



# Performance on the iSTEP and 10 m-ISWT in boys with haemophilia

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## Abstract

**Introduction:** Boys with haemophilia (BwH) have improved health outcomes. Measures of physical function in haemophilia are not challenging or sensitive enough to reflect physical limitations or guide rehabilitation. To identify meaningful tests, we aimed to: evaluate the performance of BwH on two physical performance measures: iSTEP and 10 m-ISWT; identify factors which predict performance and compare BwH to their unaffected peers.

**Methods:** BwH completed both iSTEP and 10 m-ISWT. Disease severity, age, BMI, HJHS, lower limb muscle torque, time spent in moderate to vigorous physical activity, sedentary time, were included as factors to predict performance. Results were compared to unaffected peers.

**Results:** 43 boys median age 10 (10 mild/moderate, 26 severe, 7 inhibitors) were recruited. BwH were less likely to complete the iSTEP and performed less well on the 10 m-ISWT than age matched peers. Ceiling effects were apparent for iSTEP, but not the 10 m-ISWT test. Age was the only significant predictor for performance in the iSTEP, with older boys being more likely to achieve a higher level or complete the test. Greater age, lower BMI, milder disease severity and more time spent in MVPA all predicted better performance on the 10 m-ISWT, with BMI and habitual physical activity a potential rehabilitation focus for underperforming individuals. HJHS and muscle strength did not predict performance on either test.

**Conclusion:** Despite the space need to conduct the 10 m-ISWT, it appears to be a superior performance measure than the iSTEP in BwH and provides clinically meaningful information, which can be interpreted using age-specific normative reference equations.

## KEYWORDS

accelerometry, child, exercise test, haemophilia, ISWT, obesity

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## 1 | INTRODUCTION

Boys with haemophilia (BwH) are experiencing improved health outcomes due to advances in medical therapies, and can now expect their prophylactic treatments to prevent or minimise arthropathy, and even facilitate a bleed-free life.<sup>1</sup> Clinical assessments for patients with haemophilia have previously focussed on frequency of bleeds, pain, measures of body structure and function and predominantly self-reported measures of activity and participation. However, current guidelines for haemophilia aim for zero bleeds and no joint damage, thus established measures of body structure and function, for example, the Haemophilia Joint Health Score (HJHS), may no longer be sufficiently discriminatory.<sup>2</sup>

In a recent study, more than half the boys with severe haemophilia had a HJHS (version 2.1) of zero, indicating normal joint health.<sup>3</sup> The HJHS may no longer be the most sensitive validated physical assessment of joint health in haemophilia for children on primary prophylaxis<sup>4,5</sup> and fails to offer sufficient quantitative information which reflect the physical performance and capacity of people living with haemophilia. Clinical outcomes should ideally expose not only limitations in performance, but unmasking potential causes so that modifiable factors contributing to poor performance can be targeted within treatment plans.

## 2 | AIMS OF STUDY

The iSTEP and 10 metre Incremental Shuttle Walking Test (10 m-ISWT) are two physical performance measures used in children with chronic diseases and their feasibility and safety in BwH has been established.<sup>6</sup> This study aimed to (1) Evaluate the performance of BwH of all severities on these two physical performance measures, (2) Identify factors which predicted performance in these two measures, and (3) Compare performance of BwH to their unaffected peers. Ultimately, we sought to identify physical performance tests that were sufficiently challenging to discriminate performance in BwH and potentially identify modifiable factors that were influential in the child's performance that might be responsive to rehabilitation.

## 3 | METHODS

Research ethics approval was provided by the Central London Research Ethics Committee (ref: 17/LO/1192). The study is registered with clinicaltrials.gov (ID: NCT04076306).

BwH of all severities aged 6–15 years (including those with inhibitors) at Great Ormond Street Hospital for Children NHS Foundation Trust haemophilia centre (GOSH) were invited to participate in this study. They were recruited using convenience sampling from clinic lists between January and November 2018. Demographic data including: type and severity of haemophilia; treatment status; bleeds in the previous year; known arthropathy; height; weight and body mass index (BMI) were collected. The feasibility and acceptability of the protocol, detailed below, has been published<sup>6</sup> (Figure 1).

## 4 | PHYSICAL PERFORMANCE MEASURES

### 4.1 | iSTEP

The iSTEP is a valid exercise step test,<sup>7</sup> where participants step in time to externally-paced beats on a standardised audio track, which become incrementally faster over five levels, each lasting 2 min. Stepping begins with right foot up, left foot up, right foot down, left foot down, but the leading leg is swapped at each level. A commercially available 3-height adjustable (15, 20, or 25 cm) standard exercise step was used for iSTEP testing, with step height at roughly half tibial length (measured from head of fibula to lateral malleolus) and rounded down to determine height of step during iSTEP testing. Boys were advised to work as hard as possible to complete the test; only stopping if they were too tired or unable to continue. Outcomes measured were: iSTEP level achieved before stopping (level 0–5); total duration of stepping (0–10 min); completion achieved (all levels) or not. Performance of BwH on iSTEP were compared to available normative data.<sup>7</sup>

### 4.2 | 25-Level 10 m-ISWT

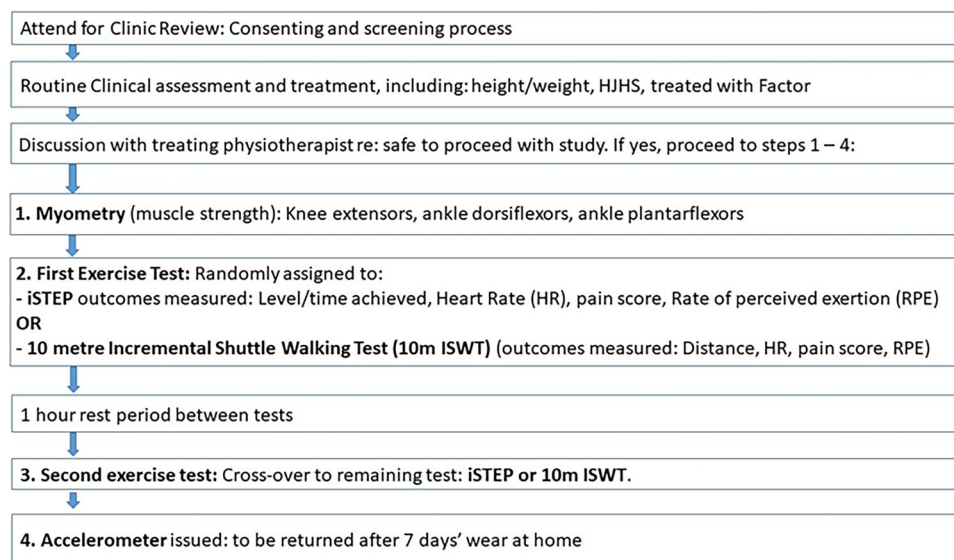
The 10 m-ISWT<sup>8</sup> has been validated in children.<sup>9</sup> The test version used in this protocol was the 25-level 10 m-ISWT, validated by Elkins et al.<sup>10</sup> for testing exercise capacity in healthy individuals and patients (who regularly exceed the 15 level 10 m-ISWT).<sup>11</sup> Each participant was allowed to start running at any point in order to keep pace with the beeps. Testing stopped when they were unable to go any further, or if they did not match pace for two consecutive shuttles. The primary 10 m-ISWT outcome was total distance achieved by each child. To compare performance with unaffected peers, the Pinho reference norms were used.<sup>12</sup> Distance (m) =  $342.06 + (283.07 \times \text{sex}) + (83.61 \times \text{age}) - (22.22 \times \text{BMI})$ ; age = years; sex: 1 = boys, 0 = girls; BMI = kg/m<sup>2</sup>. Pinho's cohort were from two Portuguese schools, permitted to participate in sport more than twice weekly; sample size 130 (60 males, 70 females), mean boys age 13.67 yrs (2.81), BMI kg/m<sup>2</sup> 20.18 (3.09), and mean height cm 163 (.16). Impairment and activity measures (secondary outcomes) were collected to identify potential impact on performance in 10 m-ISWT or iSTEP.

### 4.3 | HJHS

The HJHS version 2.1 is a validated measure of ankle, knee and elbow joint health<sup>2</sup> for children in both clinical and research settings.<sup>2,5,13</sup> Scores range from 0 to 124; lower scores indicating better joint health.

### 4.4 | Myometry

A hand-held Lafayette Dynamometer was used to measure maximum voluntary isometric muscle strength in Newton-metres (Nm) of knee



**FIGURE 1** Study protocol.

extensors, and ankle plantar and dorsiflexors, following a standardised protocol.<sup>14</sup> Muscle strength was converted to torque.

$$\text{Torque (Nm)} = 9.8 \times \text{muscle strength (kg)} \times \text{lever length (m)}$$

Individual muscle strength and torque varies between individuals, however asymmetry in Torque may have a substantial impact on outcome of functional exercise tests. Sympercents were used to describe any asymmetry between (L) and (R) muscle torque.<sup>15</sup>

#### 4.5 | Accelerometry

ActiGraph GT3X bi-axial accelerometers were worn for 7 days and returned in a stamped addressed envelope. They were removed at night or for any water-based activities. Instructions were consistent with comparable accelerometry studies in BwH.<sup>16–18</sup> Minimal wear time of 9 h a day for 4 days was used to guide inclusion of each participants' accelerometry data.<sup>19</sup> Data from each accelerometer were uploaded and using ActiGraph Firmware, standard accelerometry outcomes were calculated, including average daily time spent in sedentary, light, moderate and vigorous activity were calculated as determined by Evenson et al.<sup>20</sup> Sampling rate was set to 15 s epoc. Evenson cut off points used: Sedentary 0–100; Light 101–≥ 2295; Moderate ≥ 2296; Vigorous ≥ 4012.

#### 4.6 | Statistical analysis

Z-scores for BMI were calculated from the UK 1990 standards<sup>21</sup> and processed using the R language.<sup>22</sup> We fitted linear (for 10 m-ISWT) and logistic (for completed iSTEP) univariable and multivariable regression models. Normality and homogeneity of variances were assessed using

the Shapiro-Wilk and Bartlett tests. Model selection was based on minimising the Bayesian Information Criterion<sup>23</sup> in a stepwise way. Missing values in accelerometry variables were dealt with via multivariate imputation with chained equations.<sup>24</sup>

Factors that were considered likely to influence the iSTEP and 10 m-ISWT were included in the analysis. These included: age; type and severity of haemophilia; height and weight zBMI (standard deviation score); joint health (HJHS)- both total and ankle scores; asymmetry in lower limb muscle Torque (myometry) for ankle dorsi and plantarflexors and knee extensors and time spent in MVPA (accelerometry).

Spearman's rank correlation coefficients were calculated between 10 m-ISWT distance for each factor. We compared 10 m-ISWT distance walked data to the Pinho 2019 reference equation for the 10 m-ISWT.<sup>12</sup> iSTEP completers were compared to non-completers using a *t*-test, and demographic variables were compared across disease severity groups using analysis of variance. Odds of completion of iSTEP between our population and 24 healthy boys mean age 10.5 was explored.<sup>12</sup> All computations were performed using the R language version 4.3.<sup>22</sup>

## 5 | RESULTS

Forty-three boys median age 10 (10 mild/moderate, 26 severe, 7 inhibitors) were recruited; no boys withdrew from the study and all participated in both performance measures. Boys with an inhibitor were younger than those with severe or mild/moderate disease. Total HJHS was zero for 15/43 boys (35%); mild/moderate 6/10 (60%), severe 8/26 (31%) and inhibitor 1/7(14%) (Table 1).

Two accelerometers were not returned. Thirty-six boys met the wear time validity of 9 h a day for 4 days, with an average of 6.0 valid days of accelerometer data. There were 216 subject days with an average of 4.3 days on weekdays with at least 10 h and an average

**TABLE 1** Demographics of participants and HJHS.

Characteristics	Mild/Moderate (n = 10)	Severe (n = 26)	Inhibitor (n = 7)	Total group (n = 43)
Median age (years) (range)	10.7 (6.7-14.6)	10.3 (6.3-14.6)	8.6 (6.2-11.2)	10.0 (6.2-14.6)
Mean age (years)	11	10.5	8.73	10.28
Median height (cm) (range)	143.4 (115-169)	142.7 (112.2-175)	141.6 (113.9-150)	142.3 (112.2-175)
Median weight (kg) (range)	39 (20.7-59.85)	34.1 (19-71.9)	32.8 (17.4-46.8)	33.5 (17.4-71.9)
Median BMI (kg/m <sup>2</sup> ) (range)	17.5 (13.5-25.8)	16.3 (13.2-23.5)	16.3 (13.4-21.6)	16.8 (13.2-25.8)
<b>BMI centiles:</b>				
95 <sup>th</sup> and above (obese)	1	1	1	3
85 <sup>th</sup> -94 <sup>th</sup> (overweight)	0	3	1	4
5 <sup>th</sup> -84 <sup>th</sup> centile (normal)	8	19	4	31
Below 5 <sup>th</sup> (underweight)	1	3	1	5
<b>Diagnosis:</b>				
Haemophilia A	7	20	7	34
Haemophilia B	3	6	0	9
<b>Treatment:</b>				
Prophylaxis	6	26	n/a	32
On demand	4	0	0	4
Novel treatment	n/a	n/a	7	7
Bleeds (previous year)	2	11	0	13
Known joint arthropathy	0	0	1 (right knee)	1
Median HJHS score (range)	0 (0-2)	1 (0-12)	3 (0-8)	1 (0-12)
Median HJHS_LL score <sup>a</sup> (range)	0 (0-2)	1 (0-8)	3 (0-8)	1 (0-8)

<sup>a</sup>Of the 43 boys, 28 (65.1%) had HJHS lower limb scores >0.

of 1.4 days on weekends with at least 10 h. For analysis, we used the accelerometry data as covariates (not as outcomes) and we imputed values that were lost.

Boys with an inhibitor were more active and had a higher percent of total recorded counts (8.06%) and higher average time per day spent in MVPA (67.2 mins/day) than those with mild/moderate or severe disease. Boys with severe disease spent on average the most time in sedentary behaviour (Table included in supplement).

## 5.1 | iSTEP

Half tibial step height was 15 cm for 41 boys and 20 cm for 2 boys. Over half were able to complete all 5 levels of the iSTEP (23/43) (53%), with: 6/10 (60%) mild/moderate, 16/26 (62%) severe, and 1/7 (14%) children with inhibitors. The remaining 20/43 (47%) boys did not complete the iSTEP, with younger children less likely to complete the test. Levels completed data were skewed towards five suggesting a ceiling effect. Regression analysis thus focused on odds of completion versus non-completion rather than the number of levels (Table 2).

Data for healthy boys was compared to the iSTEP completion data in this study. Logistic regression demonstrated that the odds of completing the iSTEP was significantly lower in BwH, compared to typically developing boys, after adjusting for height and height of step used ( $\exp(B) = .075$ , 95% CI,  $p = .007$ ).

**TABLE 2** Comparison of iSTEP non-completers and completers.

	Non-completers (n = 20) Number of boys (Percent) Median age in years (range)	Completers (n = 23) Number of boys (Percent) Median age in years (range)
<b>Age</b>	Mild/Moderate n = 4 (20%) 8.25 (6.7-12.6)	Mild/Moderate n = 6 (26.09%) 13 (9.3-15.1)
	Severe n = 10 (50%) 9.05 (6.3-12.7)	Severe n = 16 (69.57%) 11.7 (7.9-14.6)
	Inhibitor n = 6 (30%) 8.6 (6.2-11.2)	Inhibitor n = 1 (4.35%) 10.5
<b>Total (n = 43)</b>	47% (20)	53% (23)
<b>Age</b>	8.77 (6.2-12.7)	11.8* (7.9-14.6)
<b>HJHS</b>	2 (0-8)	1 (0-12)
<b>BMI</b>	16.50 (13.4-25.8)	16.90 (13.2-23.5)

\*Significant difference at  $p < .05$ .

## 5.2 | 10 m-ISWT

Children with mild/moderate haemophilia ran further than those children with severe disease or an inhibitor, although those children with an inhibitor were also younger. Whilst disease severity affected

**TABLE 3** 10 m-ISWT distance by disease severity and age.

Disease Severity	10 m-ISWT	
	Median age in years (range)	Mean distance in metres (range)
Inhibitor (n = 7)	8.6 (6.2-11.2)	725.7 (330-1280)
Mild/moderate (n = 10)	10.8 (6.7-15.1)	1103.0 (710-1560)
Severe (n = 26)	10.3 (6.3-14.6)	927.7 (510-1510)
Total (n = 43)	10.0 (6.2-15.1)	962.8 (330-1560)

**TABLE 4** Predictors of distance completed on the 10 m-ISWT.

Covariates	Estimate	Std. Error	p-value
Intercept	-340.39	211.68	.116
zBMI	-94.77	23.77	.00
Disease Severity mild/moderate	307.79	102.47	.005
Disease Severity severe	154.41	85.47	.079
% MVPA	30.98	10.66	.006
Age	90.42	14.65	.000

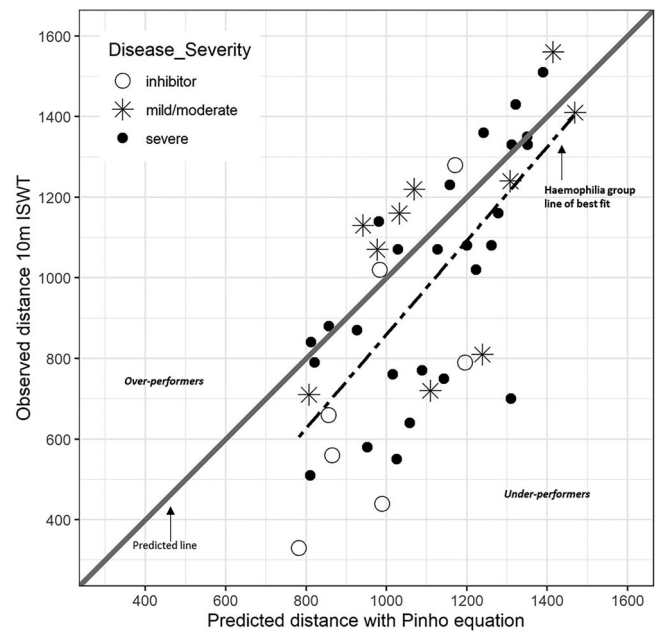
10 m-ISWT distance covered, the HJHS did not; suggesting it is not sensitive enough to identify functional impairment. Older children ran significantly further than younger children and those children with a higher zBMI did less well than those with a lower zBMI. For every absolute increase of 1SD of zBMI, the distance ran was reduced by 94.77 m.

Children who were more active as indicated by their percentage of time spent in MVPA also ran further than those who were less active. Model selection procedures resulted in a final model with age, zBMI, disease severity and %MVPA as predictors of distance completed on the 10 m-ISWT. HJHS, myometry and sedentary time were not included in the final model as they were not significant predictors for distance completed on the 10 m-ISWT (Tables 3 and 4).

An increase of 3% in % MVPA increased the 10 m-ISWT distance by  $31 \times 3 = 93$  m, which is almost equivalent to cancelling the effect of a 1SD zBMI on distance (-94.77 m) (Table 4).

We computed the predicted values of 10 m-ISWT for the BwH in our sample using the Pinho equation, which most matched our population. The equation accounts for age, gender and BMI. Compared to the Pinho cohort our group were younger, shorter and lighter. On average BwH performed worse than predicted, but 17/43 boys (40%) achieved a 10 m-ISWT distance that was greater than that predicted by the Pinho equation. The remaining 26/43 (60%) achieved a shorter 10 m-ISWT distance than predicted. A notable proportion 5/7 (71%) of boys with an inhibitor under-performed in comparison to their predicted distance (Figure 2).

Figure 3 displays the distance walked as predicted by the different factors that were significant in the model. The three lines which represent the three categories of MVPA are relatively close together. When age, severity and BMI are accounted for, the influence of a higher per-

**FIGURE 2** Observed versus predicted distance walked using Pinho equation for 10m ISWT.

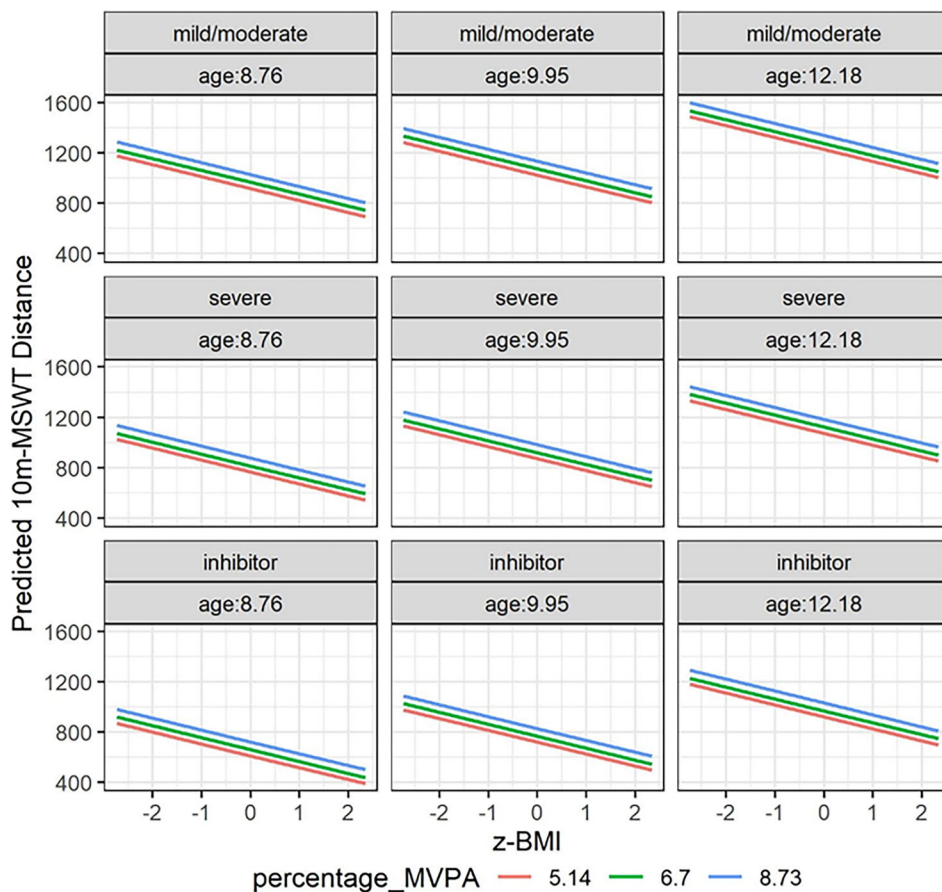
centage of MVPA has a relatively small impact on the distance walked (y-axis). In contrast the impact of increasing BMI by one standard deviation or by being younger or by having the classification of severe compared to moderate/mild haemophilia reduces the distance walked by a magnitude of about 100 m.

## 6 | DISCUSSION

This study set out to evaluate physical performance of BwH on two exercise tests (10 m-ISWT and iSTEP) and compare their performance with unaffected peers. We also looked to identify factors which predicted performance and might be amenable to rehabilitation, so that BwH might achieve their full physical potential, despite living with a significant chronic medical condition.

Performance on the two tests varied substantially between participants on both the tests, but notably, no BwH were able to complete all 25 levels of the 10 m-ISWT test, whilst more than half were able to complete all 5 levels of the iSTEP. This potential ceiling effect limits the clinical utility of the iSTEP in BwH since, it fails to discriminate performance in those with higher physical ability. Age was the only significant predictor for performance in the iSTEP, with older boys being more likely to do more levels or complete the test. The iSTEP thus potentially favours older participants and disadvantages younger boys who may have greater difficulties with co-ordination in continuing stepping or increasing pace of stepping.

The iSTEP, although previously established as both feasible and acceptable to clinicians and BwH, did not appear to provide useful clinical information in this study. Measures of modifiable factors that might be expected to influence iSTEP performance, for example, strength



**FIGURE 3** Factors affecting predicted distance walked in the 10 m-ISWT.

or torque of plantar flexors or habitual time spent in MVPA were not significant predictors of the iSTEP test. Thus, poor performance on the iSTEP could not be easily attributed to any factor other than age, which is not amenable to therapy.

By contrast, several factors were predictive of performance for the 10 m-ISWT. Older age and lower BMI were significant predictors of better performance on the 10 m-ISWT, supporting maintenance of a healthy weight in this population. For every absolute increase of 1SD of zBMI, the 10 m-ISWT distance was reduced by an average of 94.77 m.

Excess weight in haemophilia has been reported to contribute to restrictions in range of movement and loss of joint mobility adding to the cumulative burden of the disease and impacting on function.<sup>29</sup>

Time spent in MVPA was also a significant predictor; an increase of 3% in % MVPA increased the 10 m-ISWT distance by  $31 \times 3 = 93$  m, which is almost equivalent to cancel the effect of a 1SD zBMI on distance ( $-94.77$  m). BMI and MVPA are two clinically meaningful and modifiable factors that influence a child's performance on the 10 m-ISWT. This provides evidence to support clinicians to encourage BwH to maintain a healthy weight and an active lifestyle.

Promoting physical activity regardless of age and underlying disease is a WHO and haemophilia care priority as physical inactivity is a contributory risk for obesity and mortality,<sup>27,28</sup> with publications reporting sedentary behaviours comparable or reduced in comparison to their healthy peers.<sup>16,17,25,26</sup>

Importantly, children with different severities of haemophilia performed differently on the 10 m-ISWT, indicating this is a discriminative clinical measure in this population (the difference between boys with inhibitors compared to mild/moderate group was significant). Several impairment measures included in this study; the HJHS (total score and gait subset), and the myometry measures of strength and torque were not significant predictors for either performance measure. This may reflect the improved joint health of BwH associated with improved access to prophylaxis. It may be prudent to change focus to functional performance measures rather than impairment measures in routine assessment. Impairment measures may be useful for screening, following haemarthrosis or damage in a small proportion of BwH, or in those who do not have access to newer haemophilia therapies.

We identified several significant predictors of performance, but many were confounded by the interaction with age. Performance improved with increasing age for both iSTEP and 10 m-ISWT. Comparing clinical data with normative population data using age- and gender-specific equations takes account of increasing age and the impact of growth and neuromuscular maturation.

The predicted 10 m-ISWT distance in the Pinho equation is adjusted for age and gender and Figure 3 clearly demonstrates the difference between the predicted values, and the line of best fit for BwH. Interestingly, some boys did walk further than the predicted distance, supporting current management and education to improve

outcomes for some of this cohort. However, there were still many boys who were not able to walk the distance predicted for their age; a group of boys with severe disease and an inhibitor achieved much shorter distances.

This is the first study to evaluate two physical performance measures in BwH of all severities including those with an inhibitor on a novel agent and to provide insight into factors that may influence performance on them. Exercise capacity is a vital part of measuring disease severity and as medical management advances and bleeding frequency reduces physical performance measures offer a useful alternative to impairment measures.

Boys with mild/moderate disease achieved greater 10 m-ISWT distances than those with severe disease or an inhibitor. Until recently children with an inhibitor did not participate in P.E at school, let alone undertake exercise tests. Although they performed less well than their peers, their participation reflects a major achievement in medical management and highlights the potential for future improvements in functional capacity.

A systematic review of adults and children with haemophilia identified lower cardiovascular function compared with normative reference values. This is similar to our findings that on average BwH performed worse during their 10 m-ISWT than predicted.<sup>30,31</sup>

Muscle torque was not identified as a predictive factor for either performance measure in this study. Contrary to this, muscle strength of the knee extensors has been reported to show a significant correlation with performance on the 6-minute walk test and the timed up and down steps test.<sup>14</sup> This difference may be because age was not accounted for in the study and age-matched groups or normative reference values were not used for comparison. Australian and Dutch BwH have been reported to have comparable muscle strength to their peers. This may explain why muscle torque was not a predictor for either physical performance test in this study,<sup>32,33</sup> as perhaps BwH have comparable muscle strength to their peers.

## 6.1 | Limitations of the study

Boys with all severities of haemophilia were invited to participate in this study, however we used convenience sampling from clinic lists to recruit patients. There is a small risk our self-selected participants may represent a skewed picture of BwH in the UK. However, the wide range of performance observed suggests a balanced population. Further, no children with established joint arthropathy were included in this study and these physical performance measures may not be appropriate in boys with joint arthropathy.

## 7 | CONCLUSION

This study demonstrated that BwH were less likely to complete the iSTEP and performed less well on the 10 m-ISWT than age matched peers. HJHS and muscle strength were not able to predict performance on either test. Ceiling effects in the iSTEP and the fact that age was the

only significant predictor of performance suggested it was less useful as a test of physical performance in BwH. By contrast, performance in the 10 m-ISWT was predicted by disease severity, BMI, age and habitual levels of physical activity, providing useful focus for rehabilitation in individual boys. Despite the space required to conduct the 10 m-ISWT, it is a valuable measure of physical capacity and provides clinically meaningful information which can be interpreted using age-specific normative reference equations.

## AUTHOR CONTRIBUTIONS

Melanie Bladen- Chief Investigator, designed the study, major contributor in recruitment, acquisition of data, analysed and interpreted the data and drafted the manuscript Nicola Thorpe—Principal Investigator, collected the data and was funded by the Sir William Coxen Trust Fund, <http://opencharities.org/charities/206936>. Eleanor Main—contributed to data interpretation. Lucy Alderson—contributed to data interpretation. Mario Cortina-Borja-analysed the data and contributed to data interpretation. All authors contributed to manuscript revision. All authors approved the final manuscript

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

## ETHICS STATEMENT

Research ethics approval was provided by the Central London Research Ethics Committee (ref: 17/LO/1192) 2017.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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