the present study. This could be explained by intrauterine restriction of head movement, which is also thought to be the leading cause behind CMT (41, 65); an
association between torticollis at birth and the fetus being “stuck” in the same position for more than 6 weeks before delivery has already been described (57), suggesting that prolonged immobilization in utero may result in sternocleidomastoid imbalance or even CMT. Similarly, both a reduced neck ROM and a more brachycephalic or asymmetrical head shape could develop as a result of a static head position, such as when the fetus engages in the pelvis early or is in the breech position. As newborns with a smaller neck ROM have less variation in their head position, the reduced neck ROM in brachycephalic infants could be one cause behind the high co-occurrence of DP and brachycephaly.

Indeed, infants with DP at the 3-month visit did have a significantly higher CI at birth, but no further association between DP or impaired neck ROM at birth and DP or impaired neck ROM at 3 months could be found. It is therefore possible that the wider head shape itself acts as a factor predisposing to DP, possibly by leading to a more midline-oriented head position, which again increases the total amount of pressure the occiput is exposed to in the supine position. However, additional research is needed to clarify the nature and significance of this association. Another factor found to be associated with an increased likelihood of DP at 3 months was preterm birth, which was statistically significant in both groups of the RCT, coinciding with past reports of a higher incidence of cranial deformations in preterm infants (37, 51). Other factors associated with DP at 3 months were sleeping exclusively supine and slower motor development, both being statistically significant only in the control group, which, as discussed earlier, likely stems from the preventive program reducing the risk of DP in these subgroups. Due to the study setting, no further analysis of risk factors for DP at 3 months was performed in (II).

Risk factors for DP at 6 and 12 months were found to be similar to previously described risk factors for DP between 7 weeks and 4 months of age (see Table 2) (47, 48, 64). Positional preference, imbalance in neck ROM, slower motor development and supine positioning were recurring themes in the univariate analyses, but in the multivariate analyses only positional preference at 3 months increased the likelihood of having DP at both 6 and 12 months, while slower motor development increased the likelihood of having DP at 6 months. Correspondingly, positional preference at 3 months was strongly associated with failure to recover from DP by 12 months of age. LMM analyses indicated that positional preference at 3 months was the strongest predictor of an unfavorable course of cranial asymmetry between 3 and 12 months of age, too, as it influenced the course of all asymmetry-related variables in the models (OCLR, PCAI, and wAS).
6.3.2 DP, impaired neck ROM and positional preference

The incidence of DP and torticollis were found to be 7.7% and 3.9% at birth, with no difference at all in the cervical motion between newborns with and without DP. Previous studies have reported incidence rates of 6.1–13% for cranial asymmetry (47-49) and 0.3–16% for torticollis at birth (41, 65); much of this variability is thought to result from the lack of uniform definitions for these conditions (201). The lack of association between DP and torticollis at birth is in accordance with previous studies, although they have either relied on visual assessment in defining torticollis or have not reported their criteria (47-49).

Previously, some researchers have held congenital cervical imbalance as the cause behind the majority of DP cases; a hypothesis justified by the facts that past studies have described torticollis in up to 97% of infants with DP, and that torticollis seen in infants with DP seems to resolve over time, whereas the skull deformation is more likely to persist (34). However, the low incidence rates of congenital cervical imbalance and the high incidence rates of DP in later infancy show discrepancy (6, 60, 65), whereas past longitudinal studies have reported different results on the association between cervical imbalance at birth and DP in later infancy: In a cohort study of 200 infants, unilaterally restricted passive rotation during the first week of life increased the risk of DP at both 6 weeks and 4 months of age (47), while a cohort study of 380 infants found no association between neck ROM within 48 hours from birth and DP at 7 weeks of age (48). In the present study, cervical imbalance at birth was not associated with later imbalance or cranial deformation, but infants with DP at 3 months of age also more frequently had positional preference and torticollis at that point. These findings support the hypothesis of most cases of torticollis presenting with DP not being exclusively congenital, but rather developing to their full extent in early infancy (4). Although not a common occurrence, CMT does strongly predispose to DP, and infants presenting with a sternocleidomastoid tumor, persistent head tilt, or a strikingly limited passive neck ROM should be referred to physiotherapy as early as possible to minimize the risk of both DP developing and CMT persisting (73).

After 3 months, there was a fair amount of interaction between positional preference and impaired neck ROM, and based on the data at hand, drawing conclusions on causality is troublesome. There was a strong association between neck rotational imbalance and positional preference at and after 3 months, but no association between neck ROM at birth and subsequent positional preference. It is therefore likely that the window of opportunity to investigate the development of...
and causality between torticollis and positional preference was missed in this study. It is possible that intensive follow-up during the first weeks of life might reveal one factor presenting first and leading to the other, but whether further research on the subject is necessary in terms of clinical relevance can be discussed, for we see both conditions primarily as different manifestations of the same underlying factors, and there is much overlap between the conditions.

A limited active or passive ROM to one side inevitably leads to the infant more often turning the head to the opposite side, and for instance Murgia et al. found all studied infants with a restricted neck rotation to exhibit a positional preference (202). However, not all infants with a positional preference have presented cervical imbalance in previous studies (63, 167). Then again, a preferential head position to one side might weaken the contralateral cervical muscles, possibly being the cause of a restricted active neck ROM in some. It has also been postulated that asymmetrical occipital flattening itself could induce a positional preference with the flat area against the underlying surface, predisposing the infant to both DP and cervical imbalance (49). Although neither this study nor van Vlimmeren et al. found DP (defined as OCLR ≥ 104.0%) at birth to increase the risk of DP in later infancy, it is possible that more subtle localized occipital flattening sometimes acts as a precursor for positional preference, DP, and cervical imbalance (48). On the other hand, due to the lack of longitudinal data on the development of positional preference, it is too early to postulate that positional preference is always of infant-related origin; it could also be the result of parents’ one-sided caring habits and frequently keeping the infant immobilized in the same position. In fact, a recent study described a strong bias for mothers to hold infants on the left arm when the infants were under 12 weeks of age, and additional findings of the study supported maternal monitoring of infant state, not infant’s preferred head position, as the explanation for the lateralization (203). Furthermore, previous literature indicates an association between positional preference and environmental factors, such as always bottle-feeding from the same side (48) and sleep position (58). Considering these facts, along with the present results showing a reduction in the prevalence of DP and improvement in the neck ROM in intervention group infants (II), we hypothesize that the postnatal environment often plays an essential role in the development of infant positional preference as well. Nevertheless, positional preference, cervical imbalance, and asymmetrical occipital flattening appear to influence and worsen each other in a synergistic manner—a process that should be halted as early as possible to minimize subsequent problems.
6.4 Quantifying cranial asymmetry with 3D stereophotogrammetry

During recent years, 3D stereophotogrammetry has gained ground in the field of craniofacial imaging, as it enables the capturing and storing of surface data for the whole cranium quickly and accurately. Furthermore, it allows for the measurement of a vast amount of different point-to-point variables, surface variables, and volumetric variables that can be used to quantify cranial asymmetry. Although many of such variables are commonly used in clinical practice and some experts base their decisions over treatment on measurement values (113, 118, 132, 144), studies comparing the accuracy of different measurement variables are scarce and validated cut-off values for DP are lacking. Hence, the diagnostic accuracy of four stereophotogrammetry-based indices was investigated and compared in this work. Four different variables were chosen to be investigated, each of them already used in clinical practice and reportedly correlating well with the clinical evaluation of asymmetry (113, 118, 132, 144). To our knowledge, this is the first study to investigate the diagnostic accuracy of asymmetry-related variables in an unselected population and to investigate the impact of age on the threshold of cranial asymmetry required for making the clinical diagnosis of DP.

The results at hand are in favor of the ratio between the transcranial diagonals, the OCLR; it consistently produced the most accurate classification, as indicated by the Youden's J and AUC values. The only subgroups where wAS performed better were the 3-month-old group and the Argenta class ≥ 3 group, whereas PCAI did not outperform both OCLR and wAS in any subgroup. Further remarks favoring OCLR are the simplicity of the measurement and the consistent cut-off values that were not affected by age, as opposed to DD.

For OCLR, the cut-off values with the highest sensitivity and specificity were in the range of those used in previous literature (48, 113, 114). Overall, the best discrimination (affected from unaffected) was provided by OCLR ≥ 103.5%, and the results suggest that usage of the same cut-offs for OCLR, PCAI, and wAS could be justified regardless of subject age. On the other hand, the cut-offs suggested by the Youden's J indices cannot be directly assumed to be the optimal cut-offs for clinical use. A closer inspection of the ROC curves shows that, with discrepant expert ratings excluded, using 103.5% as the cut-off for OCLR leads to a relatively high false positive rate of 8% (92% specificity), whereas setting the cut-off at 104.0% results in almost equally good discrimination but also reduces the false positive rate to 3% (97% specificity), simultaneously bringing the sensitivity down to 83% from...
90%. As especially mild DP is regarded as a cosmetic (i.e., highly subjective) problem, the tolerance for false positive results should be low. Hence, we propose OCLR ≥ 104.0% as the optimal cut-off for DP in clinical use, which is also in accordance with the cut-off described by van Vlimmeren et al. (48) used in papers (I–III). For PCAI and wAS, increasing the specificity steeply decreases the sensitivity, so the optimal cut-offs are the ones shown in Table 13. Because wAS shows a relatively low bivariate correlation with OCLR and PCAI, but still performs almost as well—and in a few subgroups, better—than OCLR, it likely captures a different aspect of the deformation than OCLR and PCAI. Therefore, using both OCLR and wAS may provide more information compared to using only OCLR, and calculating both indices could be helpful, especially in monitoring cranial shape over time. However, based on the present data, it cannot be concluded that wAS is more accurate in identifying severe forms of DP (with frontal asymmetry), as the number of subjects with Argenta class ≥ 3 was low in the present study.

The suggested cut-off for DD increased with age, which is unsurprising, because as an absolute measurement DD is not relative to head size. Therefore, DD is a relatively poor instrument for diagnosing and monitoring DP, as there would not only be a need for size-specific cut-off values, but interpreting such unadjusted indices can also be confusing, especially for non-professionals. For instance, having a similar OCLR value of 105.0% at both 3 and 36 months would indicate no improvement in perceived asymmetry, but, due to head growth, a similar DD value of 5 mm at both 3 and 36 months would indicate significant improvement in perceived asymmetry, and in the light of the present results, recovery from DP. In fact, Wilbrand et al. concluded that cranial deformation does not improve spontaneously due to an observed lack of improvement in DD values of untreated infants (175). Based on the results at hand, infant age (i.e., head size) does not impact the threshold of relative asymmetry (i.e., geometric shape of the head) required for deformation to be visually perceived by professionals. Therefore, using unadjusted measurement values as the sole definition for DP or as the primary measurement in monitoring cranial asymmetry is discouraged. Furthermore, because OCLR and DD show virtually perfect bivariate correlation, there is no additional utility in calculating and monitoring both OCLR and DD opposed to calculating only OCLR.

Another interesting finding in the present study was that the CI values of the heads receiving false negative results were significantly higher than those receiving false positive results regarding all outcome measurements. This suggests that the
overall proportions of the cranium impact the visual perception of asymmetry as well, and it is possible that the oft-reported finding of infants with cranial asymmetry having higher CI values partly stems from different cranial proportions altering the subjective perception of cranial shape (47, 77, 97). Correspondingly, the perception of what is considered a normal cranial shape admittedly varies between cultures, as there is considerable geographical variation in the average cranial proportions (CI) (47, 134, 199), but whether the perception of asymmetry differs among cultures is not known.

It is noteworthy that the OCLR measurement performed much better in the present study compared to the sole previous paper available on the accuracy of OCLR. The previous paper reported an AUC of only 0.79 for OCLR, even though subjects with discrepant expert ratings were excluded (11). The difference between the results likely stems from two things impairing their OCLR scores. First, they measured the OCLR manually from a 2D snapshot of the 3D image, and at a 45° angle to the midline as opposed to the commonly used 40° angle. Second, they did not automatically adjust the image position for the measurement of OCLR, and even if the 2D snapshots were captured automatically from a standardized angle, the orientation of the images would subsequently have been lost as they used no craniofacial landmarks. Hence, the importance of consistent and reliable image positioning when processing and analyzing any kind of 3D craniofacial images deserves to be stressed.

The inconsistency of visual assessment raises the question of whether measurable indices, such as the OCLR, should be used as the primary determinant of cranial asymmetry and DP. On the other hand, DP is primarily regarded as a cosmetic condition, so it is necessary for the head to look asymmetrical to be considered abnormal; an argument sometimes used against the necessity of measurable indices (125). Then again, only relying on clinical assessment may result in a relatively high number of false positive diagnoses, which again may cause unfounded interventions resulting in both unnecessary concern and costs for the family as well as possible discomfort for the infant (174). Despite the specificity of the measurements investigated in the study not being perfect, using these measurements in a clinical setting would not necessarily produce many false positive results, for the initial need to assess cranial shape usually stems from either parental or expert concern—in other words, visual assessment—of the child's head form. Hence, the function of the measurements would mainly be to either confirm or refute the “working diagnosis”. Considering their performance in the present study, using such objective measurements in clinical practice would likely improve
diagnostic accuracy. Respectively, if active treatment for DP is chosen based on a cosmetic indication, the target values for asymmetry-related measurements should not be set below the cut-off values proposed here.

6.5 Prospects of DP treatment in the light of the present study

Positional preference at 3 months was found to predict an unfavorable course of cranial asymmetry. In an RCT by van Vlimmeren et al., 7-week-old infants with a positional preference allocated to physiotherapy developed significantly less DP during the first year of life (167); the present results lead one to speculate that physiotherapy for positional preference in older infants might be useful in alleviating subsequent cranial deformation, too.

In this study, infants with DP at and after 3 months of age showed statistically significant spontaneous improvement in all asymmetry-related measurements throughout the observation period. Therefore, it is not well-founded to proclaim any treatment for DP effective based solely on the observation of statistically significant improvement in absolute or perceived asymmetry over a treatment period. However, previous Class IV studies (109, 134, 135, 146, 185-189) on helmet therapy, as well as some studies on repositioning therapy (169, 170) listed in the literature review conclude that the investigated treatment is effective in correcting DP on such grounds; in the light of the present results, the validity of these conclusions is questionable.

A recent study showed that parents of 5-month-olds opting for helmet therapy were more likely to be unsatisfied with their child’s head shape and concerned with DP persisting if not treated with helmet therapy (204). Evidence on the natural course of DP has been scarce; thus the finding of the natural course of cranial asymmetry being favorable in most cases is significant also considering parental decision-making, and parents should be adequately informed of both the natural course and current level of evidence regarding the effectiveness of the available treatment options.

With respect to the currently available studies on helmet therapy, drawing conclusions on its effectiveness is troublesome. The RCT by van Wijk et al. described no effect compared to the natural course (174). However, subsequent studies have deemed the study flawed, citing the quality of the helmets used, as the authors had reported a high incidence of adverse events, such as problems with the helmets fitting properly (175). Nevertheless, in addition to the previously mentioned study, three case-control studies have found no difference between
helmet therapy and repositioning therapy (121, 178, 182). On the other hand, two case-control studies and one prospective cohort study comparing helmet therapy to repositioning (8, 137, 177), as well as one case-control study, one prospective cohort study, and one cohort with historical controls comparing helmet therapy to the natural course (175, 176, 179) have described statistically significant improvement in cranial asymmetry with helmet therapy. As indicated in Table 3, there is variability in how the authors of papers recommending the use of helmet therapy have interpreted their results, and what has been considered a clinically significant difference or satisfactory improvement. In general, results from studies with higher quality, a larger sample size, and a longer follow-up period speak against the effectiveness of helmet therapy. Nevertheless, a recently published review still advocates the use of helmet therapy to treat DP (36); based on the current sum of evidence, it is hard to draw this conclusion. On the other hand, the present work contemplates the evidence from a pediatrician’s point of view: Given that craniofacial surgeons usually treat the most severe cases of DP, the value of a conservative treatment option understandably appears very high, as they may be considering surgical intervention as an alternative. Then again, with respect to the associated risks of operative treatment and literature indicating no risk of increased intracranial pressure, restricted brain growth or neurological defects in DP, it is difficult to consider such a massive operation justified to treat an essentially cosmetic condition in any case (97, 152).

Although the natural course of cranial asymmetry was generally favorable in the present study, there was still a considerable amount of absolute anthropometric asymmetry present at the end of the 12-month follow-up, which appears clinically relevant. Furthermore, the potential for spontaneous correction of cranial asymmetry decreased with infant age, also in relation to remaining head growth potential. Considering the aforementioned findings as well as the persisting uncertainty on the effectiveness of the available treatment options, if active conservative treatment is chosen, commencing it as early as possible is likely to increase the chances of achieving a satisfactory outcome.

6.6 Strengths and weaknesses of the study

The strengths of this study include the randomly selected population-based cohort, the RCT setting (II), and the use of computer-based 2D and 3D quantification methods. The prospective setting allowed us to monitor the course of skull
deformation in relation to infant- and environment-related factors throughout the time period when most changes in cranial asymmetry occur.

Although the recruited population was hospital born, selection bias due to the place of delivery is unlikely, as delivering outside the hospital is very uncommon in Finland; in 2015, only 0.05% of deliveries took place outside hospitals (205). However, excluding infants born at less than 35 gestational weeks, twins, infants with obvious dysmorphic features, and infants with cleft lip and/or palate precludes generalization of the results to these subgroups.

The relatively small sample size is a limitation, particularly concerning the follow-up after 3 months; a larger sample could have revealed additional factors impacting the course of skull deformation, while the numbers are also far too small to calculate percentile curves. A larger sample would as well have been required to investigate the impact of the preventive program on the incidence of torticollis, a less prevalent condition. Indeed, the sample size was calculated prospectively with the RCT (II) in mind, based on the results of previous studies on the prevalence of DP and the efficacy of a similar intervention.

Measuring therapy compliance by relying on parent report is subject to recall bias, which is another limitation. There may also have been differences in the reporting accuracy between the study groups, as the parents of infants in the intervention group likely were more attentive regarding their infant’s behavior, positioning, and environment.

The follow-up period of only 3 months is a further limitation concerning the RCT, but due to the risk of DP and torticollis persisting and worsening increasing with time, it was considered unethical not to provide interventional instructions to parents of infants known to have one or both of these conditions. The preventive guidance might also have interfered with the course of cranial asymmetry after 3 months of age, but the LMM analyses indicated that the original group allocation had no impact on the course of the outcome measurements after 3 months. Furthermore, because all participating families were aware that skull deformation was being investigated, it is possible that they also sought preventive advice and treatment elsewhere, and the families may have also received repositioning instructions from their primary care provider at their routine check-ups. The cohort itself was homogenous in terms of these factors, mitigating their effect on the analyses, but due to both increased awareness and the preventive program, there likely is less cranial asymmetry in the study population compared to the general population.
Photogrammetric methods were chosen to be used in quantifying cranial shape, as they require little human input and generate data that can be stored and reassessed later, as needed. Using two different methods for measuring OCLR could be considered disruptive to the interpretation of the results of (II), but it was necessary to use a standard 2D photography-based method on newborns, as they are unable to support their heads and thus cannot be placed in the 3D scanner. In fact, achieving an acceptable head position occasionally proved difficult even with the 3-month-olds. Nevertheless, image quality was not affected by infant movement, as the recording time of 1.5 milliseconds is too short for movement to cause any artifacts (10, 132). Furthermore, the potential sources for inconsistency with 3D stereophotogrammetry are restricted to the subjective identification of craniofacial landmarks, which, according to past studies, has a negligibly small effect on the repeatability and reproducibility of outcome measurements (131, 132). Using 3D imaging also enabled us to calculate several different outcome variables: while the point-to-point variables provide information about the cranium as seen from above, the volumetric variables help the reader to perceive the extent of asymmetry in the whole posterior region, while the surface variables convey information about the contours, asymmetry, and flat areas apparent when observing the cranium from the posterior point of view.

Although previously described outcome variables were used, the current method for positioning of the images was slightly different from those of other studies conducted with a five-pod 3DMD camera system (132, 133). First, the mirror face technique was used in the aligning process to minimize the effect of facial asymmetry (131), which is relevant considering the higher incidence of facial asymmetry in infants with DP (96). Second, midendocanthion was used in defining the reference planes, as the endocanthion landmarks have demonstrated less inter-rater error than the nasion used by, for instance, Meyer-Marcotty et al. (132). Midendocanthion also shows less change over growth, making it suitable for longitudinal studies (140). Last, two supplementary landmarks were used to prevent the ears from interfering with the analysis of volumetric and surface variables, which again places the plane for 3D measurements slightly more superiorly than in the studies by Meyer-Marcotty et al. and Schweitzer et al. (132, 189). These methodological differences may have slightly influenced the values of the outcome measurements compared to previous studies.

The deformities were rated visually using the Argenta clinical classification (2), which enabled the testing and comparing of cut-off values for DP subtypes with different clinical features. On the other hand, the Argenta classification does not
directly serve as a severity score, because it is possible, for example, to have severe occipital asymmetry without significant frontal asymmetry, which leads to high values in asymmetry-related measurements, but only classifies as type 1 or 2 on the Argenta scale. Therefore, cut-off values for different degrees of DP (e.g., mild, moderate, severe) could not be studied nor produced, which is a limitation of (IV). In addition, the impact of measurement plane location on the accuracy of the outcome measurements was not assessed; hypothetically, the accuracy of outcome measurements could be improved through identifying the optimal measurement planes, which is something for future studies to consider. Furthermore, the visual ratings were given to still 3D images instead of live infants, and it is possible that mild asymmetry is more noticeable in images than when observing the infant directly, although there is no direct evidence of such a phenomenon as yet.

6.7 Future perspectives

Considering the reduced incidence of DP with the preventive program, it would likely be beneficial to provide such education at antenatal clinics, maternity wards, or child healthcare centers on a larger scale, for example in printed form. Awareness of DP should be promoted among medical professionals in Finland and the outlook on the condition updated; at the time of writing, the sole recent reference to DP in Finnish medical literature only recommends passive follow-up for infants with DP to facilitate the occasional surgical intervention in case the deformation persists or worsens, with no regard to conservative options in both alleviating existing and preventing further deformation (200). The fact that some consider operative treatment justified for severe DP underlines the need for an effective conservative treatment method; additional high-quality research on the subject is required to reach a conclusion on whether helmet therapy in fact is an effective option for treating DP. Further studies are needed to determine the long-term prognosis of DP, the prevalence and characteristics of associated asymmetry of the face and jaw, and whether there is a true risk of subsequent occlusal disorders in childhood secondary to DP in infancy. Future studies should also aim to develop objective measurements providing even better diagnostic accuracy than the ones studied in the present work, possibly by taking into account the effect of cranial proportions (CI). Validation of the cut-off values used in clinical practice to categorize different degrees of DP is warranted as well, while the software used for 3D stereophotogrammetry and image analysis should be developed further and simplified to facilitate routine clinical use.
7 Conclusions

- The prevalence of deformational plagiocephaly (DP) increased from birth to 3 months of age, whereafter it spontaneously gradually decreased. At 3 months, DP was present in nearly one third of the infants, whose parents had not received primary preventive guidance at birth. While the natural course of cranial asymmetry is generally favorable, the rate of correction for asymmetry decreases after 6 months of age, also in relation to the rate of head growth, and the amount of anthropometric cranial asymmetry still present in 12-month-old infants appears clinically relevant.

- Providing the parents of newborns with instructions on their infant’s environment, positioning, and handling significantly reduced the prevalence and severity of DP at 3 months of age. A better neck range of motion (ROM) was also observed in the infants of parents subject to the educational intervention. On a larger scale, such primary preventive guidelines could aid in reducing the burden from both DP itself and associated healthcare costs.

- Gestational diabetes and vacuum assisted delivery increased the risk of DP at birth, but not in later infancy. There was no association between cranial asymmetry and impaired neck ROM in newborns, and DP seen at birth appeared to resolve quickly thereafter. However, positional torticollis and positional preference were clearly associated with DP in older infants, and the prevalences of both DP and torticollis were also considerably higher in older infants. This suggests that most cases of DP and associated torticollis concomitantly develop to their full extent during the first months of life.

- Positional preference at 3 months of age was the strongest predictor of an unfavorable course of cranial asymmetry from 3 to 12 months of age, increasing the risk of DP persisting. Late preterm infants were at a higher risk for initially developing DP, but infants born at a higher gestational age were more likely to see existing DP persist to 12 months of age.

- Out of the investigated variables measuring cranial asymmetry, OCLR produces the most accurate classification of DP compared to clinical assessment. While PCAI and wAS were slightly less accurate, they may also be useful in monitoring cranial asymmetry.

- The threshold of relative cranial asymmetry required for making the clinical diagnosis of DP is not affected by infant age, and hence, there is no additional utility in calculating and monitoring both OCLR and DD compared to calculating only OCLR.
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List of original publications


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