Effect of positioning error on the Hilgenreiner epiphyseal angle and the head-shaft angle compared to the femoral neck-shaft angle in children with cerebral palsy

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Children with cerebral palsy (CP) often have changes in proximal femoral geometry. Neck-shaft angle (NSA), Hilgenreiner epiphyseal angle (HEA) and head-shaft angle (HSA) are used to measure these changes. The impact of femoral rotation on HEA/HSA and of ab/adduction on HEA/HSA/NSA is not well known. This study aimed to determine and compare the effect of rotation, ab/adduction and flexion/extension on HEA/HSA/NSA. Radiographic measurements from 384 patients with Gross Motor Function Classification System (GMFCS) levels I-V were utilized. NSA/HSA for affected hips were used with femoral anteversion averages to create three-dimensional models of 694 hips in children with CP. Each hip was rotated, ab/ adducted and flexed/extended to simulate malpositioning. HEA/HSA/NSA of each model were measured in each joint position, and differences from correct positioning were determined. Mean HEA error at 20° of internal/external rotations were -0.60°/3.17°, respectively, with the NSA error of -6.56°/9.94° and the HSA error of -3.69°/1.21°. Each degree of ab/adduction added 1° of the HEA error, with no NSA/HSA error. NSA was most sensitive to flexion. Error for all measures increased with increasing GMFCS level. HEA/ HSA were minimally impacted by rotation. NSA error was much higher than HEA/HSA in internal rotation and flexion

whereas HEA was sensitive to changes in ab/adduction. Given abduction is more easily detectable on imaging than rotation, HEA may be less affected by positioning errors that are common with children with CP than NSA. HSA was least affected by position changes. HEA/HSA could be robust, complementary measures of hip deformities in children with CP. *J Pediatr Orthop B* 31: 160–168 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Cerebral palsy (CP) is a developmental disorder that affects posture and mobility [1], and occurs in 1.6–2.5 per 1000 children [2]. Coxa valga, or increased femoral neck-shaft angle (NSA) and femoral anteversion are common in children with CP [3]. These changes in proximal femoral geometry may contribute to progressive hip displacement, which occurs in approximately 35% of children with CP [3–6].

Measurement of NSA (Fig. 1) can assist in surgical planning and be used to assess remodeling postoperatively. NSA is measured between the femoral shaft axis and the femoral neck axis. True femoral NSA can be measured on an anteroposterior pelvis radiograph, but the measurement is sensitive to patient positioning, specifically femoral internal and external rotations [7,8]. Accurate measurement requires that the radiograph be completed with the hips internally rotated to the degree of patient anteversion present [9]. Challenges with obtaining the desired position for measuring NSA may impact surgical planning when measuring the degree of correction desired with a femoral osteotomy.

Coxa valga may also be assessed by measuring the Hilgenreiner epiphyseal angle (HEA) [10,11]. HEA is measured between the proximal femoral physis and the Hilgenreiner line (H-line) (Fig. 1). Based on the poor correlation between changes in femoral positioning and HEA on sequential images, Craven *et al.*, [11] found poor correlation between changes in femoral positioning and

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HEA on sequential images and concluded that HEA values appear to be independent of internal and external rotations [11]. As these authors noted, it is likely that HEA is affected by abduction/adduction, given there are landmarks on both the femur and pelvis, but it remains unclear how sensitive HEA is to changes in abduction/ adduction. Furthermore, it is unclear how sensitive HEA is to changes in femoral rotation and flexion/extension.

Head-shaft angle (HSA) was originally developed to evaluate femoral head valgus in patients with slipped capital femoral epiphysis [12]. HSA is measured between the femoral shaft axis and a line perpendicular to the physis through the center of the proximal femoral epiphysis (Fig. 1). HSA has been demonstrated to be greater in children with CP than in typically developing children and is associated with an increased risk of hip displacement [13]. Modeling studies have found that HSA was accurately measured within $\pm 5^{\circ}$ with varying degrees of internal rotation [13,14] with one noting that accurate measurement of HSA was unaffected by flexion [14]. However, these models were limited to two HSA angles and did not evaluate the impact of abduction/adduction.

The objective of this geometric modeling study was to determine how sensitive HEA and HSA are to changes in patient positioning compared to NSA in models of simulated hip deformities in children with CP across all Gross Motor Function Classification System (GMFCS) levels.

Materials and methods

Ethics board approval was obtained at the research study sites where participant data were collected and where modeling and analysis were completed. Participant data were collected as part of a previously published study involving a consecutive series of 384 patients with spastic CP, under age 20 years, who visited a tertiary referral center and had anteroposterior radiographs available [15]. Participants were excluded if they had other neuromuscular diseases, previous surgery or unrelated hip deformities. Anteroposterior radiographs were obtained for each patient while in the supine position with hips internally rotated by 30° [7]. Extent of involvement (unilateral or bilateral), GMFCS levels and demographic data were obtained from medical records (Table 1). Out of all 768 hips evaluated, 694 were affected by coxa valga. Surgeons defined and evaluated each hip's NSA and HSA from each patient's radiograph [15].

In the present study, a typically developing hip model was first created, using a computed tomographic (CT) scan of a right hip from a typically developing adolescent (16 years old, female, $0.6 \times 0.6 \times 0.4$ mm³ resolution). Image analysis software (Mimics, Leuven, Belgium) was used to segment the CT scan's bony structures semi-automatically, which were then reconstructed into a three-dimensional geometric model [16]. The model's femoral neck and epiphyseal axes were defined by fitting a cylinder to the neck. Average femoral anteversion has been measured as 15.4° (SD 7.7) for healthy 16-year-old adolescent hips [9]. Femoral anteversion is defined as the angle measure between the femoral neck relative to the femoral condyles, from an anterior projection. Because the original CT scan did not include the femoral condyles, the typically developing subject's true femoral anteversion angle could not be measured, and the model's femoral anteversion angle was assumed to be 15.4°. Original NSA, HSA and HEA were then measured and recorded from a planar view of the model, simulating a radiographic view (Fig. 1).

Subject-specific hip deformities were then modeled based on the data collected from the 694 affected hips described

Table 1Demographics, extent of hip involvement, and grossmotor function classification system (GMFCS) levels of includedpatients

Age (years) (range, mean)	3-17, 9.1
Sex (male:female)	249:135
Extent of hip involvement (unilateral:bilateral)	77:307
GMFCS Level (I:II:III:IV:V)	146:109:69:42:18

GMFCS, gross motor function classification system.

Fig. 1



Model illustrating proximal hip angles measured from anteroposterior radiograph: neck-shaft angle (NSA), Hilgenreiner epiphyseal angle (HEA) and head-shaft angle (HSA) measurement. NSA was defined as the angle between the axis of the femoral shaft and a line passing through the femoral neck midpoint and femoral head center. HEA was defined as the angle between a line through the proximal femoral physis and the Hilgenreiner line (H-line). HSA was defined as the angle between the axis of the femoral shaft and a line through the center of the proximal femoral epiphysis perpendicular to the physis.

above (coronal plane) and mean cohort data reported by GMFCS level from the literature (axial plane) (Fig. 2). Axial deformities were created based on femoral anteversion angle averages reported in the literature for children with CP. These were defined to be 30.4°, 35.5°, 40.5°, 40.2° and 40.5° for GMFCS levels I-V, respectively [17]. Patient-specific femoral anteversion angles could not be measured due to the limitations of the available radiographs, anteversion for each GMFCS was simulated by rotating the neck axially about the shaft by the difference between the GMFCS femoral anteversion average and the original model femoral anteversion angle. NSA/HSA were measured in the model again after femoral anteversion was adjusted. Coronal deformities were simulated by rotating the neck about the shaft coronally by the difference between each subject's measured NSA and the anteverted model's NSA. Similarly, the head was rotated about its center by the difference between each subject's measured HSA and the anteverted model's HSA. This yielded models of 694 unique subject-specific hip deformities from children with CP.

NSA, HEA and HSA were measured from a planar view for all 694 models to confirm that measurements matched the provided CP subject-specific data. This radiographic view was used to define the correct imaging position for comparison. Measurements were taken from this perspective to simulate how a clinician would measure angles from an anteroposterior radiograph. Each deformed model was then manipulated in internal/external rotations, abduction/adduction and flexion/extension to simulate different patient malpositioning during a radiograph. Overall, 167 254 unique position-hip combinations were measured, with 240 malpositions and one original correct position per hip.

NSA, HEA and HSA were measured at each malposition on the simulated radiographic view, and the difference



Flowchart illustrating the process of modeling of each of the 694 subject-specific hip deformities for children with CP. Each model was developed from a typically developing adolescent right hip, using subject-specific data in the coronal plane and mean data by Gross Motor Function Classification System (GMFCS) in the axial plane.

in each clinical angle compared to the correct imaging position was calculated for each patient-specific model. In cases of external rotation where NSA exceeded 180° , measurements were recorded as angle values greater than 180° , rather than recording the acute angle.

A sensitivity test was performed on the model to assess the impact of femoral anteversion angle assumptions when manipulating in internal/external rotations and flexion/extension. Assumed femoral anteversion angle for all GMFCS V patients was each increased by 10°, and the model was manipulated again in internal/external rotations, abduction/adduction and flexion/extension. This was repeated once more, this time with the assumed femoral anteversion angle instead decreased by 10°.

Summary statistics were calculated across all imaging positions for HEA, NSA and HSA. Normalcy was tested using the Kolmogorov–Smirnov test, and data sets were found to not be normally distributed. For each measure (HEA/NSA/HSA), we tested the null hypothesis, that mean errors were not different from zero, using a one-sample Wilcoxon signed-rank test (95% confidence level). HEA error was tested for ab/adduction, internal/external rotations and flexion/extension, and NSA and HSA were tested for internal/external rotations, abduction/adduction and flexion/extension positioning error. We assigned a significance level of P < 0.001, and resulting P values were conservatively adjusted for multiple comparisons using the Bonferroni correction (483 total one-sample tests done at all 161 positions for each of the three angles as described

above). All modeling, analysis and statistics were performed in MATLAB (MathWorks, Massachusetts, USA).

Results

The error measurements for NSA, HEA and HSA at different degrees of internal/external rotations, ab/adduction and flexion/extension are shown in Table 2 and Fig. 3. At 20° of internal rotation, mean magnitude of error increased by 6.56° in NSA, 0.60° in HEA and 3.69° in HSA. At 20° of external rotation, mean magnitude of error increased by 9.94° in NSA, 3.17° in HEA and 1.21° in HSA. At 20° of flexion, mean magnitude of error increased by 4.16° in NSA, 3.27° in HEA and 3.25° in HSA. At 20° of extension, mean magnitude of error increased by 0.68° in NSA, 5.70° in HEA and 5.45° in HSA. In coronal plane malpositioning, the error in HEA increased by approximately one degree for each degree of abduction/ adduction, whereas NSA and HSA remained unaffected (Table 2, Fig. 3). Because NSA and HSA do not rely on measures relative to the pelvis, pure ab/adduction did not change these values, and therefore the error was zero in all cases. As a result, the SD for this data was also zero, so mathematically the Kolmogorov-Smirnov test could not be performed. Mean errors were found to be statistically significant for every degree of malpositioning for all angle measures (Bonferroni-corrected P < 0.001 in all cases).

Generally, all three angles were more sensitive to positioning error in hips of children with higher GMFCS levels (Fig. 4). At 20° of internal and external rotations, NSA error in participants at GMFCS level V was an average of 4.86° (in internal rotation) and 4.59° (in external rotation)

Table 2 Mea	an error in Hila	enreiner epiphyse	eal angle and	neck-shaft angle	e under positionin	a errors
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	Internal rotation			External rotation		
Position error	HEA (°)	HSA (°)	NSA (°)	HEA (°)	HSA (°)	NSA (°)
5°	-0.34 ^a (0.12)	-0.76 ^a (0.18)	-1.20 ^a (0.32)	0.53 ^a (0.22)	0.61 ^ª (0.17)	2.18ª (0.31)
10°	$-0.56^{a}(0.21)$	-1.64 ^a (0.33)	$-3.72^{a}(0.64)$	1.21 ^a (0.47)	1.04 ^a (0.39)	4.56 ^a (0.62)
15°	-0.64 ^a (0.30)	$-2.62^{a}(0.46)$	$-5.25^{a}(0.98)$	2.08 ^a (0.77)	1.25 ^a (0.65)	7.15 ^a (0.93)
20°	$-0.60^{a}(0.37)$	-3.69 ^a (0.59)	-6.56 ^a (1.33)	3.17 ^a (1.13)	1.21 ^ª (0.95)	9.94 ^a (1.23)
		Adduction			Abduction	
Position error	HEA (°)	HSA (°)	NSA (°)	HEA (°)	HSA (°)	NSA (°)
5°	-4.75 ^a (0.22)	0.00 ^b (0.00)	0.00 ^b (0.00)	4.71 ^a (0.14)	0.00 ^b (0.00)	0.00 ^b (0.00)
10°	-9.48 ^a (0.21)	0.00 ^b (0.00)	0.00 ^b (0.00)	9.43 ^a (0.14)	0.00 ^b (0.00)	0.00 ^b (0.00)
15°	-14.20 ^a (0.23)	0.00 ^b (0.00)	0.00 ^b (0.00)	14.17 ^a (0.14)	0.00 ^b (0.00)	0.00 ^b (0.00)
20°	-18.92 ^a (0.23)	0.00 ^b (0.00)	0.00 ^b (0.00)	18.91 ^a (0.14)	0.00 ^b (0.00)	0.00 ^b (0.00)
		Flexion			Extension	
Position error	HEA (°)	HSA (°)	NSA (°)	HEA (°)	HSA (°)	NSA (°)
5°	1.05 ^a (0.35)	-1.03 ^a (0.35)	-0.68 ^a (0.22)	-1.21 ^a (0.39)	1.17 ^a (0.34)	0.47 ^a (0.16)
10°	1.99 ^a (0.71)	-1.92 ^a (0.70)	$-1.58^{a}(0.46)$	$-2.56^{a}(0.71)$	2.47 ^a (0.66)	0.73 ^a (0.30)
15°	2.69 ^a (1.06)	-2.66 ^a (1.07)	-2.73 ^a (0.72)	-4.07 ^a (1.02)	3.90 ^a (1.00)	0.80 ^a (0.41)
20°	3.27 ^a (1.43)	-3.25 ^a (1.45)	$-4.16^{a}(1.00)$	-5.70 ^a (1.36)	5.45 ^a (1.34)	0.68 ^a (0.52)

The mean measurement errors in the Hilgenreiner epiphyseal angle (HEA), femoral head-shaft angle (HSA) and femoral neck-shaft angle (NSA) under 5, 10, 15 and 20 degrees of internal rotation, external rotation, adduction, flexion and extension.

Data is presented as: mean (SD).

HEA, Hilgenreiner epiphyseal angle; HSA, head-shaft angle; NSA, neck-shaft angle.

^aP<0.001 (one-sample Wilcoxon signed-rank test with Bonferroni correction), indicating mean error is statistically different from zero.

^bHSA/NSA under abduction/adduction data could not be tested statistically due to a SD of zero.



Mean angle errors for 694 hip models over a range of malpositioning (error defined as the difference between a hip angle measure taken in the original position and the same measure taken with malpositioning, for each subject-specific model) in (a) Hilgenreiner epiphyseal angle (HEA), (b) neck-shaft angle (NSA) and (c) head-shaft angle (HSA). Malpositioning in internal/external rotation (x), ab/adduction (dot) and flexion/extension (star). Dashed lines indicate no angle measurement error (horizontal) and no positioning error (vertical).

greater than in those at GMFCS level I. Similarly, the HEA error at 20° of ab/adduction in children at GMFCS level V was 4.04° (in both abduction and adduction) greater than in GMFCS I patients. The HSA error at 20° of flexion and extension in participants at GMFCS level V was an average of 4.06° (in flexion) and 3.65° (in extension) greater than those at GMFCS level I. At 20° of internal and external rotations, the HSA error was lowest in participants at GMFCS level V. For the other angle measures at 20° of internal and external and external rotations, the HSA error was greatest in participants at GMFCS level V. For the other angle measures at 20° of internal and external rotations, the HEA error was greatest in participants at GMFCS level V. For the other angle measures at 20° of internal and external rotations, the HEA error was greatest in participants at GMFCS level V. For the other angle measures at 20° of internal and external rotations, the HEA error was greatest in participants at GMFCS level V. For the other angle measures at 20° of internal and external rotations, the HEA error was greatest in participants at GMFCS level V. For the other angle measures at 20° of internal and external rotations, the HEA error was greatest in participants at GMFCS level V.

Results from the femoral anteversion angle sensitivity test (Fig. 5) showed that the modeling results were all impacted by femoral anteversion angle assumptions. The NSA error was most impacted by changes in femoral anteversion angle in external rotation, with 3.47° of change when femoral anteversion angle was increased by 10° . The HSA and HEA error results were both most impacted by extension, changing by 3.72° and 3.71° , respectively when femoral anteversion angle was increased by 10° .

Discussion

A three-dimensional geometric model of 694 simulated hips of children with CP demonstrated that the femoral rotation had a minimal effect on HEA and HSA but was significant for NSA. Measurement error for NSA was found to be 10.9 times higher than that of HEA with 20° of internal rotation. As anticipated, HEA was impacted by changes in ab/adduction while NSA and HSA were not. NSA was most sensitive to flexion, but HEA and



Mean angle errors by Gross Motor Classification System (GMFCS) level (I, II, III, IV and V) for 694 hip models over a range of malpositioning (error defined as the difference between a hip angle measure taken in the original position and the same measure taken with malpositioning, for each subject-specific model). Dashed lines indicate no angle measurement error (horizontal) and no positioning error (vertical). Error when in internal/external rotation for (a) Hilgenreiner epiphyseal angle (HEA), (b) neck-shaft angle (NSA) and (c) head-shaft angle (HSA). Error when in ab/ adduction for (d) HEA, (e) NSA and (f) HSA. Error when in flexion/extension for (g) HEA, (h) NSA and (i) HSA mean errors for each GMFCS level (I, II, III, IV, V) at each point.

HSA were significantly more impacted by extension. To the authors' knowledge, no other studies have been conducted analyzing HEA's sensitivity to patient positioning, nor have HEA, NSA and HSA been compared in varying patient positions.

Our results indicate that every degree of ab/adduction from the neutral position adds approximately one degree of error to HEA. These results confirm the validity of our model, as it is empirically evident that HEA would change by one degree for each degree of change in hip abduction/adduction. Our results also found that large variations in the femoral rotation have minimal impact on HEA. Craven *et al.*, [11] reported high reliability in measuring HEA among very young children and a limited relationship between femoral position and HEA. These conclusions were based on their finding of poor correlation between changes in femoral positioning and HEA. However, the radiographs assessed were completed in standardized positioning with hips in neutral abduction/ adduction, noting the images required an absence of significant abduction/adduction of greater than 10° [11]. Our study has tested these assumptions and shown that HEA is sensitive to abduction/adduction but fairly independent of changes in femoral rotation and extension.

Hip internal and external rotations can be challenging to control when positioning a child with CP for imaging and cannot accurately be assessed from the image. It is expected that HEA can be accurately measured despite variations in femoral rotation. In contrast, assessment of positioning in the coronal plane is more easily assessed by measuring the femoral shaft position [18]. When positioning in the coronal plane cannot be easily controlled, this will be clearly identifiable on the imaging and measurements can be used cautiously.

HSA was least affected by malpositioning; it was unaffected by abduction, was least affected by flexion, and was minimally impacted by internal/external rotations. This supports previous findings that found HSA was accurately measured within $\pm 5^{\circ}$ when the femur was



Mean change in angle error results when femoral anteversion (FA) angle assumptions are changed in the model. Original mean results (.), change in mean results when FA angle is decreased by 10° (x), and change in mean results when FA angle is increased by 10° (*). Dashed lines indicate no angle measurement error (horizontal) and no positioning error (vertical). Sensitivity to FA angle assumption when in flexion/extension for (a) Hilgenreiner epiphyseal angle (HEA), (b) head-shaft angle (HSA) and (c) neck-shaft angle (NSA). Sensitivity to FA angle assumption when in internal/external rotation for (d) HEA, (e) NSA, and (f) HSA.

positioned between 20° of internal rotation and 40° of external rotation [14]. The authors are unaware of literature investigating the impact of abduction/adduction on HSA. Recent evidence suggests that HSA may have prognostic value in progressive hip displacement in children with CP [19,20]. While Lee *et al.* (2010) found that NSA seemed more clinically relevant in evaluating femoral deformity than HSA in children with CP [15], HSA has the advantage of being the least impacted by changes in patient positioning. Further investigations into the clinical utility of HSA in children with CP are required.

Measurements of NSA were substantially more sensitive than HEA and HSA to differing degrees of internal/ external rotations. The effects of femoral rotation on NSA found in our study are consistent with other reports in the literature. Previously developed two-dimensional mathematical models found that 40° of internal/external rotations leads to 10° of NSA error [8]. Another mathematical model measuring NSA in varying positions of femoral rotation from a normal adult dried femoral specimen found approximately 8° and 3° of the NSA error when in 20° of external and internal rotations, respectively [7]. These findings are just slightly lower than our results of 9.9° and 6.6° of the NSA error in 20° of external and internal rotations, respectively. However, these studies assessed only a single normal cadaveric hip, in contrast with our assessment of 694 simulated CP deformities spanning the range of severities. Additionally, NSA was quite sensitive to flexion, which is common in children with CP [21]. A mathematical model predicting NSA changes in hip flexion-extension found NSA error did not exceed clinical significance (defined as 5–10° of error) until over 50° of flexion was induced [8]. Our results of only 4.16° of change in NSA at 20° of flexion concur with this study.

Increasing GMFCS level generally correlated to higher sensitivities in all three angles. There are known differences in geometry of the proximal femur with differing GMFCS levels [17]. Higher GMFCS levels resulted in increased error in measurement of NSA, HEA and HSA, with two exceptions. First, the absolute HEA error at 20° of internal and external rotations was greatest for those at GMFCS levels IV and III rather than V. We hypothesize that the lower sensitivity correlated to the GMFCS V cohort is attributed to the small sample size of 18 GMFCS V patients. Second, the HSA error at 20° of internal/external rotations was lowest in GMFCS II and III patients. However, differences found in these measurement errors were under 5° and, hence, the clinical significance of these findings needs further evaluation.

Strengths of this study include the large set of 694 unique coronal plane CP deformities that were modeled from the hips of children with CP, allowing for thousands of unique position-hip combinations to be measured. Previous mathematical studies have been limited to measurements from a single cadaveric femur [7,8]. This study is the first instance of HSA, NSA and HEA being compared directly in CP patient-specific hip models, with the same level of accuracy due to consistently defined vector lines on the models. As all geometrical manipulation and analysis was conducted retrospectively in MATLAB, no additional radiation exposure to children was required. Although many clinicians understand the qualitative phenomenon surrounding changes in HEA, NSA and HSA with patient positioning, the three-dimensional comparison between each angle in this work confirms and quantifies what clinicians have previously suspected.

There are limitations to note in this study. Threedimensional images of each CP participant's hips were unavailable and, therefore, all models were manipulated from a typically developing adolescent CT scan. Because each model was created using real CP participant data, this limitation would have minimally impacted the results of this study. Additionally, the radiographs did not include the femoral condyles so unique femoral anteversion angles could not be used for each CP model, which may have created small errors in the data obtained. However, angles specific to children with CP were approximated, by GMFCS level, from the literature. While each model did not capture every patient-specific angle used, the ranges of CP femoral anteversion angles across GMFCS levels drastically improved our model compared to using a single femoral anteversion angle for every hip. The results from the femoral anteversion angle sensitivity test indicate that even drastic changes of 10° in femoral anteversion angle would impact results by less than 4°, thereby indicating that the results from this model are clinically valid. Previous mathematical models used only two-dimensional data for analysis [7,8], making our proximal femur model, which takes axial plane deformity into account, more comprehensive. Another limitation was the differences in the normal hip CT and the radiographs taken of the 384 CP patients. The different technologies and parameters may have led to slight inconsistencies in the angles measured from the radiographs compared to the CT-based MATLAB model.

Nevertheless, our results were consistent with previous studies, and any differences caused by this limitation are likely small. Finally, this model assumed a spherical femoral head, although femoral head deformities are common in patients with CP. This consideration was out of the scope for this modeling analysis, and the impact of this requires further study.

Patient positioning can lead to errors in NSA, HEA and HSA measurements from anteroposterior pelvis radiographs in children with CP. The errors in clinical measures of hip geometry observed in this geometrical model for 694 unique CP hips across all GMFCS levels indicate that HEA and HSA may be robust measurements of CP hip deformity. Although HEA is impacted by abduction and adduction, coronal plane malpositioning is more easily detectable on an anteroposterior radiograph than internal/external rotations malpositioning. Further study on the clinical utility of HEA and HSA is required.

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Conflicts of interest

There are no conflicts of interest.

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