**1. TITLE PAGE**

Full title of the paper: Identifying biomechanical gait parameters in adolescent boys with haemophilia using principal component analysis

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## 2. ABSTRACT

Introduction: Improvements in the medical management for those with haemophilia have resulted in improved clinical outcomes. However, current treatment regimens do not alleviate all joint haemarthroses with the potential for long-term joint deterioration remaining. The evaluation of functional activities such as gait, using standardized tools to monitor children with haemophilia is emerging. Aim: This study explored differences in sagittal plane biomechanics of walking in adolescent boys aged 11-18 years with haemophilia and an age-matched group of typically developing boys. Methods: A motion capture system and two force platforms were used to collect sagittal plane kinematic, kinetic and temporal spatial data during level walking. Principal component analysis was applied to kinematic and kinetic waveform variables. Group differences in temporal spatial and principal component scores for each kinematic and kinetic variable were evaluated using independent t-tests. Results: Significant alterations ($p < 0.05$) in temporal spatial and kinetic parameters were found in adolescent boys with haemophilia. Compared to typically developing adolescent boys, boys with haemophilia walked with reduced stance phase duration and altered pattern of external ankle joint moments during push off and the beginning of swing. Conclusion: The use of principal component analysis (PCA) rather than predetermined discriminatory variables provided additional insight into biomechanical alterations in adolescent boys with haemophilia, with adaptations occurring during terminal double support and early swing, affecting the ankle joint. This finding might be a key biomechanical marker that could be used to evaluate the joint function and the progression of early haemophilic arthropathy.

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## 3. MAIN BODY OF TEXT

### INTRODUCTION

Current evaluation of the physical status of joints is monitored radiologically using x-ray and MRI [1]. Investigations such as these focus on joint structure and integrity providing little information on joint function and performance. In addition, regular multi-joint investigation is expensive, time consuming and challenging in children due to movement artefact. The development of more recent haemophilia specific clinical tools has been used to evaluate functional limitations but are based on symptoms of end stage musculoskeletal impairment. Stephensen *et al.,* evaluated sagittal plane gait biomechanics and reported subtle alterations in joint motion and moments of force to be early musculoskeletal impairments following lower limb haemarthrosis [2].

Increasingly, motion capture technology is being used to evaluate movement disorders and provide details about mobility imperceptible to the naked eye [2-5]. Bladen *et al.,* evaluated temporal-spatial walking parameters using a GAITRite electronic walkway in 20 adolescent boys with severe haemophilia aged 7-17 years compared to age matched control subjects and reported increased swing, reduced stance, increased single support times and reduced double support times in the group of boys with haemophilia [3]. Stephensen *et al.,* evaluated 14 preadolescent boys with haemophilia aged 7-13 years with a history of ankle joint bleeding using a three-dimensional (3D) motion capture system and two force platforms and reported: greater flexion angles at the knee during early to mid-stance and swing phase of gait, greater external moments at the knee throughout stance, greater ankle plantarflexion external moments during early stance and lower hip flexion external moments during mid stance [2]. In contrast to the findings of Bladen *et al.,* no alterations were found in temporal spatial parameters between the groups. Forneris *et al*., evaluated 42 children and adolescents with haemophilia aged 4-18 years using a 3D motion capture system to calculate the Gait Deviation Index and Profile Scores. Compared to normative reference data, children with haemophilia were found to walk with functional gait alteration [4]. Lobet *et al.,* evaluated the walking patterns of eighteen adults with haemophilia (aged 40 ± 10 years), reporting gradual infra-clinical alterations in temporal spatial, kinematic and kinetic parameters in those with advanced joint pathology [5].

Previous studies evaluating gait biomechanics in those with haemophilia [2-3, 5] have evaluated parameterised values, such as maximum and minimum joint angles extracted at specific points of the gait cycle (for example, heel strike) [2-3, 5]. However, such techniques ignore the pattern of

movement that occur between these predetermined points. The use of waveform analytical techniques may provide additional insight into biomechanical alterations in adolescent boys with haemophilia. Principal component analysis (PCA) is an exploratory method of data analysis in the field of biomechanics [6-9], enabling exploration of the entire waveform and does not require an a priori determination of variables to extract. To our knowledge, waveform statistical techniques have not been used to examine differences in kinematic and kinetic patterns in adolescent boys with haemophilia. Therefore, the aim of this study was to identify differences in kinematic and kinetic gait patterns in adolescent boys with haemophilia aged 11-18 years compared to age matched typically developing boys. It was hypothesised that the pattern of sagittal plane joint motion and moments would be altered in adolescent boys with haemophilia.

## MATERIALS & METHODS

### Subjects

Two groups of children participated in this study (Table.1). Fourteen boys with haemophilia (H) and 14 age and puberty status matched typically developing boys (TD) were recruited. Puberty status was self-rated by the participants according to the Tanner Scale [10]. Boys were excluded if they presented with a history of lower limb fracture, major ligamentous injury or trauma to the lower limb, orthopaedic surgery, acquired brain injury or any other disturbance to the central nervous system or any lower limb joint or muscle bleed in the preceding six weeks prior to testing. Eleven boys had severe haemophilia (<1 iu/dl), one had moderate haemophilia (1-5 iu/dl) and two boys had mild form of the disease (5-50 iu/dl). Lower limb bleeding episodes over the previous 12-months were measured using a self-report questionnaire. Ethical approval was obtained from both the NHS and local University Ethics Committee (11/LO/1202).

### Protocol

Gait analysis was performed using an eight-camera Vicon 612 (VICON Motion Systems Ltd, Oxford, UK) system to capture and record motion of skin mounted reflective markers at 200 Hz. Two force platforms (Bertec, Model 4020 H, MIE Ltd, UK) embedded in the laboratory floor captured ground reaction forces during gait trials at 1000 Hz. Children wore shorts and were barefoot during testing. Anthropometric measurements were recorded for height, mass, leg length, and knee and ankle width. Sixteen reflective markers (14 mm) were attached bilaterally to the anterior superior iliac spine,

posterior superior iliac spine, lateral condyle of the knee, lateral malleolus of the fibula, posterior surface of the calcaneus and midline of the lateral thigh and shank (Plug-In-Gait PiG) lower limb model [2]. Subject preparation and measurement was performed by a single assessor (LS). Boys were asked to ambulate at a self-selected walking speed through the capture volume. A single trial was considered for analysis if two sequential full steps were simultaneously captured by the cameras and force platforms. Six gait trials were captured and saved for subsequent analysis.

Data management

Marker trajectories were reconstructed using Vicon software to ensure visibility throughout the gait cycle. Only trials where trajectories were visible over the whole gait cycle were used for analysis. Marker trajectories were gap filled to a maximum of five frames using a cubic spline technique. The gait cycle was defined from initial contact with the force platform (20 N threshold) to subsequent foot contact of the same foot, with data expressed as a percentage of the gait cycle. Data from the limb with greatest number of joint bleeds in the boys with haemophilia and the right limb from the age matched typically developing controls were used for analysis.

Temporal spatial parameters determined from motion capture data included gait velocity, cadence, stride distance, stride time and single and double support duration. The influence of body anthropometrics on temporal spatial characteristics were accounted for by normalisation to the dimensionless values described by Hof [11]. Length parameters were normalised to leg length, time parameters to [leg length/ gravity (9.81 $m/s^{-2}$)]$^{½}$, and velocity and cadence parameters to [acceleration due to gravity (9.81 $m/s^{-2}$)/ leg length]$^{½}$.

Data points corresponding to every 1% of the gait cycle were extracted to represent the sagittal plane joint motion and moment waveforms of hip, knee and ankle. Kinematic data were derived from the PiG lower limb model. Sagittal plane kinetic data consisting of external joint moments at the hip, knee and ankle, normalised to body mass were calculated using the principles of inverse dynamics using estimated segmental inertial properties, kinematic and ground reaction force data. Segmental inertial properties were estimated from participant anthropometric data with ground reaction forces obtained from the force platforms. Joint moments were smoothed using a Butterworth filter with a cut-off frequency of 10 Hz.

### Statistical analysis

Statistical analysis were performed in SPSS version 20.0. Data were assessed for normality of distribution using the Kolmogorov-Smirnov test. Waveform matrices for sagittal plane kinematics and kinetics were constructed on 28 subjects and corresponding data points (kinematic matrices: 28 x 101), (kinetic matrices: 28 x 101). Waveform matrices were transformed into principal components following eigenvector analysis of the covariance structure. Variation in the waveforms data were extracted by rotating the variables using orthogonal rotation into components that maximally explain variance in original waveforms. To interpret which factors contribute to a given principal component, the rotated components were used for analysis. Rotated factor loadings were evaluated to determine which aspect of the gait cycle contributed to each principal component (PC). Rotated factor loadings ± 0.748 were considered as contributing to a component [12]. Factor scores were calculated for each participant for extracted PCs, providing a measure of magnitude and direction of deviation from the mean gait curve [7]. For each component factor score, between-group comparisons using independent t-tests were performed. Statistical significance was set to $p<0.05$.

## RESULTS

### Joint haemarthrosis history

Median and inter-quartile range (IQR) of lower limb joint bleeding reported by the H boys over the preceding 12 months was 1.00 bleed (IQR: 2.00). The ankle joint was the most frequent site of bleeding (0.5 bleeds; IQR: 1.75), followed by the knee (0 bleeds; 1.00) and hip (0 bleeds; 0.00) joints. Six boys with haemophilia reported no haemarthroses in the previous 12-months prior to testing, with 8 boys reporting at least one lower limb joint bleeding episode during this period.

### Temporal spatial parameters

Absolute and normalised temporal spatial (TS) parameters are presented in Table 2. Stance phase duration was significantly lower and swing phase significantly greater in the H boys compared to TD boys (between-group difference 1.2%; $p<0.05$). No other significant between-group differences were observed during level walking.

### Sagittal plane kinematics

Table 3 presents the results of PCA on sagittal plane joint motion of the hip, knee and ankle joints. Variation in lower limb joint motion waveforms was explained by three hip, four knee and six ankle joint PC's. No significant between-group differences were found for retained PC factor scores (Figure 1).

Sagittal plane kinetics

Table 4 presents the results of PCA on sagittal plane joint moments of the hip, knee and ankle and vertical ground reaction force (VGRF). Variation in lower limb joint kinetic waveforms was explained by; six hip PC's, six knee PC's and six ankle PC's. Three VGRF PC's were identified. Factor scores for ankle joint moment PC2, representing the end of stance and beginning of swing, were significantly lower in the H boys compared to the TD boys (TD: 0.20 ± 0.18, H: -0.20 ± 0.26; $p<0.05$, Table 4 and Figure 2). No significant between-group differences were found for retained PC factor scores for the hip and knee joints or VGRF waveforms.

## DISCUSSION

The aim of this study was to determine whether walking patterns of adolescent boys with haemophilia differed from typically developing boys. We identified shorter stance duration and, by utilising PCA, showed alterations in ankle joint moments during push off and at the beginning of swing phase in boys with haemophilia, compared to their typically developing peers. However, no differences in joint kinematics were identified. These findings partly support our hypothesis that lower limb joint angular motion and moments would be altered in the H group of boys. Furthermore, waveform analysis identified alterations in movement patterns not previously reported in adolescent children with haemophilia.

Boys with haemophilia spent significantly less time (1.2%) in stance phase and more time in swing phase compared to those without haemophilia. It is acknowledged that this difference is small and whether this finding is clinically relevant is not currently known. The shorter stance phase concurs with the study of Bladen *et al.,* who found significant reductions (group difference: 2.52%) in an adolescent group of hemophiliac boys with no radiographic evidence of joint pathology (mean age: 12.7 ± 2.5 years) compared to typically developing boys (mean age: 12.0 ± 2.0 years [3]. Lobet *et al.,* also reported significant alterations in stance phase duration (mean difference: 0.4%) between

repeated testing 18 ± 5 weeks apart (range 13-33 weeks) in adults with haemophilia (aged 40 ± 10 years) [5]. In contrast, Stephensen *et al.,* reported comparable stance phase duration in a younger group of boys with haemophilia aged 10.43 ± 2.13 years, despite kinematic and kinetic impairments [2].

The mechanism for the subtle reduction in stance phase duration observed in the haemophilic boys is not clear from the current study. Although, annual lower limb joint bleeding rates in the preceding 12 months were low and not confirmed by clinical records, the walking pattern alterations found in the haemophilic boys in the current study might be a protective mechanism due to early blood-induced arthropathy. Future studies exploring early signs of arthropathy and gait are required. Secondary to concerns regarding the accuracy of self-reported records [13] and the small sample size evaluated in the current study, no further analysis on the bleeding history data was performed. Reductions in stance phase duration have previously been reported in adults with medial knee arthrosis [14] and proposed to occur as a result of altered walking speed [15]. The finding of reduced stance duration despite comparable gait velocity in the boys evaluated in this study, suggests the presence of an alternate underlying adaptive strategy in adolescent boys with haemophilia.

Factor scores for ankle joint kinetics at the end of stance and beginning of swing (PC2) were significantly different in the H boys compared to the TD boys. Inspection of the moment curves and PC loading plots (Fig. 1) suggest that the external ankle dorsiflexor moment toward the end of stance may be reduced or declining at a different rate together with a larger external ankle plantarflexor moment in early swing in the boys with haemophilia when compared to the typically developing boys. External joint moments are counteracted by opposing internal muscle moments. The actions of pre-swing are commonly referred to as push off and relate to limb progression and foot clearance for the subsequent step. The finding of reduced external ankle dorsiflexor moment at the end of stance reported in the current study may be equivalent to reduced ankle plantarflexor muscle activity and subsequent push off. Stephensen *et al.,* examined the strength of the ankle plantarflexors in young children with haemophilia and found significant muscle weakness compared to age matched controls [16]. Lobet *et al.,* (2010) reported a trend towards reduced power generated at the ankle joint at the end of stance, interpreting this as a deterioration in ankle joint function [5]. Furthermore, the larger plantarflexor moment in early swing may reflect greater ankle dorsiflexor muscle activity and coupled with longer swing duration may be a strategy to aid foot clearance and minimise the potential risk of falling as a consequence of the reduced push off [17]. De Souza et al., examined postural adjustment

during unexpected perturbation in children (mean age 10.3 ± 1.3 years) with haemophilia and reported alterations in balance mechanisms in boys with haemophilia compared to typically developing children [18].

Extracted PC's were compared between groups in order to identify gait waveform alterations between H and TD boys. Although we were able to make some interpretation of the biomechanical features captured by the PC, further work is required to determine whether magnitude, phase shift and timing features, together with additional inter subject variance are responsible for the significant PCs identified [19] and is a limitation of the current study. Several of the extracted PC's also explained a relatively small amount of variation in the entire waveform and it is unclear whether the identified alterations are clinically relevant. Future work on a larger sample is needed to confirm our findings. The sagittal plane hip kinetic waveform also appears to be subject to noise artifact and should be interpreted with caution. Furthermore, participants were asked to walk at a self-selected waking speed in this study. Although walking speed was comparable between groups, individual differences between participants may have contributed to the variability in joint motion and moments identified [15]. Inclusion of mild and moderate disease severity types may have additionally influenced the results of the current study. Boys with mild and moderate forms of the disease suffer fewer haemarthrosis [20] and may be less prone to sub-clinical bleeding episodes than those with severe forms of the disease [21].

## CONCLUSION

This study presents novel information evaluating sagittal plane gait waveforms in adolescent's boys with haemophilia and those of age-matched typically developing boys. The use of PCA rather than predetermined discriminatory variables provided additional insight into biomechanical alterations in adolescent boys with haemophilia, with adaptations occurring during push off and early swing affecting the ankle joint. Altered patterns of external ankle joint moments might be a key biomechanical marker that could be used to evaluate the joint function and the progression of early haemophilic arthropathy in children with haemophilia.

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## AUTHOR CONTRIBUTIONS

LS has contributed to the design of the study, the data collection and analysis and preparation of the manuscript. DS, MC, RM and WD have contributed to the design of the study and preparation of the manuscript.

## DISCLOSURES

The authors have no competing interests which might be perceived as posing a conflict or bias.

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