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Using reference equations to standardise incremental shuttle walk test performance in children and young people with chronic conditions and facilitate the evaluation of exercise capacity and disease severity

Nicole Filipow ,[1] Melanie Bladen,[1,2] Emma Raywood ,[1] Elisabeth Robinson,[1] Deepti Chugh,[2] Helen Douglas,[1,2] Nikki Thorpe,[2] Rachel O'Connor,[3] Nicky Murray,[4] Eleanor Main [1]

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For numbered affiliations see end of article.

Correspondence to
Professor Eleanor Main;
e.main@ucl.ac.uk

ABSTRACT

Aims The aim was to evaluate whether standardised exercise performance during the incremental shuttle walk test (ISWT) can be used to assess disease severity in children and young people (CYP) with chronic conditions, through (1) identifying the most appropriate paediatric normative reference equation for the ISWT, (2) assessing how well CYP with haemophilia and cystic fibrosis (CF) perform against the values predicted by the best fit reference equation and (3) evaluating the association between standardised ISWT performance and disease severity.

Methods A cross-sectional analysis was carried out using existing data from two independent studies (2018–2019) at paediatric hospitals in London,UK. CYP with haemophilia (n=35) and CF (n=134) aged 5–18 years were included. Published reference equations for standardising ISWT were evaluated through a comparison of populations, and Bland-Altman analysis was used to assess the level of agreement between distances predicted by each equation. Associations between ISWT and disease severity were assessed with linear regression.

Results Three relevant reference equations were identified for the ISWT that standardised performance based on age, sex and body mass index (Vardhan, Lanza, Pinho). A systematic proportional bias of standardised ISWT was observed in all equations, most pronounced with Vardhan and Lanza; the male Pinho equation was identified as most appropriate. On average, CYP with CF and haemophilia performed worse than predicted by the Pinho equation, although the range was wide. Standardised ISWT, and not ISWT distance alone, was significantly associated with forced expiratory volume in 1 s in CYP with CF. Standardised ISWT in CYP with haemophilia was slightly associated with haemophilia joint health score, but this was not significant.

Conclusions ISWT performance may be useful in a clinic to identify those with worsening disease, but only when performance is standardised against a healthy reference population. The development of validated global reference equations is necessary for more robust assessment.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A strength of the study is the inclusion of incremental shuttle walk test (ISWT) data from two relatively large populations of children and young people with chronic conditions.
⇒ This study demonstrates a combined methodology for the evaluation of published reference equations for predicting ISWT distance in children and young people with chronic conditions.
⇒ The study's methods identify children who perform below a limit of normal on the ISWT, which may be used in the future for targeted intervention.
⇒ The accuracy of the comparison between ISWT distance and disease severity was limited by a lack of global, validated paediatric reference equations in the literature.
⇒ The absence of sex-based differences in ISWT performance within this population of children and young people limits the interpretation of exercise performance in women.

INTRODUCTION

The National Institute for Clinical Excellence estimates 1.7 million children and young people (CYP) in the UK live with chronic conditions.[1] As treatments advance, CYP with chronic conditions are experiencing better outcomes and full involvement in regular physical activity is possible.[2 3] An average of 60 min of physical activity per day over a week is recommended for all CYP, and many healthcare teams now incorporate routine measures of exercise capacity at clinical visits to assess, monitor and prevent disease progression

through the evaluation of levels or limitations of physical functioning.[4–7]

The incremental shuttle walk test (ISWT) is a well-established standardised field test for measuring near-maximal exercise performance in both adults and children.[8] Participants run a 10 m long shuttle track in time with incrementally faster beeps until they can no longer keep pace. The greater the distance ran, the better the exercise performance. In a large tertiary hospital in London, the ISWT is commonly used in clinical care and research to evaluate exercise performance in CYP with chronic conditions, for example, haemophilia and cystic fibrosis (CF).[3 9] Reduced exercise capacity in both conditions has been associated with poorer prognosis.[10–12] Furthermore, both conditions have been transformed by improvements in recent therapeutic advances and focus has evolved towards facilitating full active participatory lives.[13 14]

Substantial variation not only in distances observed during the ISWT can exist within and between individuals due to the physical impact of the chronic medical condition but also in relation to biological factors unrelated to disease (ie, age, sex or body mass index (BMI)).[13] Thus, the interpretation of ISWT performance, especially in CYP undergoing normal growth and development, is often hampered by a lack of normative value reference ranges developed using data from healthy CYP. This context is necessary to determine which CYP with chronic conditions would benefit from targeted rehabilitation interventions to minimise activity limitations and participation restrictions in their daily life.[3 7]

This study aimed to evaluate whether ISWT distance standardised against a normative reference range can be used to discriminate performance and assess disease severity in CYP with chronic conditions. The objectives were to (1) identify any published reference equations for ISWT distance involving healthy school-aged children and assess whether they were appropriate for benchmarking exercise capacity in CYP with CF and haemophilia in terms of range, correlation with demographics and proportional bias, (2) assess how well our two cohorts of demographically matched CYP with chronic conditions (haemophilia and CF) performed against the values predicted by the best fit reference equation and (3) evaluate whether standardised ISWT performance using the best fit reference equation was significantly associated with disease severity and whether there were distinguishing characteristics of those CYP who performed much lower than predicted for their age.

METHODS

Study design and setting

This was a cross-sectional analysis using existing clinical data and ISWT distances collected during (1) a feasibility performance measure study[9] in 42 boys with haemophilia (January–November 2018) from Great Ormond Street Hospital (GOSH) and (2) a prospective study of 74 boys and 71 girls with CF from three London paediatric CF centres (September 2018–July 2019) during a separate observational study[14] (figure 1). Inclusion and exclusion criteria for participation are defined in the respective publications.[9 14]

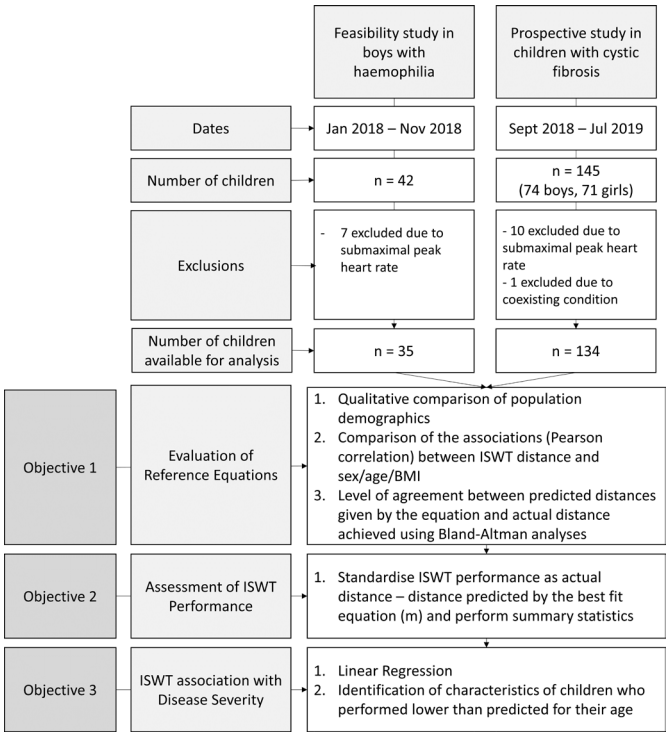

Figure 1 Flowchart of study protocol. BMI, body mass index; ISWT, incremental shuttle walk test.

The two chronic conditions are characterised as follows: haemophilia is an X-linked inherited bleeding disorder due to low or absent blood clotting factor VIII or IX (haemophilia A or B), which affects approximately 8000 people in the UK, almost all men.[15] Novel treatments have reduced annual bleed rates and allow boys greater exercise participation, further improving quality of life.[2 16 17]

CF is an autosomal recessive condition characterised by defects in chloride ion transport across cell membranes, affecting more than 10 500 people in the UK.[12] Reduced chloride transport in the lungs results in a build-up of thick, sticky mucous and repeated respiratory infections, which can lead to irreversible lung damage and early death.[18] Better exercise capacity is associated with improved lung function, specifically forced expiratory volume in 1 s (FEV_1) and has prognostic significance.[19]

ISWT data collection

An identical protocol for the 25-level ISWT was used for both groups of CYP, administered by their respective clinical teams. Participants were asked to walk and then run around two cones, set 9 m apart with an allowance of 0.5 m at either end for turning, resulting in a 10 m long shuttle track. They aimed to keep pace with incrementally faster beeps (beginning at 0.5 m/s and increasing by 0.17 m/s every level). The test was only stopped for clinical reasons

(eg, excessive coughing, drop in oxygen saturation of >5%, stress urinary incontinence or feeling faint), failure to keep pace for two consecutive runs or inability to keep going. Total distance achieved in metres was recorded as the sum of full 10 m shuttles completed. Peak heart rate (PHR), rate of perceived exertion (RPE) (measured with the Children's OMNI Scale of Perceived Exertion: walk/run scale) and demographic data including sex, age, height and BMI were recorded. Height and BMI were converted to z-scores using the WHO growth charts.[20]

Disease severity

In boys with haemophilia, disease severity was classified as per cent of normal levels of clotting factor: mild (5%–40%), moderate (1%–5%), severe (<1%). Disease severity was also measured using the haemophilia Joint Health Score (HJHS; V.2.1), a validated measure of the ankle, knee and elbow joint health.[21 22]

In CYP with CF, disease severity was measured using FEV_1, the most frequently used primary outcome measure in this cohort. FEV_1 was converted to %predicted using the Global Lung Function Initiative reference equations.[23] Disease severity was represented as: severe <70%, mild/moderate >70% FEV_1% predicted.

Reference equations

Studies reporting ISWT reference equations in healthy CYP were identified from a review of the literature. In January 2021, a search was conducted in MEDLINE database using the search terms and Boolean operators: ('reference equation' OR 'normative values') AND 'incremental shuttle walk' AND ('children' OR 'paediatric').

Statistical analysis

Data exclusions

Only CYP reaching a valid near-maximal effort test (PHR >180 bpm) were included in the analysis to ensure quality control, as failure to reach PHR could stem from a variety of reasons unrelated to illness, including lack of motivation. CYP with coexisting conditions were also excluded.

Comparison of equations

The single most appropriate equation for our population was identified through a combined approach: (1) comparison of demographics and methods used during the ISWT, (2) comparison of associations (Pearson correlation values (r)) between ISWT distance and demographics (ie, sex, age, BMI) and (3) level of agreement between predicted distances given by the equation and actual distance achieved using Bland-Altman analyses.[24]

Evaluation of ISWT performance

Using the best fit equation, standardised ISWT performance was calculated as the difference between actual distance completed minus predicted distance given by the reference equation in metres and is termed $ISWT_{ACT\text{-}PRED}$ throughout. $ISWT_{ACT\text{-}PRED}$ values were negative for those achieving lower distances than predicted.

Association with disease severity

Linear regression analyses were used to evaluate the relationships between measures of disease severity and both absolute ISWT distance and $ISWT_{ACT\text{-}PRED}$.[25] In the absence of previously determined limits of normal for the ISWT, we elected to use 1SD below the predicted values to define the lower limit of normal (LLN). Within a normal distribution, values falling below this threshold represent CYP who perform in the bottom 15.9% expected for a healthy population. Significance between those who performed above and below the LLN was assessed using unpaired t-tests for numerical variables and χ^2 tests for categorical variables. Analyses were stratified by sex.

Patient and public involvement

No patients involved; research study was designed in collaboration with three paediatric clinical physiotherapists.

RESULTS

Participant data

The two populations, haemophilia and CF, were analysed independently throughout the study. See figure 1 for study flow chart.

There were seven boys with haemophilia excluded due to submaximal PHR, resulting in a final dataset of 35 boys aged 6.3–15.1 years (online supplemental table 1). The average total HJHS score was low (mean=2.1); 12 boys (34%) had a score of zero, indicating normal joint health. ISWT distance was normally distributed, with a mean of 1040 m.

There were 11 CYP with CF excluded from analysis: one had a coexisting condition, and 10 had submaximal PHR. Thus, 134 CYP (66 boys, 68 girls) aged 5.9–16.7 years were analysed (online supplemental table 1). The range in FEV_1 was wide at 46–121 %pred (mean=89 %pred). ISWT distance was normally distributed, with a mean of 994 m.

Identification of ISWT reference equations

Three studies which met search criteria for ISWT reference equations in CYP were identified, termed Lanza, Vardhan and Pinho.[26–28] Equations for all three publications were derived from single centre, small sample populations and each varied in terms of geography, exclusion criteria, demographics of study participants and ISWT methodology (online supplemental table 1). The Pinho equation had a higher model fit (r^2=0.54) than Lanza (r^2=0.48), while Vardhan did not report a metric of fit. The equations are as follows:

Lanza: ISWT Distance (m)=845.599 + (sex * 193.265) + (age * 47.850) - (BMI * 26.179).

Vardhan: ISWT Distance (m)=28.930 + (40.784 * age) – (20.739 * sex) – (3.479 * BMI).

Pinho: ISWT Distance (m)=342.06 + (283.07 * sex) + (83.61 * age) - (22.22 * BMI).

Evaluation of reference equations

Comparison of study populations

A quantitative comparison of populations is described in online supplemental table 1. Demographic data in the Vardhan paper were not available for comparison,[26] except for BMI data, which were comparable with our populations. Compared with the Lanza and Pinho populations, the CYP with chronic conditions were slightly younger, shorter and smaller, and the gender distribution was different since haemophilia predominantly affects boys (ratio M:F: Lanza=13:14, Pinho=6:7, CF & Haemophilia=101:68). CYP with CF also had lower lung function. A higher post-test RPE compared with rest was observed for all study populations, although differences in scores (Borg vs OMNI) prevent a direct comparison of scale. Lanza used the 15-level ISWT, while Pinho and Vardan used the 12-level test, but Pinho permitted audio signals to continue until individuals reached their maximal effort, exceeding 12 levels if necessary. All tests measured the same endpoint, total distance completed, and thus the reference equations could be equally applied to the CYP with chronic conditions.

Comparison of correlations between ISWT and demographics

Our data, in accordance with Lanza, Vardhan and Pinho,[26–28] demonstrated a significant association between ISWT and age (haemophilia: r=0.58, p=0.00; CF: r=0.42, p=0.00), such that on average, older CYP achieved greater distances than younger CYP. There was also a negative association between ISWT distance and BMI (haemophilia: r=−0.47 p=0.00; CF: r=−0.19 p=0.04), which was also observed in the Lanza and Pinho studies but not in the Vardhan study.

There was no significant sex difference in ISWT distance in our CYP with CF (p=0.13), which contrasted with all three prior studies that identified a greater ISWT distance in boys compared with girls. As such, the male reference equations were used to predict ISWT distance in girls with CF to avoid overestimating ISWT performance.

Agreement between reference equations

The Vardhan equation was excluded from further consideration since the average predicted ISWT distance (girls=445 m, boys=450 m) was substantially lower (~600 m on average) than the actual distances completed by CYP with Haemophilia or CF (combined mean=1009 m) (online supplemental table 1). By contrast, both the Lanza and Pinho reference equations predicted ISWT performance in ranges that resembled those observed in our cohorts.

There was a significant proportional bias between the ISWT distances achieved by CYP in our cohorts and those predicted by both the Vardhan and Lanza reference equations (figure 2A,B), such that the predictive equations systematically overestimated actual performance for lower distances and underestimated performance for the higher distances (ie, exceeded differences of 300 m at the extremes). Furthermore, the Lanza study excluded children who participated in sport more than two times a week, potentially resulting in a reference equation biased towards less active children. Thus, both the Lanza and Vardhan equations were excluded from any further consideration or analyses.

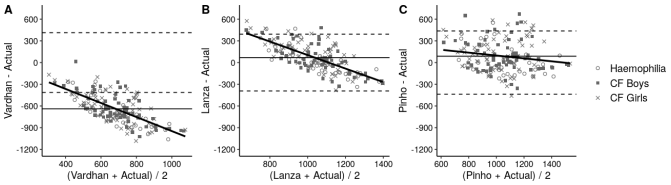

Figure 2 Bland-Altman plots showing the agreement between actual and predicted ISWT values. (A) Vardhan, (B) Lanza, (C) Pinho. Horizontal lines indicate the mean difference (solid thin), mean±1.96 times the SD (dashed line) and zero (dotted line). Solid thick diagonal line is a linear regression. CF, cystic fibrosis; ISWT, incremental shuttle walk test.

While a proportional bias also existed between our study population and the Pinho equation, it was relatively low, and minimal by comparison with the other two reference equations. This did not preclude the Pinho equation from possible clinical use and confirmed it as the most appropriate equation to evaluate performance in our populations (figure 2C). Thus, the remaining analyses use standardised performance against the Pinho equation only.

Evaluation of ISWT performance in CYP with CF and haemophilia (using Pinho equation)

On average, CYP with haemophilia and CF performed slightly worse during the ISWT than predicted by the Pinho male equation, however the range was wide; some CYP performed exceptionally well, while others performed very poorly (mean (range) of standardised performance $ISWT_{ACT\text{-}PRED}$ (m): haemophilia=−83.5 m (−610 to 188), boys with CF=−89.9 m (−672 to 358), girls with CF=−112.0 m (−586 to 461)) (figure 3). There were 6 boys with haemophilia, 7 boys with CF and 13 girls with CF who performed below the LLN, identified as 1 SD below the predicted values (1 SD=359.78 m, reported by Pinho) (figure 3C).

Association of ISWT performance with disease severity (using Pinho equation)

Linear regression

There were no significant associations between disease severity measures and actual ISWT distance completed (figure 4A). However, there was a significant relationship between FEV_1 in CYP with CF and standardised $ISWT_{ACT\text{-}PRED}$ performance; those who performed poorly compared with predicted had significantly lower FEV_1 (figure 4B ii,iii).

There was a slight trend towards a higher total HJHS score with lower standardised $ISWT_{ACT\text{-}PRED}$ performance in boys with haemophilia, which was not observed with actual ISWT distance, however, this was not significant (figure 4i). There was no significant difference between

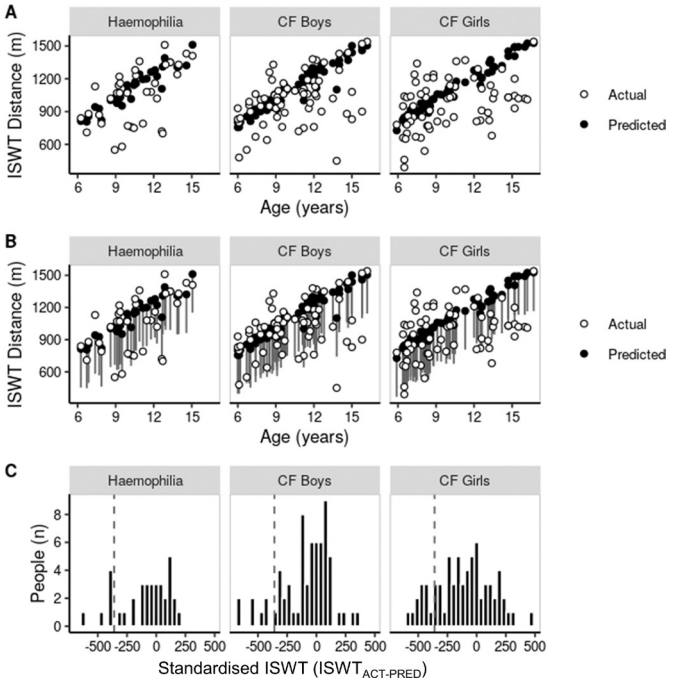

Figure 3 Comparison of standardised ISWT distance using the Pinho male reference equation for boys with haemophilia (left), boys with CF (middle) and girls with CF (right). (A) Association between age and ISWT, (B) association between age and ISWT and the lower range of normal indicated by 1SD (359.78 m) below predicted (grey lines). (C) Histograms showing standardised ISWT distance (individual differences from predicted ISWT). Values above zero indicate enhanced performance compared with predicted and values below zero indicate reduced performance. Dotted line indicates lower limit of normal (LLN), with values left of this line consistent with those performing in the bottom 15.87% of a healthy population. CF, cystic fibrosis; ISWT, incremental shuttle walk test.

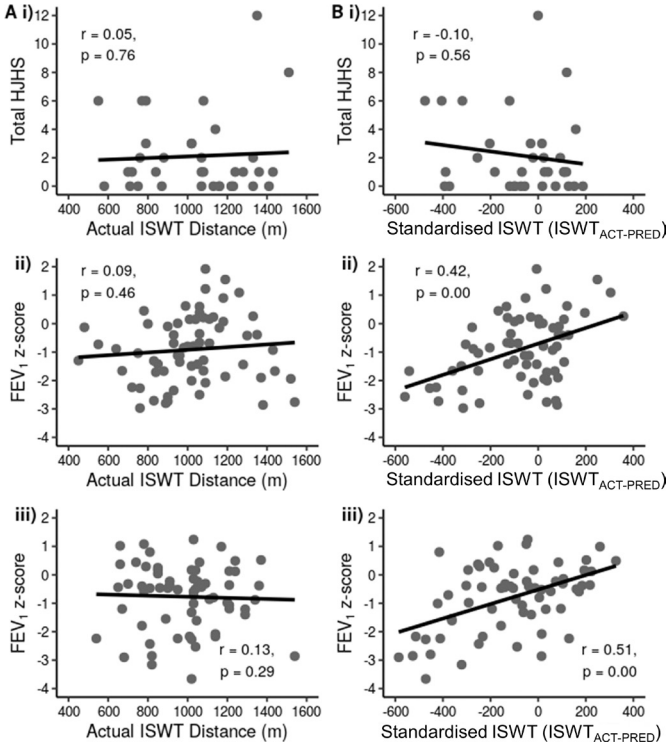

Figure 4 Relationships between disease severity and ISWT performance. (A) Actual distance completed, and (B) standardised ISWT distance, compared with (i) total HJHS in haemophilia, (ii) FEV_1 %predicted in boys with CF, (iii) FEV_1 %predicted in girls with CF. Correlation (r) and significance (p) of results displayed on figures. CF, cystic fibrosis; FEV_1, forced expiratory volume in 1 s; HJHS, haemophilia Joint Health Score; ISWT, incremental shuttle walk test.

haemophilia disease severity measured by clotting factor and actual or standardised ISWT performance (p=0.32).

Characteristics of CYP performing below the LLN

CYP with CF who performed below the LLN of ISWT distance were significantly older compared with those who performed above this threshold, but this was not observed in boys with haemophilia (online supplemental table 2). Height and BMI were not significantly associated with low exercise performance in either cohort, although boys performing below predicted had a slightly higher BMI.

Both boys and girls with CF who performed below the LLN had significantly lower lung function than those above (online supplemental table 2). There were higher HJHS scores in boys with haemophilia who performed below the LLN, however this difference was not significant (online supplemental table 2).

Notably, a proportion of the CYP who performed poorly on the ISWT only had mild or moderate disease (one boy with haemophilia, five boys and eight girls with CF). These CYP might, therefore, be expected to have potential for targeted improvement in exercise capacity (online supplemental table 2).

DISCUSSION

This study allowed for the evaluation of standardised $ISWT_{ACT-PRED}$ performance in two populations of CYP with chronic conditions, by comparing ISWT performance against predicted values calculated from published paediatric reference equations. None of the three reference equations were entirely suitable for clinical use in these cohorts of CYP with haemophilia or CF, due to incompatibility of population sex, distance ranges and proportional bias. However, the male Pinho equation mitigated these biases the most in predicting performance and was able to, and appropriate for, interpreting and discriminating ISWT performance, and assessing disease severity in CYP with chronic conditions.

Standardised $ISWT_{ACT-PRED}$ distance was significantly associated with lung function in CYP with CF, such that those with low FEV_1 had reduced exercise capacity. Conversely, actual ISWT distance alone was not associated with lung function in CYP with CF, reinforcing the need for, and potential clinical usefulness of, standardising performance against predicted distances given from reference equations. This is especially relevant as CYP-prescribed

CFTR modulators become healthier, maintain normal lung function and demonstrate an improvement in exercise capacity. Consequently, the need for reference/normative values will be more necessary.

In boys with haemophilia, HJHS was slightly higher in those performing below the predicted range, however, the small sample size may have influenced the significance of the results. Previous studies[21 29] have observed correlated HJHS scores and disease severity, but as medical treatment for haemophilia has improved, HJHS may no longer be sensitive enough. Conversely, it is possible that exercise capacity is not associated with disease; Australian and Dutch children with haemophilia demonstrated comparable cardiovascular fitness to their healthy peers using the 20 m shuttle run and bicycle ergometer.[30–32] Further investigation is necessary to confirm any association between disease severity and standardised exercise capacity.

All three reference equations predicted that boys would perform better than girls, yet our population did not show a significant sex difference in ISWT distance. This might be explained by the age of our cohort. A previous study concluded that before puberty, there was no sex difference in habitual activity of children with CF.[33] Most of the CYP with CF in this study (80%, n=107) were aged below 13 years, which may correlate to less advanced pubertal stage although we did not evaluate this within the scope of this study. Furthermore, a European-IDEFICS study showed sex-specific and age-specific differences in physical fitness in typically developing children aged 6–10.9 years with boys performing better.[34] This would suggest that girls in this study were more active than predicted. However, without a validated equation for ISWT, it is difficult to make conclusions on the activity status of girls with CF and further investigation is necessary.

Exercise capacity is an important marker of disease severity,[10 12 19] and promoting physical activity is an integral part of the management of CYP with both haemophilia and CF.[2 16 35] The LLN is necessary to identify CYP underperforming at point of test in a clinic. These are currently not defined or incorporated into the ISWT reference equations; however, in this study, 1 SD below the predicted ISWT not only highlighted 14 CYP who had mild/moderate disease but also underperformed on the ISWT. In practice, these CYP may benefit from enhanced exercise management or have additional problems undetected by traditional measures of disease severity that may benefit from further investigation. However, 1 SD below predicted ISWT does not consider any potential age or BMI-related changes in normal variability, as they were not reported in the original studies. As such, it is not clear if the threshold of 1 SD is appropriate across all demographics, limiting the interpretation of the results. Reference equations that include limits of normal should be developed for clinical use in providing more personalised exercise assessment and management.

The accurate evaluation of standardised ISWT distance in CYP with chronic conditions and its association with disease were ultimately limited by a lack of validated reference equations. This lack of research within young populations limits the interpretations of changes in physical capacity and its relation to normal growth and development versus disease. Furthermore, it was unclear how best to use the reference equations where sex differences were not observed, which limits the interpretation of exercise capacity in women in this study. Moreover, the majority of CYP assessed in the study were familiar with the ISWT having performed it previously at regular exercise testing undertaken at GOSH; however, a learning effect may have been present for some CYP newer to the test, which may have introduced bias into the actual distances achieved.

CONCLUSION

Only one of the three existing published reference equations for ISWT distance in typically developing healthy children was appropriate for benchmarking performance in CYP with chronic conditions (Pinho).

It was encouraging that CYP with haemophilia and CF performed only slightly worse on average in the ISWT, than healthy peers. In CYP with CF achieving ISWT distance below the LLN for their age, weight and BMI, there was a significant association with disease severity that was not seen with absolute ISWT distance alone. Thus, standardised $ISWT_{ACT\text{-}PRED}$ may be very useful for evaluation of exercise performance in similar populations. The development of global ISWT distance reference equations from large, geographically diverse populations is essential for accurate standardisation and assessment of exercise performance in all CYP, including those with chronic conditions, in order to facilitate and support safe exercise prescription in the future.

Author affiliations
[1]Physiotherapy, Great Ormond Street Institute of Child Health, University College London, London, UK
[2]Physiotherapy, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK
[3]Paediatric Cystic Fibrosis Centre, Barts Health NHS Trust, The Royal London Hospital, London, UK
[4]Paediatric Physiotherapy, Royal Brompton Hospital, London, UK

Twitter Emma Raywood @fizzyocf and Eleanor Main @MainEleanor

Contributors EM, NF, MB, ERa, DC, HD conceptualised the study. ERa, HD, MB, DC, NT, RO'C, NM performed data collection. NF carried out the formal analysis. NF, MB, EaR, ERo, EM, HD wrote and edited the manuscript. EM supervised and acted as guarantor. All authors approved the final version of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Central London Research Ethics Committee (ref:17/LO/1192), and from London-Brighton and Sussex, NREC (ref:18/LO/1038). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement Data are available upon reasonable request. The data are stored at Great Ormond Street Hospital within the secure Digital Research Environment. Access is possible with permission from the corresponding author upon reasonable request.

ORCID iDs
Nicole Filipow http://orcid.org/0000-0003-3544-6136
Emma Raywood http://orcid.org/0000-0002-0993-5115
Eleanor Main http://orcid.org/0000-0002-9739-3167

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