Physical Performance of Children and Adolescents with Longitudinal Fibular Deficiency

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Thesis presented for the degree of

Master of Research

Submitted 8th October 2018

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Preface

The following thesis includes 4 chapters. Chapters 1 and 2 contain a literature review of current evidence pertaining to the understanding of physical performance in Longitudinal Fibular Deficiency (LFD), particularly in regard to children and adolescents. **Chapter 1** considers the background of the condition, including the anatomical features of LFD, the incidence and aetiology of the condition, and the published classification systems currently available. **Chapter 2** explores and critiques the available evidence published on management of LFD including the various outcomes. The discussion of outcomes is divided between outcomes in adults with LFD and outcomes in children and adolescents with the condition. **Chapter 3** is an original research paper presented in the exact format of the manuscript that has been submitted to the Journal of Pediatric Orthopaedics. This paper is a cross-sectional study assessing physical performance in children and adolescents with LFD using standardised, validated objective measures, and the comparison of these results to unaffected peers using the same measures. **Chapter 4** is a systematic, in-depth discussion of the findings of this thesis. Each novel finding of the research paper is explored according to both the implications for clinical practice and research; and includes both the recommendations of this thesis in addition to a discussion of the limitations. The references for chapters 1, 2, and 4 are presented together after Chapter 4, whilst the references for Chapter 3 are presented at the end of the submitted manuscript as per publisher guidelines.

Thesis Aims

The aim of this thesis is to improve the understanding of the physical performance of children and adolescents with a diagnosis of Longitudinal Fibular Deficiency (LFD). In particular, through the use of standardised, validated objective outcome measures this thesis seeks to provide novel, relevant and clinically important information regarding the physical performance of these children and adolescents that has not been previously available.

The objectives of this thesis are to:

- Critically appraise the available literature on LFD, including all areas relevant to physical performance such as management and functional outcomes, with particular reference to children and adolescents (Chapter 1-2).
- Assess the physical performance of children and adolescents using validated objective measures and to compare this performance with that of unaffected peers using the same measures. In addition, to compare the physical performance of children and adolescents with different subgroups of LFD (Chapter 3).
- Evaluate the findings pertaining to physical performance of children and adolescents with LFD, and explore the limitations, recommendations and implications for clinical practice and future research. (Chapter 4).

Abstract

This thesis builds on the current available literature concerning the physical performance of children and adolescents with Longitudinal Fibular Deficiency (LFD).

Currently, the understanding of physical performance in LFD is predominantly limited to small studies of low methodological quality that have used non-validated or subjective-report measures. The only examples of physical performance being assessed with objective measures and compared to norms are limited to the adult population of LFD, which demonstrated adults with LFD perform at a much lower level than their unaffected peers. It is unknown if this is also true in children with LFD.

Therefore, a cross-sectional study was conducted to compare the physical performance of 39 children and adolescents with LFD, to 284 unaffected peers of the same age, using validated objective measures. Children and adolescents with LFD performed significantly worse than their peers in strength, walking performance, performance on stairs, and balance. The difference between the physical performance of children and adolescents with LFD and those without was smallest in younger children and greatest in the older adolescents.

These findings suggest close monitoring of children with LFD may assist in the timing of interventions to potentially improve such performance. Further research is recommended, both of a longitudinal nature to understand how the physical performance of children with LFD changes with age, in addition to research assessing the efficacy of interventions aiming to improve physical performance in these children and adolescents.

Candidate Statement

I, Eleanor Morris, certify that the work in this thesis entitled "Physical Performance of Children and Adolescents with Longitudinal Fibular Deficiency" has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree to any other university or institution other than Macquarie University.

I also certify that the thesis is an original piece of research and it has been written by me. Any help and assistance that I have received in my research work and the preparation of the thesis itself have been appropriately acknowledged.

In addition, I certify that all information sources and literature used are indicated in the thesis. The research presented in this thesis was approved by Sydney Children's Hospital Network Human Research Ethics Committee (LNR/17/SCHN/121) and by Macquarie University Ethics Review Committee (Reference number: 5201827003073).

Eleanor Morris

Signed: _____

Date: 7.10.18

Supervisor Statement

As the supervisor of Eleanor Morris' Master of Research work, I certify that I consider her thesis "Physical Performance of Children and Adolescents with Longitudinal Fibular Deficiency" to be suitable for examination.

Dr Verity Pacey

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Date: 7.10.18

Acknowledgments

First and foremost, to my fabulous and fearless supervisor, Verity Pacey. Thank you for having faith in me, by both encouraging me to “take the masters plunge” in the first place and maintaining that faith throughout this process. Thank you for your endless patience, encouragement, and advice; for knowing when I needed a gentle push or when I just needed a kind word - I could not have done this without you. Your wisdom and insight were invaluable, and the sacrifice of your time to help me has not gone un-noticed. Thank you!

To Louise Tofts, who had the idea for this project in the first place. Thank you for supporting me and making this project possible. Thank you for valuing meaningful clinical research alongside clinical practice and fighting for opportunities to make it happen. Thank you for your encouragement, advice and patience! Thank you also to the rest of my beloved Limb Clinic team, particularly Adrienne Epps, Margaret Patterson, and Kate Knox. Thank you for supporting this project and making your own sacrifices of time and energy to ensure it was a success. It is a pleasure working alongside you.

To my orthopaedic colleagues, particularly Oliver Birke, David Little, Paul Gibbons, Michael Bellemore and Quang Dao. Thank you for all that you have taught me about LFD, and for being so patient with my endless questions. A particular shout out to Paul for his remarkable efforts in helping our participant recruitment. This is one of the bigger cohorts of individuals with LFD in a clinical study and that is in large part thanks to you!

To Roger Adams, statistician extraordinaire! Thanks for going the many extra miles to help me make sense of this data and to de-mistify the scary world of statistics with humour and enthusiasm.

To my colleagues/friends/fellow-students at CHW and MQ – I'm so thankful for 2 years of encouragement from all of you, and to the 1000 Norms team, Marnee McKay, Jennifer Baldwin and Joshua Burns – thank you for your support and advice.

My beloved family and friends. Thank you for loving me and supporting me in this endeavour. I know this project has taken a lot of our time together away from us, and I'm so grateful for your understanding and for encouraging me to make the most of this opportunity. Thank you also for putting up with me talking about this project so much – I know you're all experts on LFD now, and I couldn't be happier about it!

Finally, to all of the children and adolescents with LFD and their families who participated in this project. Thank you for the sacrifice of your time, and your commitment to this project. You are the most remarkable bunch of young people and it is such a joy and privilege to work with you. I know hospital visits are far from fun, and yet you've all shown such grace and enthusiasm, I am truly humbled. Know that you are the reason that this project has meant so much to me and I hope this is just the start of us making a real and positive difference to your lives.

List of Abbreviations

AAOS FAM	American Academy of Orthopaedic Surgeons Lower Limb Module
AAOS LLM	American Academy of Orthopaedic Surgeons Foot and Ankle Module
ACL	Anterior Cruciate Ligament
ADL	Activities of Daily Living
ANOVA	Analysis of Variance
ANcOVA	Analysis of Covariance
ASAMI	Association for the Study and Application of Methods of Ilizarov
BMI	Body Mass Index
CFD	Congenital Femoral Deficiency
CI	Confidence Interval
CM	Centimetres
CSF	Congenital Short Femur
CT	Computed Tomography
CTEV	Congenital Talipes Equino Varus
HREC	Human Research Ethics Committee
IKDC	International Knee Documentation Committee
LEFS	Lower Extremity Functional Scale
LFD	Longitudinal Fibular Deficiency
LLD	Leg Length Difference
M	Metres
MFAQ	Musculoskeletal Functional Assessment Questionnaire
N	Newtons
NHMRC	National Health and Medical Research Council
NM^{-1}	Newton Metres
PCL	Posterior Cruciate Ligament

PedsQL	Pediatric Quality of Life
PFFD	Proximal Femoral Focal Deficiency
QLQ	Quality of Life Questionnaire
QOL	Quality of Life
ROM	Range of Motion
SCHN	Sydney Children's Hospital Network
SD	Standard Deviation
SF36	Short Form 36
SIGAM	Special Interest Group in Amputee Medicine
SMFA	Short Musculoskeletal Functional Assessment
TSCS-R	Tennessee Self-Concept Scale-Revised
WAIS-R	Wechsler Adult Intelligence Scale-Revised
6MWT	Six Minute Walk Test

List of Tables

Chapter One:
Longitudinal fibular deficiency

1.1. Description of condition

Longitudinal Fibular Deficiency (LFD) is the most common congenital long bone deficiency.[1-3] Also known as Congenital Fibular Deficiency, Fibular Hypoplasia or Fibular Hemimelia, LFD is defined as the complete or partial absence of the fibula according to the most widely accepted classification (Achterman & Kalamchi).[4,5] The condition, however, is typically not an isolated entity, but includes a varying spectrum of dysplasia of the lower limb as outlined below in Table 1.[3,4,6-10] Individual presentations of individuals with LFD vary greatly within this spectrum from mild isolated hypoplasia of the fibular, through to severe limb deformity with many of the associated anomalies.[4,5] LFD can occur bilaterally in 3-29% of cases,[4,6,11-13] and the upper limb is involved in 15-20% of cases.[4,6] Individuals with bilateral LFD are far more likely to experience upper limb involvement (41% in comparison to 9% of those with unilateral LFD).[6] Most studies quote a gender bias in the LFD population of 0.5-0.8:1 females to males.[4,6,11,14-17] The right side is more often affected than the left.[4,6,11,15,18] Due to the rare nature of this condition, there are a relatively small number of studies that provide prevalence data. A number of these studies have a very small cohort of individuals with LFD and all features are not consistently reported. This leads to large discrepancies reported in certain anatomical variations as seen in Table 1.

TABLE 1. Anatomical variations associated with LFD

Location	Anatomical Variation	Prevalence in LFD
Femur/Pelvis	Proximal Femoral Focal Deficiency	21-26%[4,12]
	Coxa Vara	7-10%[4,6]
	Coxa Valga	21%[6]
	Abnormalities of the Proximal Femur[α]	4-68%,[4,6,12,15]
	Congenital Shortening of the Femur	47% -85.4%[4,6]
	Dysplasia of the Distal Femur[β]	77-100%[4,19-21]
Knee	Genu Valgum	31%[4]
	Hypoplasia or Aplasia of the Anterior Cruciate Ligament	94-100%[22-24]

TABLE 1. continued. Anatomical variations associated with LFD		
	Hypoplasia or Aplasia of the Posterior Cruciate Ligament	45-60%[22-24]
	Altered Lateral Collateral Ligament and Biceps Femoris Tendon	100%[20]
	Altered Popliteus Musculotendinous Complex	50%[20]
Knee (cont)	Patellae Alta or Hypoplasia	99-100%[4,20]
	Absent Patella	2%[4]
	Recurrent Patellar Subluxation	6%[4]
	Absent/Altered Menisci	60%[20]
Fibula	Aplasia	42-53%[4,6,13,21]
	Hypoplasia	47-58%[4,6,13,21]
Tibia	Abnormality of the Proximal Tibiaχ	94%[24]
	Anterior/Anteromedial Bowing with of the Tibia	48%[4]
Ankle	Ball and Socket Mortise	24-58%[4,13,25,26]
	Tibiotalar Ankle Joint	7%[4]
	Absence of the Peroneal Artery	(Incidence not reported)[27]
	Absence of the Tibial Artery	1-10%[11,12]
	Equinovalgus Hindfoot	50-59%[4,13]
	Equinovarus Hindfoot	4-10%[4,6]
	Congenital Talipes Equino Varus (CTEV)	16%[#11]
Foot	Tarsal coalition	43-80%[4,14,21]
	Absent Lateral Rays	58-77%[4,6,13,15,21]
	Hypoplasia	80%[4]
Other	Upper Limb Anomaliesδ	15-20%[4,6]
	Cardiac Anomalies	1%[4]
	Renal Anomalies	1%[4]

α Includes varus/valgus deformities of the femoral neck and femoral retroversion.

β Includes (absent/poorly formed intercondylar notch, shallow trochlear groove and hypoplastic lateral femoral condyle).

χ Includes convexity of the proximal tibial epiphysis with absent/hypoplastic tibial spine.

δ Includes absent ulnar rays and syndactyly of remaining digits, dislocation of the head of radius, and entire absence of an upper limb.

* Includes only a cohort of LFD patients who had undergone Syme amputation.

3% of this cohort had a diagnosis of "fibular hemimelia syndrome" with a radiological normal fibula.

LFD is commonly associated with congenital femoral deficiency (CFD), which is divided into two diagnoses; Proximal Femoral Focal Deficiency (PFFD), occurring when there is dysplasia of the iliofemoral joint, and Congenital Short Femur (CSF), when the iliofemoral joint is normal, but there is dysplasia or shortening in the femur alone.[1,9,22] To meet the criteria of CSF or PFFD, an individual must have at least 10% shortening of the affected femur.[9] Unfortunately LFD prevalence studies have not always consistently reported whether femoral involvement met the criteria of CSF or PFFD, and furthermore there are also reported cases of individuals with LFD who do not meet this diagnostic criteria of CFD but still have some degree of femoral shortening.[4,6] As represented in Table 1, the reported prevalence of individuals with concurrent CSF and LFD varies between 47 and 85%, however this large difference is likely due to both inconsistency in use of the diagnostic criteria and the variation in number of participants included in the reporting studies as highlighted above.

The severity of femoral and fibular deficiencies is not correlated.[4] When individuals with PFFD are excluded, the tibial shortening correlates to the degree of fibula shortening and the extent of deformity of the lateral part of the foot.[4] Whilst remaining shorter, growth of the affected limb in both LFD and CFD is typically in proportion to growth of the unaffected limb.[4,6]

As a result of the strong association between LFD and CFD, the two are often considered to be variations of a more global lower limb deficiency, sometimes referred to as postaxial hypoplasia.[5,21] For this reason there have been reported cases that present with some features of LFD but have a radiological normal fibula. This presentation has given rise to the term "Fibular Hemimelia Syndrome"[28] to reflect the overlap between conditions. These cases will not be included in the following discussion, instead only those that meet the Achtermann & Kalamchi classification, hence complete or partial absence of the fibula, will be referred to by

the term LFD. LFD is typically diagnosed after birth by clinical features and supported by plain radiography, however a diagnosis can be made by prenatal ultrasonograpy.[1,29,30]

1.2. Incidence

LFD incidence data is difficult to acquire due to the overlap between presentations of femoral and fibular deficiencies. There are only 2 published incidence data sets. The first, based on all live births in the Province of British Columbia, Canada, during the years 1952 to 1984, reported 6 children per million live births having a fibula defect.[31] Twenty five per million live births were reported as having a femoral defect, and 11 per million to have a fibula/tibia defect but in sufficient detail was provided to determine if individuals in these latter categories included children with LFD, and if so how many. Hence the incidence of 6 per million live births is likely to be an underestimate. The second publication draws on data from a nation-wide German birth registry between April 2000 and April 2004. It reports an incidence of 22.9 per million live births. Again, it was not clear if this number included children with both fibular and femoral deficiencies.[32] Many authors quote Edinburgh birth statistics for incidence of LFD, however there is insufficient detail in this publication to differentiate between cases of LFD and alternate lower limb deficiencies, and hence an accurate incidence rate is not possible from this dataset.[33] Whilst rare, LFD is the most common congenital deficiency of all the long bones, documented as more common than deficiencies of the radius, femur or tibia.[2,3,12]

1.3. Aetiology

The cause of LFD is unclear.[1] Embryological studies suggest the condition originates from a defect occurring in the 6-8th gestational week.[18,34] Proposed mechanisms include defects in the apical ectodermal ridge, defects secondary to an absent anterior tibial artery, and the "developmental fields" theory.[7,35] The first mechanism describes LFD resulting from a disruption to the apical ectodermal ridge during the 8th week of embryonic life. This is

significant as the apical ectodermal ridge acts as a "signaling center" which ensures proper limb development in the embryo.[7] This disruption is thought to be due to one of a variety of environmental mechanisms. Experimentally, LFD has been reproduced in animal models with exposure to radiation, insulin and dietary deficiency during this period of embryonic development.[7] The second proposed mechanism, is that the anatomical deficiencies seen in LFD are due to the absence of the tibial artery. This has been reported in between 1 and 10% of the population with LFD,[11,12] however it has also been reported as a normal finding in 5% of the general population unaffected by LFD.[7] A final theory is that of "developmental fields" where it is hypothesized that the fibula "drives" deformity in its "field," or surrounding anatomical area, which includes the femur, cruciate ligaments and lateral aspect of the foot.[7] Whatever the initial cause, the rate of inhibition of growth of the fibula and related surrounding anatomy has been shown to begin in utero and remain constant throughout prenatal and postnatal growth periods.[30]

Regardless of these mechanisms, the vast majority of cases of LFD are reported to occur sporadically, with no identifiable cause or genetic association.[35] There have been rare isolated cases where LFD has occurred in the presence of chromosomal anomalies or other broader developmental syndromes.[7] One author refers to this latter group as "Syndromal hypo/a-plasia of the fibular", however this term has not been adopted elsewhere.[35] In the case of these rarer, "syndromal" presentations of LFD; autosomal dominant, autosomal recessive, and x-linked transmission have all been documented.[1,7,36]

1.4. Classification

A number of classification systems for LFD have been described to differentiate individuals with varying presentations of the condition (Table 2). First proposed in 1952, initial classifications considered only the proportion of fibula present,[4,18] however subsequent classifications from 1993 onwards have also included the extent of deformity in the foot and

ankle, in addition to leg length difference and upper limb involvement. Most classification systems were developed as treatment algorithms highlighting different management pathways, with all stemming from the orthopaedic surgery discipline. The Achterman and Kalamchi classification remains the most widely used in LFD published literature, however the newest classifications from Birch, and Paley are also referred to in recent orthopaedic publications.[37,38]

TABLE 2. LFD Classification Systems *Images used with permission (Appendix 6).*

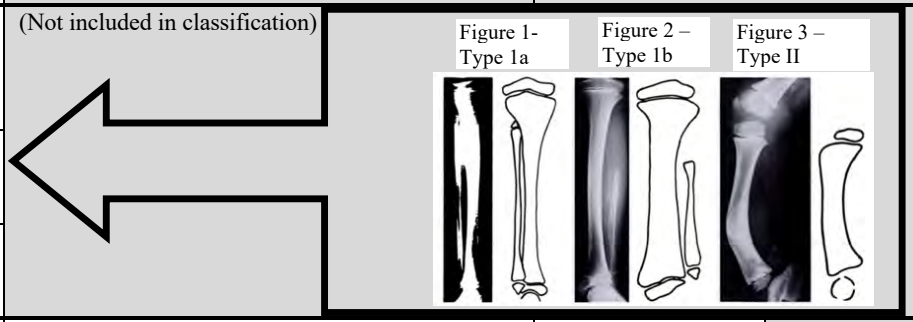
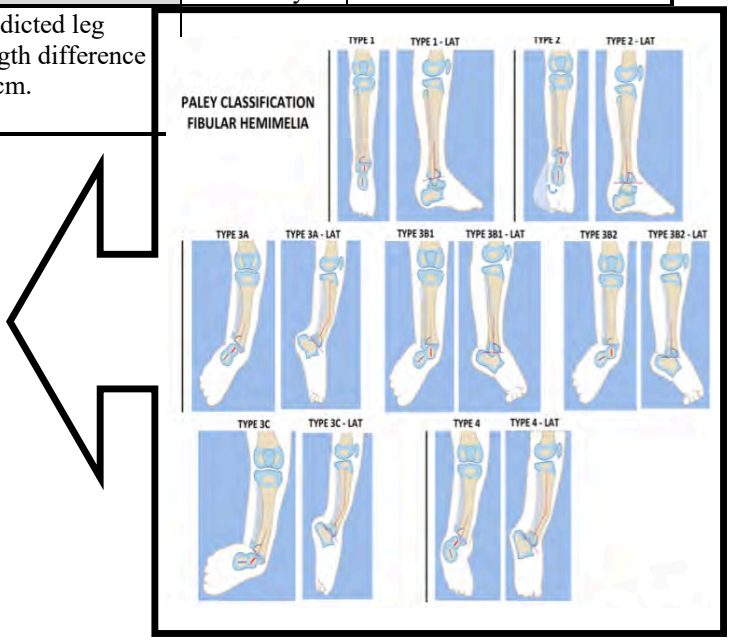
	Fibular Deficiency		Foot/Ankle Deformity	Leg Length Difference	Upper Limb Anomaly	Recommended Surgical Management
1952 Coventry[18]	Fibula Present	Type 1: Hypoplastic Fibula	(Not included in classification)	(Not included in classification)		Equalisation
	Fibula Absent	Type 2: Rudimentary /Absent Fibula				Early Amputation
	Bilateral Presentation	Type 3: Bilateral fibular deficiency or presence of "associated anomalies"				Probable limb preservation
1979 Achterman & Kalamchi[4]	Fibula Present	Type 1a: Proximal Fibular epiphysis distal to the level of the tibial growth plate. Distal fibular growth plate proximal to the dome of the talus	(Not included in classification)			Limb Equalisation
		Type 1b: Partial proximal absence of the fibula: 30-50%. Distally the fibula does not support the ankle.				
	Fibula Absent	Type 2: Complete absence of the fibula or the presence of only a distal, vestigial fragment.				Foot Ablation
1993 Letts & Vincent[39]	Unilateral Fibular Deficiency		Minimal foot deformity (and minimal femoral shortening)	Type A: < 6cm shortening	(Not included in classification)	Fibular analogue excision, shoe lifts
				Type B: 6-10cm shortening		Fibular analogue excision, shoe lifts, limb-equalizing procedures
			Major foot deformity (and/or major femoral shortening)	Type C: >10cm shortening		Fibular analogue excision, foot amputation/prosthesis
	Type D: Bilateral Fibular Deficiency		(Not included in classification)	(Not included in classification)		Fibular analogue excisions, bilateral foot amputation/prosthesis.
2003 Stanitski[13]	Fibula Present	Type I: Nearly normal fibula	H: Horizontal tibiotalar joint	(Not included in classification)		
			V: Valgus tibiotalar joint			
		Type II: Small or miniature fibula	S: Spherical (Ball and Socket Tibiotalar joint)			
	Fibula Absent	Type III: Complete absence of fibula	C: Presence of Tarsal Coalition			
			1-5: Number of foot rays			

TABLE 2. continued. LFD Classification Systems					
2011 Birch[6]	(Extent of fibular deficiency not specified in classification.)	Type 1: Foot of at least 3 rays that can provide a stable weight-bearing base for walking, with or without re-positional reconstructive procedures.	1A: 0-6% overall shortening	(Not included in classification.)	No treatment, orthotics, contralateral epiphyseodesis (CE)
			1B: 6-10% overall shortening		CE or single lengthening
			1C: 11-30% overall shortening		1-2 lengthenings +/- CE or extension prosthesis
			1D: >30% shortening overall		>2 lengthenings or extension orthosis +/- amputation.
		Type 2: A foot that is unsuitable for salvage irrespective of the extent of limb shortening.	(Not included in classification.)	2A: Intact	Early amputation
				2B: Bilateral upper extremity deficiency.	Foot ablation deferred until substitution patterns for upper limb function established.
2016 Paley[40]	Fibula is slightly shorter at proximal end but may be completely absent.	Type 1: Ankle appears normal.	Predicted leg length difference <5cm.		
	Fibular is short compared to the tibia at the level of the ankle joint.	Type 2: Foot can achieve plantargrade position. No fixed equinovalgus but dorsiflexion may be limited. Most have a ball and socket ankle joint. Patient stands and walks in valgus.			
	The condition can occur with (3b1) and without (3b2) the presence of a fibula.	Type 3: Fixed equino-valgus deformity 3a: Malrotation of the ankle joint (distal tibial epiphysis is in procurvatum-valgus, Lateral Distal Tibial Angle is decreased, and anterior distal tibial angle is increased. 3b: Malunited subtalar coalition. Calcaneus is lateral to the talus and often tilted into valgus. 3c: 3a and 3b features present			
	(Not specified in classification.)	Type 4: Subtalar coalition malunited in varus. Distal tibial is usually also maloriented into procurvatum and valgus.			



Chapter Two:

Management and Outcomes of Individuals with Longitudinal fibular deficiency.

2.1. Management of LFD

The management of individuals with LFD is documented to involve a broad range of surgical, and conservative methods. These methods may be grouped under 3 categories that are directly related to the common anatomical differences seen in individuals with LFD and described above. These include the management of leg length difference, the management of foot and ankle deformities and the management of knee deformity and instability.[1] The choice of method(s) utilised is influenced by the underlying anatomy, preference of the individuals with LFD and/or their families, and the preference and experience of the treating health professionals.[1] A significant volume of literature has been published to date to compare these various treatment approaches to LFD and will be discussed throughout this chapter. The management of hip deformity is also an important consideration; however, this is predominantly a treatment goal of individuals with PFFD rather than LFD. Therefore, this is more helpfully considered in the context of PFFD, hence will not be discussed directly within this thesis.

2.1.1. The management of leg length difference

The challenge of leg length difference in individuals with LFD can be managed by a variety of conservative or surgical methods. These methods include no treatment, orthotic/prosthetic build-ups, epiphyseodesis on the unaffected side to slow/stop growth, leg-lengthening procedures via external-fixator frames or intra-medullary nails, or amputation at the ankle joint (Syme amputation).[1,6,26] A combination of both conservative and surgical strategies is commonly employed, most notably the combination of Syme amputation to allow for a prosthesis to equalize leg length. As demonstrated in Table 2, the predicted leg length difference is one of the key factors used in the decision-making process of clinicians and families when choosing an appropriate management pathway for individuals with LFD.[6,7,26] Typically, a predicted difference of greater than 20 centimetres results in a recommendation

of amputation, whereas smaller differences will be treated either with leg lengthening, guided-growth or orthotics, however this recommendation is contested.[7,16,26,40-44]

2.1.2. The management of foot and ankle deformity

Children with LFD are noted to have variations in foot pathology from a rigid foot deformity including CTEV, a relatively normal foot, or an unstable foot or ankle, as demonstrated in Table 1. These anatomical variations have been widely discussed and a number of classifications have been developed to quantify the extent of the deformity (Table 2). Management of the foot and ankle in LFD has focused on obtaining a plantigrade and painless foot, with various surgical and orthoprosthetic strategies being recommended.[6,16] These strategies include orthotic support, bracing and physiotherapy, or surgical intervention including joint reconstruction and osteotomies to correct bony deformities.[6,7] Ankle amputation (Syme) may also be performed in the event that a foot is deemed "non-salvageable" or in the presence of a large leg length difference (as described in the preceding section).[43,45] Feet with fewer than 3 rays are more likely to be deemed "non-salvageable."[6]

2.1.3. The management of knee deformity and instability.

Common anatomical differences around the knee in LFD include hypoplasia of the distal femur, cruciate deficiency, changes in the size or position of the patella and other variations in the soft tissues that attach to the lateral femur or fibula (Table 1). These anatomical differences commonly produce impairments of malalignment, particularly genu valgum, and reported knee instability in this population.[22,46] As reported in Table 1, genu valgum occurs in approximately one third of the LFD population. It may be managed with corrective osteotomies and/or guided-growth techniques. Frequently these techniques will be used to simultaneously correct both this malalignment and the individual's leg length difference as described above.[1,45]

The presence of knee instability, particularly in an antero-posterior direction is seen in almost all individuals with LFD, however the best management pathway of this instability is not clearly established. Confounding the picture is the discrepancy between objective signs of instability and participant-reported instability during activities. Objective instability assessed by means of validated clinical tests such as the Lachman, Anterior Glide, Pivot Shift Test or the use of the KT-1000 knee arthrometer has been shown to be present in between 90 and 100% of individuals with LFD.[23,47,48] In contrast, reported instability during activities of daily living by individuals with LFD differs from between 0 and 50%.[19,23,47,48] The presence of pain associated with this instability is also highly varied with reports ranging between 0 and 60%,[19,47,48] however when present, pain has been associated with degenerative changes of the knee[20] or with soft tissue injuries.[23] In light of this variability, it is generally recommended that no intervention be performed in individuals who do not report concurrent instability symptoms.[1] Cases of symptomatic instability have been managed with conservative methods including physiotherapy and bracing of the knee, minor surgical procedures not involving ligamentoplasty (ligament reconstruction) including arthroscopy and meniscal repair or debridement, or major surgical procedures incorporating a ligamentoplasty (ligament reconstruction or "construction").[46,49,50]

2.1.4. Treatment Success

The level of success achieved by these treatment strategies has been explored to varying degrees in published literature to date. Success has typically been described in terms of participant satisfaction with treatment, the occurrence of complications or resolution of the non-favourable anatomical outcome such as leg-length discrepancy or malalignment, and symptomatic and functional outcomes. Participant and clinician satisfaction with various treatment strategies and the occurrence of complications will be outlined below. The symptomatic and functional outcomes of these management approaches will be discussed in greater detail in the following section.

2.1.4.1. Treatment Satisfaction

Participant satisfaction with treatment has been recorded in numerous studies, predominantly by means of non-validated participant report measures. Satisfaction with lengthening procedures alone is reported to vary between 53-100%.[16,51] Comparison between satisfaction levels of amputation and lengthening procedures varies from no difference in overall satisfaction,[52] 88% satisfaction with amputation versus 55% satisfaction with lengthening,[17] and 100% satisfaction with amputation versus 50% satisfaction with lengthening.[53] The large variations are likely due to the heterogenous nature of the LFD population, the large variation in treatment methods and the absence of validated outcome measures used to assess this satisfaction. Furthermore, the timeframe between treatment and question is not reported, nor the method of delivery of the questions or the specific nature of the questions asked. The only study to use a validated outcome measure to assess treatment satisfaction, used the Prosthesis Evaluation Questionnaire and found in general those who had undergone an amputation were generally satisfied with their prosthetic management, with younger adults tending to be more satisfied than older adults.[52]

2.1.4.2. Treatment Complications

A large number of treatment complications in this population group have been documented in the published literature. The published frequencies of all varied complications are described in Table 3. The timeframe after surgery that these complications arose is not consistently reported. The residual leg length difference after lengthening procedures was reported as being measured by differing methods in each study referenced below, including radiograph, measuring blocks, CT scan or no method reported. The reasons reported for residual leg length difference post lengthening surgery varied from participant preference to the occurrence of other complications. Other bony alignment complications including genu valgum, bowing of the tibia, other bowing/angulation/axial deformity, delayed union and

malunion were reportedly measured by radiograph but no additional clarification of measurement was provided. All other complications listed below were measured according to clinician report alone, with no evidence of assessor blinding.

TABLE 3. Complications of Management Strategies in LFD

Management Strategy	Complication			Incidence of Complication
Syme Amputation & Prosthetic Management	Bone-related complications	Genu valgum		8%[15] or mean of 4[0 44]
		Unequal knees		8%[15]
		Bowing of tibia		8%[15]
		Non-union		13%[53]
		Stump deformity		8%[15]
	Soft tissue-related complications	Callosity over anterior tibia		20%[44]
		Callosity over medial malleolus		10%[44]
		Necrosis of skin flap		3%[17]
		Wound breakdown		8%[15]
		Skin Breakdown secondary to prosthesis		9%[17]
		Minor skin irritation secondary to prosthesis		8 – 100%[15,44]
		Pain or sensitivity of stump		33%[53]
		Migration of heel pad		8 – 38%[15,17,44]
	Other	Needing to repair/replace broken prosthetic parts		100%[44]
Lengthening Surgery	General bone-related complications	Residual Leg Length Difference	1-3cm	10-86%[15-17,51,54]
			>3cm	19 – 60%[15-17,54]
		Bowing/angulation/axial deformity of lengthened bone.		20% - 78%[12,15,53,55]
		Delayed union		3 – 36%12,[17,38,51,55-57]
		Premature union		10 – 11%[12,53]
		Painful hypertrophic non-union of the fibula		14%[54]
		Revision osteotomy required		10 – 18%[17,54]
		Bone-graft dislodgement		10%[53]

TABLE 3. continued. Complications of Management Strategies in LFD			
		Fractures	3 – 66%[12,15,17,42,51,56,]
		Failure of hardware	12 – 27%[17,53,56]
	Soft tissue-related complications	Decreased range of motion / Soft tissue contractures /Joint stiffness	8 – 75%[12,15,16,37,38,42,51,53,55-58]
		Pressure sores	9%[56]
		Pin site infections	10% - 100%[12,15,17,38,42,51,53-56]
		Wound haematoma	9 – 10%[17,53]
		Hypertrophic scar	8%[55]
		Calf swelling	9%[57]
		Transient paraesthesiae	8 – 25%[15,53,55,56]
		Compartment syndrome	8%[55]
	Specific hip complications	Hip subluxation	9%[17]
	Specific knee complications	Knee subluxation	9 – 20%[16,17,38,42,57]
		Knee valgus deformity/Genu valgum	3 – 30%[16,38,42]
	Specific ankle/foot complications	Equinus deformity	10 – 44%[12,16,37,53,58]
		Equinovalgus	45%[17]
		Valgus hindfoot	10 – 25%[37]
		Unspecified recurrent foot deformity	21%[38]
		Rocker bottom feet	17%[38]
	Other complications	Pain after activity	8%[56]
		Depression	11%[56]

2.2. Symptomatic and Functional Outcome Measures in LFD

The majority of published literature regarding LFD to date has focused on the outcomes of varying surgical interventions as outlined above. These studies have predominantly been retrospective in nature, and of low-quality according to the NHMRC Levels of Evidence (Appendix 4.). Furthermore, the outcomes of these studies have frequently been based on non-validated outcome measures. The following will review the adult literature followed by the paediatric literature according to the type and quality of symptomatic and functional outcome measures reported.

2.2.1. Symptomatic and Functional Outcome Measures in Adults with LFD

A number of cross sectional and retrospective cohort studies have assessed individuals with LFD during adulthood to give an indication of long-term prognosis of these interventions (Appendix 1.). Outcomes assessed include pain and instability, range of motion, strength, gait pattern, walking and stair performance, activities of daily living and participation in sport, quality of life, social status and psychological factors.

Pain and Instability

Pain and instability have predominantly been measured by non-validated outcome measures. A retrospective study found 63% of 36 adults reported pain post lengthening surgery,[16] and a cross-sectional study of 10 adults post amputation reported 20% of participants reporting some general limb instability but no reports of pain.[44] In contrast, a cross-sectional study of 62 adults reported no significant difference between pain levels of adults who had undergone amputation or limb lengthening procedures.[52] However all of these studies used non-validated reporting methods of pain.

One cross-sectional study used a validated hip and knee pain questionnaire and found that in 11 adults with LFD and ACL deficiency, there was no difference between pain scores of

affected and unaffected legs in either lower limb joint.[47] With only one instance of a validated measure being used to measure pain or instability, and the use of it in a such a small case series, it is difficult to extrapolate a valid understanding of the true prevalence of pain and instability in adults with LFD.

Range of Motion (ROM)

Range of motion values have been reported in two studies, however neither study reported the method of measurement used. The first was a cross-sectional study that reported "full and normal" range of motion in 10 adults with LFD but did not specify which joints were measured.[7] The second, a retrospective study; reported in the context of recovery at a mean of 9 years post-lengthening surgery that only 25% of 32 adults had full range of motion at the knee, and 50% of the same group had normal ankle range of motion with a foot that could achieve the plantigrade position.[16] Without the use of a reliable and valid method of measurement, these findings should be considered with caution.

Strength

Strength has only been measured by one cross-sectional study in adults with LFD.[44] An isokinetic dynamometer was used to measure maximum torque strength of extension and flexion of both affected and unaffected knees in 10 adults who had undergone a Syme amputation. The mean maximum torque strength of extension of the affected knee was 63% of the unaffected side and mean maximum torque strength of flexion of the unaffected side was 73%. No comparison of strength measures to unaffected norms was performed.

Gait pattern and the presence of a limp

One cross-sectional study of 10 adults who had undergone an amputation reported that 9 of these adults had a normal gait pattern, whereas one had an antalgic gait pattern.[44] These findings were measured by means of a non-validated clinician report. Another cross-sectional

study, describing 11 adults with LFD and concurrent cruciate ligament insufficiency, found half reported a slight limp, however this was by means of the validated Lysholm Knee score and hence more trustworthy data.[47]

Performance of Walking and Stairs

One cross-sectional study used a non-validated participant report to describe that none of their cohort of 10 adults with LFD who had previously undergone an amputation had difficulty walking or running with their prosthesis and that 5 could tolerate distal loading through their stump for walking without a prosthesis.[44] A second cross-sectional study however, used validated objective measures to report both walking performance and performance on stairs in 20 adults with LFD.[59] The adults with LFD performed significantly worse than the unaffected population on the six minute walk test, with no significant difference between those who had undergone an amputation and those who had undergone lengthening surgery. Stair performance was assessed with the 'Stair test', a test requiring individuals to ascend and descend 20 steps 3 consecutive times. Similarly to walking performance, stair performance was worse in the LFD population than norms but no difference was demonstrated between those who had undergone different surgical pathways. This is one of the only studies to use validated objective functional measures in the LFD population, and one of the very few studies that have compared this objective data to similar performance data in unaffected adult peers. Hence this study has provided novel and valuable data in understanding the true impact of LFD in adults.

Activities of Daily Living & Sports Participation

General levels of function, activity and sport participation have been reported by numerous studies using both non-validated and validated participant-reported outcomes.

One retrospective study of 32 adults with LFD who had undergone lengthening surgery as children, rated the participant's level of activity on 4-point scale that was completed by the

assessing clinician.[16] Amongst these adults, 63% had limitation of activity and a further 9% had severe limitation of activity. A second study reported no difference between adults post-lengthening or amputation in terms of sports participation or activity restriction by means of a non-validated questionnaire. [52] Two other studies reported 9/10 adults with LFD participating in recreation sports as both children and adults,[44] and 9/11 adults with LFD and cruciate deficiency having relatively active hobbies by report of the participants.[47] The variation in method of collecting this data and paucity of detail makes comparison or inference difficult.

Two of the aforementioned studies also used validated participant-report outcome measures; the first used the Tegner-Lysholm Knee score to demonstrate that of 11 adults with LFD and concurrent cruciate deficiency, 2 had difficulty with stairs and 4 had difficulty with squatting, none required a supportive device to walk and 4 experienced instability with sport.[47] Overall participants achieved a mean score of 90/100, where 100 indicates best knee function and 0 worst knee function. Alternatively, another study used the validated Association of American Orthopaedic Surgeons' Lower Limb Module; and Foot and Ankle Module, to demonstrate that there was no difference in overall knee or foot and ankle function between adults with LFD who had undergone difference surgical management pathways and between those with LFD and normative reference values.[52] These two validated measures would suggest that adults with LFD generally have reasonable lower limb function in daily activities, however with such varied case numbers (11 and 62 respectively), and only cross-sectional studies available, further exploration of this outcome would be useful.

Social Status

Two studies have considered the social status of adults with LFD, however both used non-validated measures to do so. The first described no difference between adults with LFD who had undergone and amputation or limb lengthening surgery in participant reported levels of educational achievement, employment, income, public assistance or disability payments.[52]

The second, also by means of participant report, described how 10/11 adults with LFD and concurrent cruciate deficiency were employed in a broad range of occupations.[47] With no validated data it is difficult to extrapolate meaningful conclusions from this data.

Quality of Life

Quality of Life has been assessed in adults with LFD by 4 studies using various validated participant-rated outcome measures. The first, a cross-sectional study found no difference between 10 adults with LFD who had undergone an amputation and reference norms on the Quality of Life Questionnaire.[44]

A second study to use the Quality of Life Questionnaire to compare two groups of adults who had undergone with amputation or lengthening procedures found no overall difference between treatment groups.[52] Three studies have used the Short Form-36 to assess quality of life in adults with LFD. Two of these compared adults who had undergone amputation or lengthening and found no difference between groups. [52,59] Two of the studies also compared adults with LFD to reference norms, however one found those with LFD reported their quality of life as worse than norms,[59] whereas the second study found no difference between adults with LFD and norms.[47] The first had 30 participants, consisting of 87% recruitment compared to the second study with only 17% recruitment (11 participants). This may open the latter to selection bias and account for the variation. Additionally, one cross-sectional study previously mentioned also used the EuroQOL, finding adults with LFD reported their Quality of Life generally worse on both measures than the normal reference population but found no difference in report between LFD adults who were managed by either amputation or lengthening.[59] Another formally mentioned study reported quality of life in terms of a participant reported mean Co-morbidity Index of 5.63, where 100 indicates the highest level of co-morbidities and 0 no co-morbidities.[47] When synthesising the above findings, there is a clear trend revealing no difference in quality of life between varying treatment groups of

adults with LFD, however whether those with LFD have similar quality of life to unaffected adults is less clear.

Psychological Outcomes

Two studies have assessed specific psychological outcomes of adults with LFD, both of whom utilised validated participant-reported outcome measures. The first, using the Wechsler Adult Intelligence Scale-Revised and the Tennessee Self-Concept Scale-Revised, found no difference between 10 adults with LFD who had undergone Syme amputations as children and reference normative values on levels of intelligence and self-concept scores.[44] The second cross-sectional study found no difference in depression scores on the Beck Depression Inventory II between 62 adults with LFD who had undergone an amputation or lengthening surgery, and no difference when compared to 28 unaffected adults.[52]

Summary of Outcome Measures in Adults with LFD

In conclusion, the available evidence on adults with LFD comes exclusively from retrospective or cross-sectional studies, many of which include very small case numbers. Most outcome measures suggest only small differences between different treatment pathways. Considering the management pathway is typically chosen based on the severity of the presentation, this may indicate that individuals are receiving the most appropriate treatment, since the final result is equivalent. However, whilst data that compares adults with LFD to norms is scarce, the data that is available suggests adults with LFD are generally performing worse than unaffected peers when measured with objective measures of performance, but the performance is more variable, and typically more similar to unaffected peers when participant reported subjective measures are used.

2.2.2. Symptomatic and Functional Outcome Measures in Children with LFD

There are a much larger number of studies published that consider children with LFD, however the majority are in the context of surgical intervention with few using validated subjective outcome measures and almost none reporting validated objective measures (Appendix 2.). As with the adult literature, the majority are low level evidence (Level 3 or 4 evidence). Outcomes assessed include pain and instability, range of motion, strength, gait pattern, walking performance, activities of daily living, participation in sport and quality of life.

Pain and Instability

The prevalence of pain and other symptoms has been largely reported in children with LFD using non-validated measures. Three retrospective studies with 25, 43 and 119 participants reported the presence of pain in children with LFD using non-validated measures.[17,53,56] Two of these studies found children who had undergone lengthening generally had more pain than those children who had undergone amputation.[17,53] The third study found 37% of children had ankle or knee pain prior to limb lengthening procedures, however post-lengthening pain was not reported.[56] One cross-sectional study has used a validated measure to report pain levels in 32 children and adults with LFD. On the verbal rating scale of pain, those who had undergone an amputation reported less pain than those using an extension prosthesis who had not undergone an amputation.[41] This data would seem to suggest those who undergo an amputation have the least pain of varied treatment pathways, however with only 4 studies and only one using a validated measure, further investigation of pain in children with LFD both pre and post operatively is warranted.

Subjective knee instability is reported in one cross-sectional study of 66 children.[23] Seventeen percent of children reported some knee instability with general activity, and 3% reported that this instability was troublesome, however these reports were collected by non-validated

means. A second retrospective case series of 3 children found all of these children reported some knee instability.[50] The instance of objective antero-posterior knee stability is reported by 3 studies that formally assessed this stability with validated measures prior and post cruciate ligamentoplasty.[50,60,61] The validated measures used included the KT 1000 Arthrometer, the Lachman Test, Anterior Drawer Test, Pivot Shift Test and presence of cruciate ligaments on MRI and arthroscope. All of these measures were clinician-reported with no assessor blinding. All 3 studies reported instability on these measures prior to ligamentoplasty and nil instability after ligamentoplasty, in small numbers of adolescents (n=1-3). These findings would seem to suggest that ligamentoplasty is effective in minimising objective knee instability in children with LFD, however without assessor blinding there is a risk of bias. There is insubstantial evidence to understand the true incidence of subjective knee instability in this population.

Range of Motion

Numerous studies have reported range of motion in children with LFD, however this has predominantly been post-operative range of motion measured almost exclusively by non-validated outcome measures. Three retrospective studies with relatively small participant numbers (i.e. 2, 8 and 22) reported between 40 and 60% of children having a knee flexion contracture post lengthening surgery.[15,51,62] A fourth retrospective study of 11 children reported no incidence of flexion contracture post lengthening.[55] In all four studies, the method of measurement was not reported nor was the value of range of motion consistently reported.[15,51,55,62]

Three retrospective studies describe knee range of motion after cruciate ligamentoplasty surgery, again no method of measurement was reported in any of these studies.[50,60,61] Two of these studies were single case reports and the 3rd a case series of only 3 adolescents with LFD. When considering the results of these 5 individuals together, only 1 adolescent maintained

full knee extension post-operatively, and 3 achieved full flexion post-ligamentoplasty. Timeframes of measurement post-surgery were not consistently reported.

One retrospective and one prospective study report ankle position after surgical procedures. The former reported 22% of 119 children having a residual equinus or valgus ankle post-surgery whereas the latter reported 10% of limbs having persistent equinus.[37,56] A third retrospective study reported no incidence of equinus but found 27% of ankles had decreased range of motion post-lengthening.[55] None of these studies reported the method or value of measurement.

The only study that reports range of motion in children with LFD using a validated objective measure is a prospective study that describes 13 individuals with LFD who had undergone intramedullary lengthening procedures.[57] Range of motion of the hip, knee and ankle was measured by goniometry. Results demonstrated the range was not different between pre and post-operative measures other than some improvement in ankle plantarflexion post-lengthening. Hence in summary whilst there are a number of non-validated reports to suggest children lose ankle and knee range of motion after both lengthening and ligamentoplasty procedures, the only study to provide reliable data collected by a validated method indicates minimal post-operative difference.

Strength

Strength in children with LFD has been measured in two retrospective studies, one a single case study and the second a case series of 7 children. Both reported the presence of muscular atrophy but normal strength post-surgical intervention in all children studied, however with the exception of one child who was assessed using the straight leg raise, no details of magnitude or method of measurement was reported for either the described atrophy or strength.[54,61]

One cross-sectional study assessed lower limb strength of ankle plantarflexion, knee flexion and knee extension in ten children with LFD by means of a cybex isokinetic dynaometer.[63] The authors reported ankle plantarflexion was 50% weaker in the affected limb compared to the unaffected limb of children who had undergone lengthening (4 children). It was also reported that knee flexion and extension were significantly greater in the unaffected limbs than affected limbs in all children with LFD. The 4 children who had undergone lengthening had stronger knee flexion than the 6 children who had undergone amputation, whereas no difference was seen in knee extension strength comparing the two groups. With the exception of ankle plantarflexion however, no values of strength were reported, and no comparison was made to normative data. This study and the previously mentioned study that used the straight leg raise,[61] are the only two publications to report validated measures of strength in children with LFD, however with such small participant numbers, the lack of reported values of strength, and with no comparison to normative data, it is difficult to extrapolate these findings to the wider population of children with LFD.

Gait pattern and the presence of a limp

Gait pattern and the presence of a limp post-surgical intervention in children with LFD has been reported in three retrospective studies using non-validated participant or clinician report. Two of these were case series and described 71-91% incidence of limp post lengthening, and 75% limp post amputation.[17,54] The third study was a single case report of a child with a 'normal' gait pattern post valgus and cruciate corrective surgery.[60] In all studies further descriptive detail was minimal. One published abstract from the 31st Annual Congress of the French Society of Physical and Rehabilitation Medicine reported using "walk analysis" to examine the gait pattern of an adolescent with LFD prior and post amputation and found no difference; however unfortunately this study has not been formally published and hence full methodology and results are unavailable.[64]

The only full-form published study that has used a validated method to assess the gait pattern of children with LFD, used kinematic and kinetic gait analysis to examine 10 children with LFD after either amputation or lengthening procedures.[63] Detailed methodology of the gait analysis was not reported. The findings were that children who had undergone lengthening procedures demonstrated "foot drop" in their affected limbs, loss of dorsiflexion during stance phase, and mild hyperextension of the knee in stance. In children who had undergone a Syme amputation, no unusual sagittal plane kinematics were seen in the affected limbs but increased plantarflexion at toe-off was seen on the unaffected side (compensating for the lack of ankle power on the prosthetic side). Increased knee valgus on the affected side was seen in these children in the coronal plane. Both groups demonstrated a mild increase in stance phase pelvic obliquity, caused by a residual shortening, on the affected side. Power generation (ankle push-off) on the affected side was significantly less than on the normal side in Syme's limbs, unsurprisingly given the presence of a prosthetic ankle; whereas in lengthened limbs there was less difference. The affected ankle in patients with lengthened limbs also did significantly more work than the ankles in patients with Syme's. This is, again, unsurprising. The affected hip performed more work than the unaffected hip in those with a Syme amputation (compensating for the decreased power at the ankle). The normal hips in patients with lengthened limbs produced more power and performed more work than the hip on the affected side. In summary there were greater deviations in gait patterns of children who had undergone an amputation compared to those post-lengthening, however these were predominantly compensations for the loss of the ankle joint and the presence of a prosthesis. Given this study is now 20 years-old, it is unknown if all of these gait deviations persist with progress in the prosthetic domain. Further investigation is required before these results can be transferred with confidence to current populations of children with LFD.

Walking Performance

Three retrospective studies have assessed walking performance in children with LFD however none have used validated measures to do so. These studies varied from 3,8 and 22 participants. Two of the studies reported 100% of the children were ambulating and the third study reported 73% of the children were ambulant.[51,56] In this study no information was given regarding the remaining 27%.[15]

It was reported in one conference presentation reports no significant difference between children with LFD who have undergone limb reconstruction or amputation in performance of the "25-yard dash". Unfortunately, these findings have not been published and therefore full methodology and results are not available.[65] These findings suggest children with LFD are typically able to walk, however there is no reliable and valid data to accurately describe the quality of this walking performance. There is also no available data to compare the walking performance of children with LFD to unaffected peers as is now available in the population of adults with LFD.

Activities of Daily Living & Sports Participation

Activities of Daily Living and Sports Participation in children with LFD have been reported by numerous studies. Three retrospective studies of 22-43 participants used non-validated outcome measures to assess activity and sport-levels of children with LFD who had undergone lengthening procedures or amputation.[15,17,53] All three studies report a greater proportion of children post-amputation participating in sport without limitation compared to children post-lengthening procedures. Insufficient data is reported to provide an exact quantitative difference, and due to the lack of validated outcome measures, accurate comparison and extrapolation to other populations of children with LFD is difficult.

A further 4 studies assessed activity and sport participation with non-validated measures in the context of ACL instability. Three of these studies were retrospective case studies of 1-3

children.[50,61,66] These studies reported all of the described children were unable to continue with sport participation due to worsening symptoms of knee instability and half of the children returned to sport after cruciate ligamentoplasty. Further detail as to the reason why the remaining children did not return to sport was not reported. The fourth study was a cross-sectional study of 66 children with LFD and objective signs of knee instability. [23] This study found 'some' children with knee instability played sports but did not report specific frequencies or any further detail.

Seven studies have assessed activity and/or sport participation with validated participant-reported or clinician-reported outcome measures, however there is little overlap between measures used which makes comparison difficult. Most of these studies have assessed activity or sport in the context of post-operative performance. One study retrospectively reviewed 7 children with LFD, 5 of whom had undergone lengthening surgery.[54] The children were assessed before and after surgery with the Lower Extremity Functional Scale which assesses general activities of daily living including walking and running before and after surgery. The mean score improved from 70.9% to 89.4%. The age of the individuals when they provided this final score is not clear and may have occurred in early adulthood. A second assessed 119 children post-reconstructive and lengthening procedures with the Musculoskeletal Function Assessment Questionnaire.[56] All showed favourable results with satisfaction, 70 scoring a functional rating of excellent and 49 a rating of good. A third study used the ASAMI (Association for the study and application of methods of Ilizarov) score in assessing function after ankle reconstruction and lengthening in 29 children.[38] Fifteen scored "excellent" post treatment which included being described as active with no limp, 6 scored "good" which was active with a limp or stiffness, 4 scored "fair" equating to active but with a limp and stiffness and 2 "poor", who were children described as inactive. A fourth study assessed function in 31 children after amputation, lengthening or guided-growth techniques alone using the Short Musculoskeletal Functional Assessment (SMFA).[12] This assessment has 2 components:

dysfunction and "bother," both rated on a 0-80 scale where a higher score is worse. Children post-amputation scored 12.5 on the dysfunction scale and 6.25 on the bother scale. Children post-lengthening alone scored 32 on dysfunction and 31 on bother and children who had undergone epiphyseodeses alone scored 51 on dysfunction and 52 on bother. Children who had undergone a combination of lengthening and epiphyseodesis scored best of all with 11 on dysfunction and 2 on bother. The fifth study used 2 validated clinician-reported outcome measures, the K-level and the SIGAM score (Special Interest Group in Amputee Medicine) to compare outcomes between those who had undergone a Syme amputation and those who wore an extension prosthesis.[41] Those who had undergone amputation demonstrated better activity level on the K-level, allowing them to perform high impact activities compared with only community ambulation, but no difference was found between the groups as measured by the SIGAM. This was not compared with a normal reference population.

Two of the studies assessed function or sports after cruciate ligamentoplasty with validated participant-report measures. The first assessed 3 adolescents with LFD and knee stability using the Lysholm II before and after surgery.[50] Pre-oepratively the mean score was 38 and post-operatively the mean was 81 where the best score is 100. The second also used the Lysholm II in addition to the International Knee Documentation Committee Score (IKDC) to assess 44 children after cruciate ligamentoplasty, where 1 of these children had LFD.[66] The mean Lysholm score was 95.7. The mean IKDC score was 96.7, however it was unclear what the particular score was in each measure for the child with LFD.

Overall it is clear that a proportion of children with LFD participate in sport. While this is the outcome that has the highest number of validated measures used, due to the large variation between measures and the lack of comparison to norms it is difficult to extrapolate a true accurate picture of activity and sporting levels. The availability of objective data and a comparison to norms would be helpful in improving understanding in this domain.

Quality of Life

Two studies have measured quality of life in children with LFD, both of which used the PedsQL, a validated questionnaire. The first, a cross-sectional study of 32 individuals found no statistically significant difference in Quality of Life between treatment groups of children with LFD but did not compare these children to norms.[41] The second, a retrospective study of 8 children found those with LFD had a lower score than norms, but statistical analysis including testing for a significant difference was not performed, likely due to the small sample size.[51] An aforementioned conference presentation described no difference between children with LFD who had undergone amputation or limb reconstruction procedures, nor between children with LFD and unaffected children, when assessed on psychosocial and quality of life measures; however, this study has not been published and therefore full methodology and results have not been reported.[65] Based on the available validated data, it appears likely that there is no difference between children with LFD who have undergone different treatment pathways but children with LFD possible have lower quality of life than their unaffected peers. Further investigation with greater participant numbers is required to confirm these preliminary findings.

Summary of Outcome Measures in Children and Adults with LFD

In conclusion, many studies have assessed numerous outcomes in both children and adults with LFD, however the vast majority have involved small numbers of participants, used a retrospective research method and been of low methodological quality. To date there have been no randomised controlled trials or systematic reviews published in any population with LFD. The majority of outcome measures used have either been non-validated or based on participant or clinician-report. Very few standardised objective measures have been performed in this population overall but particularly in the paediatric group. Furthermore, rarely have results in the population of LFD been compared to comparative norms.

Considering physical performance in particular, in adulthood at least one study has used objective measures to assess strength, walking performance and stair performance, and compared these values to normative reference data. This study found that adults with LFD performed significantly worse than unaffected peers.[59] Unfortunately, no such data is available in children. Almost all of the available paediatric literature has studied individuals with LFD in the context of surgical procedures, rather than performance at different ages and developmental stages. Considering the results in adults with LFD were consistent despite varying surgical approaches, it is unknown if this global poor physical performance when comparing adults with LFD to their unaffected peers is consistent throughout childhood or not. There has been no formal consideration as to how physical performance may change throughout the developmental stages of childhood and how this may differ from the development of children who do not have LFD. Hence, these individuals, their families, and their treating clinicians are dependent on subjective reports or non-validated information to understand and predict the physical performance of children with LFD.

To assist clinicians managing individuals with LFD throughout their childhood, it would be of high value to have available reliable objective measurements. In particular, measurements of lower limb strength would be of significant usefulness, in addition to reliable functional measurements including walking performance and other functional components relevant to a child's physical performance such as jump performance, performance on stairs and balance. The availability of such measures and their comparison to the performance of unaffected peers, would not only inform the day-to-day clinical management and education of children with LFD and their families, but would also serve to provide prognostic information. This prognostic information may assist surgeons when timing procedures in light of confounding management factors such as the potential consequence of weakness post-lengthening procedures[67-69] or functional balance in the context of cruciate ligamentoplasty. Therefore, the following research study sought to amend this lack by assessing the physical performance of a

consecutive population cohort of children with LFD using validated objective measures and to compare their performance with that of their unaffected peers.

Chapter Three:

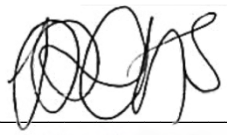
Physical Performance of Children and Adolescents with Longitudinal Fibular Deficiency: A cross-sectional study.

This chapter is presented in the exact format of the manuscript which has been submitted to the Journal of Pediatric Orthopaedics with the exception of tables and figures embedded throughout manuscript (rather than in separate document) for ease of reading. (See Appendix 5. for submission guidelines for the Journal of Pediatric Orthopaedics.)

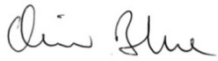
Statement from co-authors confirming authorship contribution of the Master of Research candidate

As co-authors of the paper "Physical Performance of Children with Longitudinal Fibular Deficiency (Fibular Hemimelia)", we confirm that Eleanor Morris has made the following contributions:

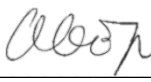
- conception and design of the research
- collection and extraction of data
- analysis and interpretation of the findings
- writing of the manuscript and critical appraisal of the content

Dr Louise Tofts  Date: 25.9.18

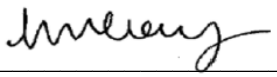
Margaret Patterson  Date:28.9.18

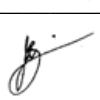
Dr Oliver Birke  Date:27.9.18

Dr Roger Adams  Date:27.9.18

Dr Adrienne Epps  Date: 25.9.18

Kathrine Knox  Date:27.9.18

Dr Marnee McKay  Date: 26.9.18

Dr Jennifer Baldwin  Date: 26.9.18

Prof Joshua Burns  Date: 26.9.18

Dr Verity Pacey  Date: 25.9.18

To Whom it may concern,

Please find enclosed the manuscript “Physical Performance of Children with Longitudinal Fibular Deficiency (LFD) (Fibular Hemimelia)”. This is the first study to examine strength and functional performance with validated outcome measures in a substantial cohort of the paediatric LFD population. These novel and significant findings will play an important role in guiding the paediatric orthopaedic specialist when providing prognostic education to families of children with LFD, and in determining appropriate timing and method of orthopaedic interventions. For all of these reasons, we feel this manuscript is well-suited to publication in the Journal of Pedatric Orthopaedics and would be highly welcomed by your readership.

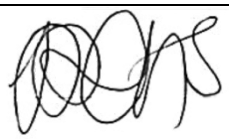
We certify that all authors of “Physical Performance of Children with Longitudinal Fibular Deficiency (Fibular Hemimelia),” fulfil each of the following requirements for authorship:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and
- Drafting the work or revising it critically for important intellectual content; and
- Final approval of the version to be published; and
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriate investigated and resolved.

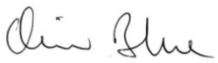
We look forward to hearing from you.

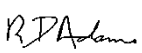
Kind regards,

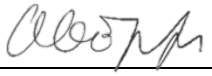
Eleanor Morris  Date: 11.9.18

Dr Louise Tofts  Date: 11.9.18

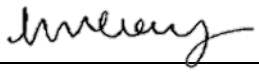
Margaret Patterson  Date: 12.9.18

Dr Oliver Birke  Date: 14.9.18

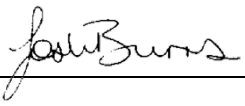
Dr Roger Adams  Date: 11.9.18

Dr Adrienne Epps  Date: 11.9.18

Kathrine Knox  Date: 12.9.18

Dr Marnee McKay  Date: 12.9.18

Dr Jennifer Baldwin  Date: 12.9.18

Dr Joshua Burns  Date: 12.9.18

Dr Verity Pacey  Date: 11.9.18

Manuscript Title:

Physical Performance of Children with Longitudinal Fibular Deficiency (Fibular Hemimelia).

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Sources of Support:

EM was funded part-time as a research physiotherapist for the Limb Clinic, Kids Rehab at The Children's Hospital at Westmead from funds donated by the Limbless Soldiers Association.

The 1000 Norms Project was supported by the National Health and Medical Research Council of Australia (NHMRC, #1031893), and Australian Podiatry Education & Research Fund, Australasian Podiatry Council.

Author Disclosures:

OB is a paid consultant and invited faculty of Orthofix.

Acknowledgments

Children with LFD in NSW and their families for generously donating their time to participate in this study.

Professor David Little, Dr Paul Gibbons and Dr Kristy Rose for additional advice and guidance.

Abstract

Background

Longitudinal Fibular Deficiency (LFD) is the most common congenital long bone deficiency, with a varying spectrum of lower limb dysplasia. Whilst the anatomical pathology of LFD is well-established, the impact of this pathology on physical performance is much less clear.
The primary aim of this study was to objectively assess the physical performance of children and adolescents with LFD and compare their performance to that of unaffected peers.

Methods

Children with a diagnosis of LFD aged 3- 18 years in New South Wales, Australia, were recruited and compared with unaffected age-matched children. Five objective measures of physical performance were completed: lower limb muscle strength dynamometry, 6-minute walk test, timed up and down stairs test, star-excursion balance test, and standing long jump. Performance differences between children with LFD and their unaffected peers were examined with independent groups t-tests. Age group comparison was analysed with ANOVA, and ANcOVA used to examine age-adjusted subgroup variation within the cohort of children with LFD.

Results

Thirty-nine children with LFD (46% male, mean age 9 years) and 284 unaffected peers (50% male, mean age 10 years) participated. With the exception of jump performance (p-value 0.27), children with LFD performed worse on all measures of physical performance, including lower limb strength (mean of 2.2 standard deviations below norms, all $p<0.01$), and other functional measures (mean 2.1 standard deviations below norms, all $p<0.01$). There was a significant difference in the linear trend component of the slope of the rise on all strength measures and walking performance,

indicating the difference in strength and walking performance between children with and without LFD was smallest in children of a young age (3-6 years) and largest in the oldest children (15-18 years) (all $p<0.015$).

Conclusion

Children with LFD performed significantly worse than their unaffected peers in all measures of physical performance other than jumping, and the difference was greatest in older children.

Level of Evidence

Cross-sectional cohort study. Level III evidence: Case-control.

Introduction

Longitudinal Fibular Deficiency (LFD) is the most common congenital long bone deficiency.[1,2] LFD, often referred to as Fibular Hemimelia, is defined as the complete or partial absence of the fibula[3,4]. LFD presents as a varying spectrum of lower limb dysplasia including absent lateral rays and a hypoplastic foot, tarsal coalitions, calcaneovalgus or varus, ball and socket ankle mortise, cruciate deficiency of the knee, genu valgum and femoral shortening.[1,5]

Management of individuals with LFD has historically involved a variety of surgical and conservative approaches that include amputation with prosthetic restoration, extension prosthetics and leg lengthening.[1] Management choice is influenced by anatomical severity, technical possibilities, and what the individual, their family and healthcare team believe will offer the best functional outcome with acceptable cosmesis and reasonable burden of intervention.[6] However, prediction of functional outcomes for such rare and heterogenous presentations can be difficult.[1]

Based primarily on retrospective assessments with subjective measures in adult cohorts, functional performance of individuals with LFD is generally reported to be "acceptable",[7,8] despite recent data to suggest adults with LFD perform well below their peers in physical performance.[9] To date, no data are available on the physical performance of children with LFD compared to their peers, nor how this may change through childhood. Hence prognostic functional data that could guide management is limited.

Therefore, the primary aim of this study was to objectively assess the physical performance of children and adolescents with LFD and compare their performance with that of unaffected peers. A secondary aim was to examine differences in physical performance between subgroups of children

with LFD, including different age groups, bilateral/unilateral presentation, differing anatomical classification levels and management pathways.

Materials and Methods

Ethical approval for this study was obtained from the Sydney Children's Hospital Network Human Research Ethics Committee (LNR/17/SCHN/121), and Macquarie University (5201827003073).

LFD Participants

Children and adolescents (hereafter "children") with LFD in New South Wales, Australia, were recruited via orthopaedic and rehabilitation clinics of Sydney Children's Hospital Network, Sydney, Australia. Children aged 3 – 18 years with a confirmed diagnosis of LFD through clinical and radiographic assessment by an experienced orthopaedic surgeon, were eligible for inclusion in this study. Children with LFD with other limb deficiency co-diagnoses of congenital short femur (CSF), or proximal femoral focal deficiency (PFFD) were also eligible. Children were excluded if they had comorbidities not related to their LFD that affected lower limb function, such as a neurological condition, or if they had a previous lower limb joint injury or surgery not related to their LFD.

Unaffected Participants

The 1000 Norms Project recruited one thousand people (males n= 500) aged 3 – 101 years from the Sydney metropolitan area, Australia, between January 2014 and September 2015.[10,11,12] Ethical approval was granted by the University of Sydney ethics committee (HREC 2013/640). Participants were included if they considered themselves healthy and able to participate in age-appropriate activities of daily living. Participants were excluded if they had a significant health

condition that affected their physical performance or if unable to follow age-appropriate instructions. Individual level data collected on participants aged 3-18 years was used here as normative reference data.

Study Design

Cross-sectional study

Assessment

All children, with parental support as required, undertook a short interview with a senior physiotherapist. Medical records, including radiological scans, were reviewed. Demographic information collected included age, gender and school year. Medical and surgical history included any diagnoses or conditions relevant to LFD or physical function, and the use of any orthotics, prosthetics or walking aids. The Achterman & Kalamchi,[3] and Paley[13] classifications of fibular deficiency and, where relevant, the Aitken[14] classification of femoral deficiency, were recorded.

Anthropometric data was collected, and body mass index (BMI) percentiles were calculated.[15] Leg length was measured from the anterior superior iliac spine to the base of heel,[16] and the multiplication method used to calculate leg length discrepancy predictions.[17] Static lower limb alignment for knee varus/valgus, Foot Posture Index categorising feet on a pronation/supination spectrum, and lower limb dominance were collected.[12] Active hip, knee and ankle joint range of motion were assessed by goniometry.[12,18]

All children completed a physical assessment with a senior physiotherapist. Outcomes with demonstrated validity and reliability in the paediatric population were collected following the 1000

Norms Protocol (Table 1).[12] Participants with prior amputations or fused lower limb joints were assessed on all practicable measures.

Table 1. Physical Outcome Measures

Physical Performance	**Outcome Measure**	**Details of Outcome Measure**
Lower limb muscle strength [β]	Hand-held dynamometry of: 1. Ankle dorsiflexion 2. Ankle plantarflexion 3. Knee flexion 4. Knee extension 5. Hip external rotation 6. Hip internal rotation 7. Hip abduction. (Newtons) [α]	A measure of muscle performance via a maximal voluntary isometric contraction. Each measure was repeated three times on each side with the mean measure used for all analyses. The Citec dynamometer (CT 3001, Citec Technics Groningen, The Netherlands) was used.
Sub-maximal walking endurance [β]	Six minute walk test (metres)	A measure of the distance walked in 6 minutes when asked to walk as quickly as possible, without running, along a 25-metre track.
Capacity to ascend and descend stairs [χ]	Timed up and down stairs test (seconds)	A measure of the time taken to ascend and descend an 11-step flight of stairs (step height 14.5cm).
Lower limb balance [δ]	Star excursion balance test (% of leg length)	A measure of the maximum distance reached with one leg in a posteromedial direction whilst maintaining balance on the other leg. Both sides were assessed.

		The test was repeated three times on each leg with the mean measure used for all analyses.
Jump performance [ε]	Standing long jump (metres)	A measure of the maximum distance able to be jumped using both legs from a standing position. The test was repeated three times with the mean measure used for all analyses.

[α]The torque measurements of knee flexion and knee extension were recorded in Newton/metres.

[β]Completed by all children

[χ]Completed by children aged 8 years and over

[δ]Completed by children aged 7 years and over

[ε]Completed by children aged 4 years and over

Statistical Analysis

Demographic variables were assessed for normality and descriptive statistics calculated. Independent groups t-tests compared both the most affected and least affected side (unaffected side in children with unilateral LFD) of children with LFD to unaffected peers on all physical performance outcome measures. Z-scores were calculated by age and gender. The most affected side in children with bilateral LFD was the limb with the most severe anatomical presentation.

To analyse change in functional performance across ages, a 2 x 4 ANOVA with factors Condition Group (LFD, Norms) and Age Group (3-6 years, 7-10 years, 11-14 years, 15-18 years) was carried out with polynomial trend contrasts on the Age Group factor. Trend contrasts were used to partition variance into independent linear, quadratic and cubic trend components in the functions of the dependent variables across age groups, on all outcome measures of physical performance.

ANcOVA's with age as a covariate were performed to control for the effects of age in the between-group analysis when examining differences between subgroups within the LFD cohort on the 6 minute-walk test, standing long jump, star excursion balance test and timed up and down stairs test. Differences were examined between the following binary subgroups: unilateral versus bilateral LFD presentation, PFFD diagnosis vs not PFFD, Paley fibular classifications 1 and 2 versus 3 and 4, prior amputation versus no amputation, and prior lengthening surgery versus not lengthened. Posthoc power analysis was also performed. All tests were conducted using IBM SPSS Statistics, Version 24.

Results

Three hundred and twenty-three children aged 3 – 18 years participated (Table 2). Two hundred and eighty-four (284) unaffected peers from the 1000 Norms Project included 20 children recruited per age-year from 3 to 9 years, and 16 per age-year from 10 to 18 years. Based on current estimated incidence of LFD it was expected that there would be 33 eligible participants, not accounting for migration.[19,20] Forty-nine (49) children with LFD aged 3 – 18 years were identified between June 2017 and May 2018, in New South Wales. One child was excluded due to significant concurrent neurological impairment. Of the remaining 48 potential participants, eight could not be contacted and one family declined participation. The remaining 39 children represented a recruitment rate of 81% of all eligible children with LFD.

Table 2. Demographics and Characteristics of Participants

Demographics & Characteristics		**Unaffected Peers N = 284**	**Children with LFD N = 39**
Age (years) mean (SD)		10.06 (4.6)	8.9 (4.9)
Sex n (%)	Male	142 (50)	18 (46)
Lower Limb Dominance n (%)	Right	260 (92)	27 (69)
BMI percentile mean (SD)		59.8 (27.9)	56.1 (31.8)
Frontal Alignment[Ψ] (degrees[†]) Mean (SD)		0.9 (2.8)	-0.25 (4.4)
Foot Posture Index[ϕ] (category) N (%)	Highly Pronated	1 (0)	7 (23)
	Pronated	68 (24)	14 (47)
	Normal	207 (73)	9 (30)
	Supinated	7 (2)	-
	Highly Supinated	1 (0)	-

[Ψ] *Dominant side measured of unaffected peers. Most affected side measured of children with LFD.*

[†] *Valgus = negative values, Varus = positive values*

[ϕ] *Children with an amputation on the most affected side are excluded from these numbers.*

The 38 participating children represent the broad spectrum of anatomical variation within LFD (Table 3, Figure 1). Four of the 5 children with upper limb involvement were affected bilaterally. Over half of the children (n=22) had femoral involvement (CSF or PFFD). Subsequently, children

with LFD had received multiple management pathways (Figure 2). Seven had a previous Syme amputation, and two children with an equivalent congenitally missing foot were using a prosthesis for ambulation. Two children who had concurrent PFFD and Type 2 Achterman & Kalamchi fibulae had also undergone knee fusions. All children with type 2 classification had undergone Syme amputations, leaving one other child (bilateral presentation) with an amputation and a type 1a fibula. Eleven children had previous leg lengthening surgery, and eleven children were planning to undertake lengthening surgery when older. Future lengthening candidates were using shoe raises or extension prostheses. Nine children were using partial foot prostheses. In total, 22 children had undergone some surgical intervention on their most affected limb (Table 4). Of the 3 children who were unable to achieve a plantigrade position of their most affected foot (those with amputations excluded), 2 were Paley type 3 and 1 was type 1. Two had undergone 2 lengthening procedures, 1 had undergone 1 lengthening procedure with a mean total lengthening of 7cm. The 2 children with type 3 Paley classification had also undergone foot/ankle surgery.

Table 3. Features of LFD Presentation

LFD Anatomical Variations		**N (%)**
Bilateral LFD	Bilateral	7 (18)
Most affected side	Right	24 (61.5)
Upper limb involvement	Affected	5 (13)
Femoral involvement	CSF	14 (36)
	PFFD	8 (21)
	Aitken Classification of PFFD:	
	A	4
	B	1
	C	1
	D	2

Fibular involvement:	Achterman & Kalamchi Classification	1a	29 (74)
		1b	2 (5)
		2	8 (21)
Foot and ankle involvement:	Paley Classification: [η]	1	1 (3)
		2	21 (54)
		3	10 (26)
		4	4 (10)
	Number of missing rays (at birth):	0	12 (31)
		1	12 (31)
		2	11 (28)
		(All)	4 (10)
	Dorsiflexion range of motion = < plantigrade.		3 (8)
Limb length difference (LLD)	LLD at time of assessment[#] [▽]cm (SD)		4.4 (4.6)[▽]
	Predicted LLD prior to lengthening[#] [▽]cm (SD)		9.6 (7.9)[▽]

[η]3 unable to be scored due to early amputation.

[#]Children with amputations excluded

Figure 1. Relationship between missing rays, femoral involvement and Achterman & Kalamchi Classification.

The incidence of classification for each femoral involvement classification and Achterman & Kalamchi classification is represented by the size of the bubble and number next to each bubble.

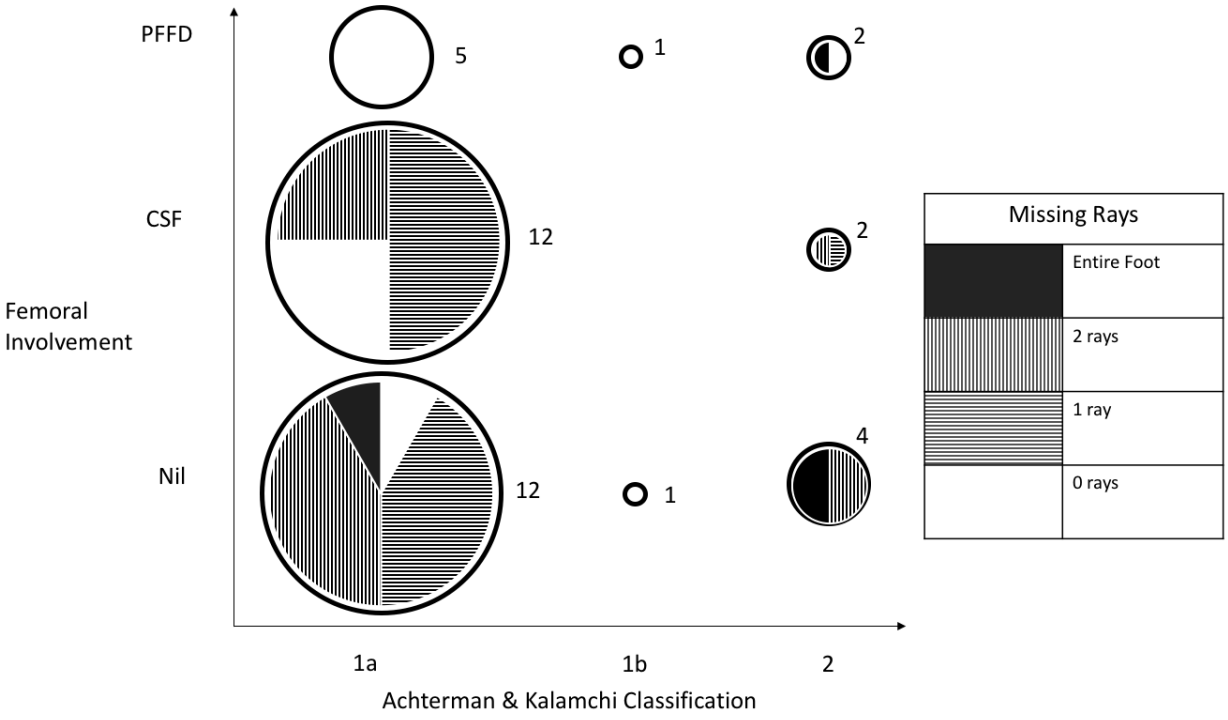


Figure 2. Surgical management pathways according to femoral involvement and Achterman & Kalamchi classification.

The incidence of classification for each femoral involvement classification and Achterman & Kalamchi classification is represented by the size of the bubble and number next to each bubble.

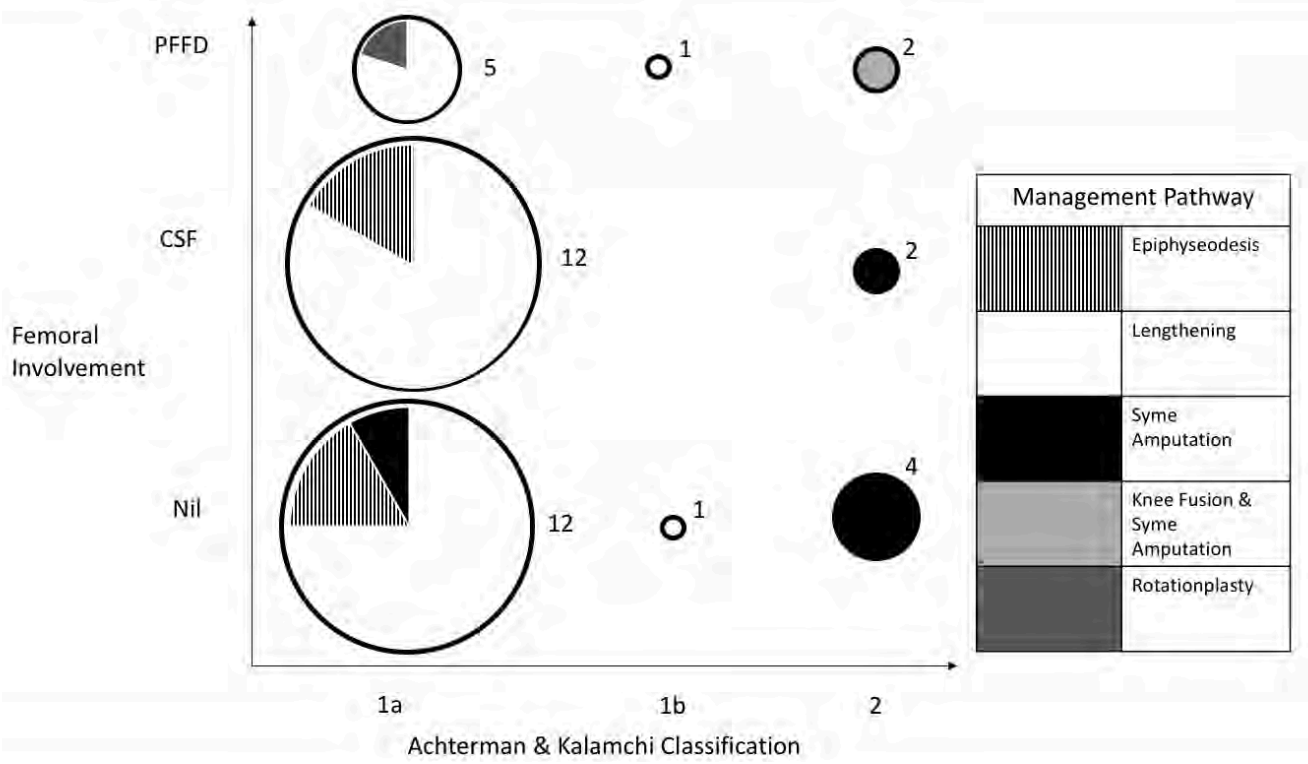


Table 4. Type & Frequency of Surgical Intervention

Unless specified N reflects number of children, rather than number of surgeries. % indicates proportion of the 22 children who had undergone some form of surgical intervention.

Surgical Intervention		**N (%)**
Pelvic and/or Femoral Osteotomies[ƒ]		7 (32)
Anterior Cruciate Ligamentoplasty		1 (5)
Knee Fusion (Concurrent with a Syme amputation in PFFD)		2 (9)
Foot/Ankle Surgery[µ]		7 (32)
Syme Amputation		7 (32)[λ]
Guided growth (angular)		11 (50)
Guided growth (longitudinal)		7 (32)
Lengthening Surgery		11 (50)
Number of Lengthening Surgeries	1	8
	2	3
Distance of Total Long Bone Lengthening/ lengthening patient (mean) [*]Cm (SD)		5.5 (2.2)[*]
Time since lengthening procedure (mean) [♦]Years (SD)		3.7 (2.7)[♦]

[ƒ]Included SUPERHip, Pemberton Osteotomy, Shelf Osteotomy and Pelvic Support Osteotomy.

[λ]2 children were born without a foot and did not require a conversion amputation.

[µ]Amputations and isolated neonatal tenotomies excluded**.**

Overall group comparison between LFD and Unaffected Peers:

Lower Limb Strength Performance

Lower limb strength in all muscle groups was significantly reduced in children with LFD, compared to their unaffected peers (Table 5), controlling for age and gender (Figure 3). Whilst the difference from norms was greater on the most affected side, both sides were significantly weaker.

Table 5. Lower Limb Muscle Strength

Muscle Group		**Unaffected Peers (n = 284) Mean (SD)**	**Children with LFD Mean (SD)**	**Mean Difference (95%CI)**	**p-value**
Ankle dorsiflexion (Newtons (N))	Least affected side	132.1 (63.9)	N = 34 68.3 (28.3)	63.8 (51.6-76.1)	< 0.01*
	Most affected side		N = 26 49.2 (19.7) (72%♣)	82.9 (72.1-93.6)	< 0.01*
Ankle plantarflexion (N)	Least affected side	216.8 (90.8)	N = 32 92.7 (33.1)	124.1 (108.3-139.8)	< 0.01*
	Most affected side		N = 24 73.3 (26.5) (79%♣)	143.5(128.3-158.6)	< 0.01*
Knee extension (Newton Metres (Nm-1))	Least affected side	83.3 (64.6)	N = 38 34.7 (27.6)	48.6 (36.9-60.2)	< 0.01*
	Most affected side		N = 36 29.7 (22.9) (86%♣)	53.5 (42.8-64.2)	< 0.01*

Knee flexion (Nm-1)	Least affected side	51.1 (33.5)	N = 33 26.9 (16.0)	24.2 (17.4-31.0)	< 0.01*
	Most affected side		N = 31 22.9 (12.3) (85%♣)	28.2 (22.3-34.2)	< 0.01*
Hip abduction (N)	Least affected side	90.7 (50.7)	N = 35 47.9 (22.8)	42.8 (33.1-52.5)	< 0.01*
	Most affected side		N = 35 45.0 (23.8) (94%♣)	45.6 (35.7-55.6)	< 0.01*
Hip internal rotation (N)	Least affected side	110.7 (66.0)	N = 31 51.2 (17.6)	59.5 (49.6-69.5)	< 0.01*
	Most affected side		N = 30 45.5 (17.3) (89%♣)	65.2 (55.2-75.1)	< 0.01*
Hip external rotation (N)	Least affected side	84.1 (51.3)	N = 31 50.9 (21.5)	33.2 (23.4-43.0)	< 0.01*
	Most affected side		N = 30 45.9 (19.8) (90%♣)	38.1 (28.7-47.5)	< 0.01*

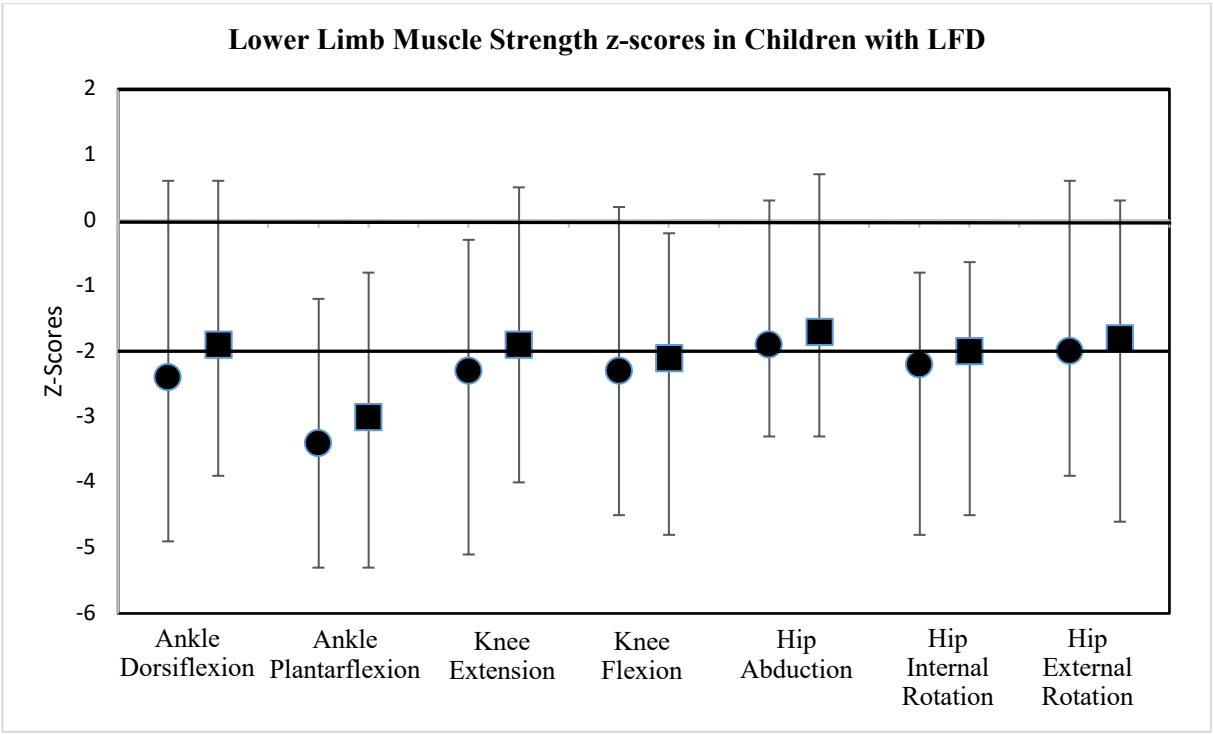
* Statistical significance at $p<0.05$

♣ % of least affected side value.

Figure 3. Strength performance of children with LFD compared with peers, represented by z scores (adjusted for age and gender).

Markers indicate mean z-scores with error bars indicating 95% Confidence Intervals.

Line at 0 indicates normal performance. Lines at 2 and -2 indicate 2 standard deviations from normal and hence where 95% of the population would be expected to perform.



Lower Limb Functional Performance

Children with LFD walked significantly shorter distances in the six minute walk test and took significantly longer to complete the timed up and down stairs measure, than their unaffected peers (Table 6.), including when adjusted for age and gender (Figure 4.). Children with LFD performed worse than their peers on the star excursion balance test on both legs, with the most affected side performing worse than the least affected side. There was no significant difference between the Standing Long jump distances of children with LFD and their unaffected peers.

Table 6. Functional Lower Limb Performance

Measure		**Unaffected peers mean (SD)**	**Children with LFD mean (SD)**	**Mean difference (95% CI)**	**p-value**
Six minute walk test (metres)		636.8 (136.1)	470.5 (95.3)	166.2 (130.9-201.5)	< 0.01*
Timed-up-and-down-stairs test (seconds)		6.7 (1.5)	9.5 (4.4)	-2.8 (-3.7- -1.8)	< 0.01*
Star excursion balance test (% of leg length)	Least affected side	100.7 (16.4)	70.7 (17.2)	30.0 (22.7 – 37.3)	< 0.01*
	Most affected side		63.3 (21.5)	37.5 (30.0 – 45.0)	< 0.01*
Standing long jump (metres)		127.4 (35.3)	120.1	7.3	0.27

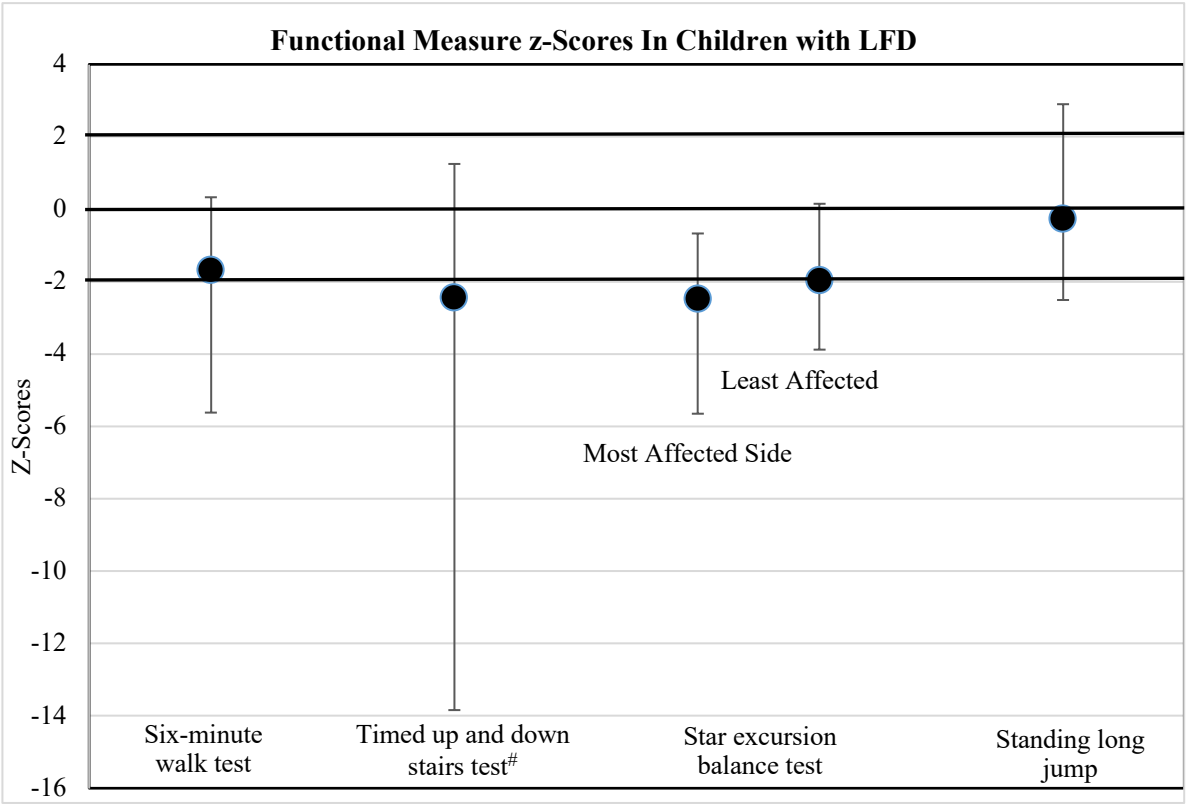
	(33.5)	(-5.8 – 20.5)

***** Statistical significance at p<0.05

Figure 4. Functional performance of children with LFD compared with peers, represented by z scores (adjusted for age and gender).

Markers indicate mean z-scores with error bars indicating 95% Confidence Intervals.

Line at 0 indicates normal performance. Lines at 2 and -2 indicate 2 standard deviations from normal and hence where 95% of the population would be expected to perform.



[#] Z scores inverted since a bigger Timed up and down score reflects a worse performance

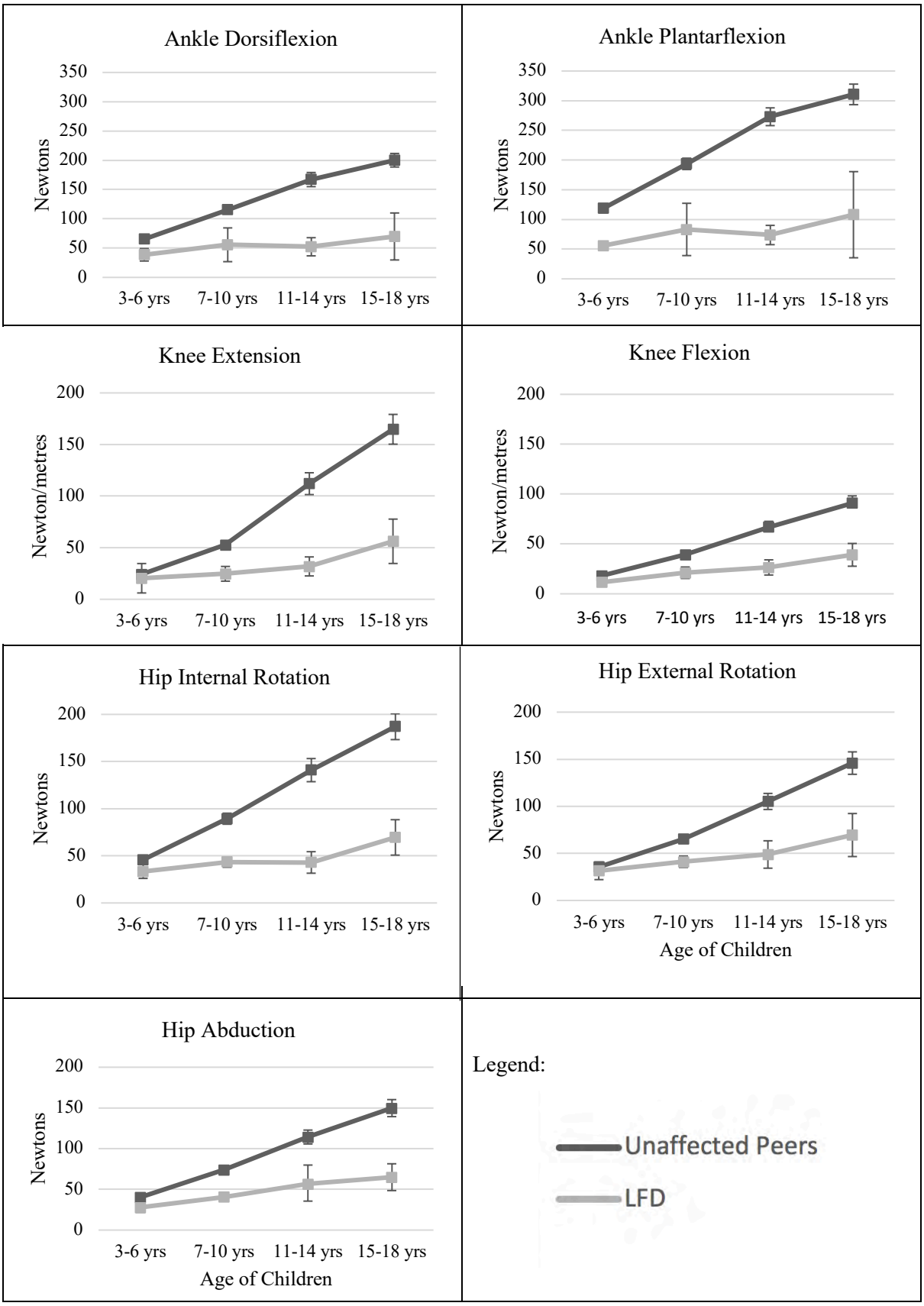
Change in physical performance per age group of children with LFD compared to unaffected peers:

To examine change in performance throughout childhood, strength and functional performance were compared across age groups.

Strength Performance

There was a significant difference in the linear trend component of the rise on all strength measures, indicating that the slope of the rise in strength in all muscle groups was steeper for unaffected children (all $p < 0.01$, Figure 6). No cubic or quadratic trend tests were significant (all $p>0.05$). Children with LFD were thus weaker than their unaffected peers, with the difference in strength significantly greater in older children.

Figure 5. Lower Limb Strength Performance of Children with LFD compared to Unaffected peers by Age Group. *Means indicated by data points, and 95% confidence intervals by error bars.*

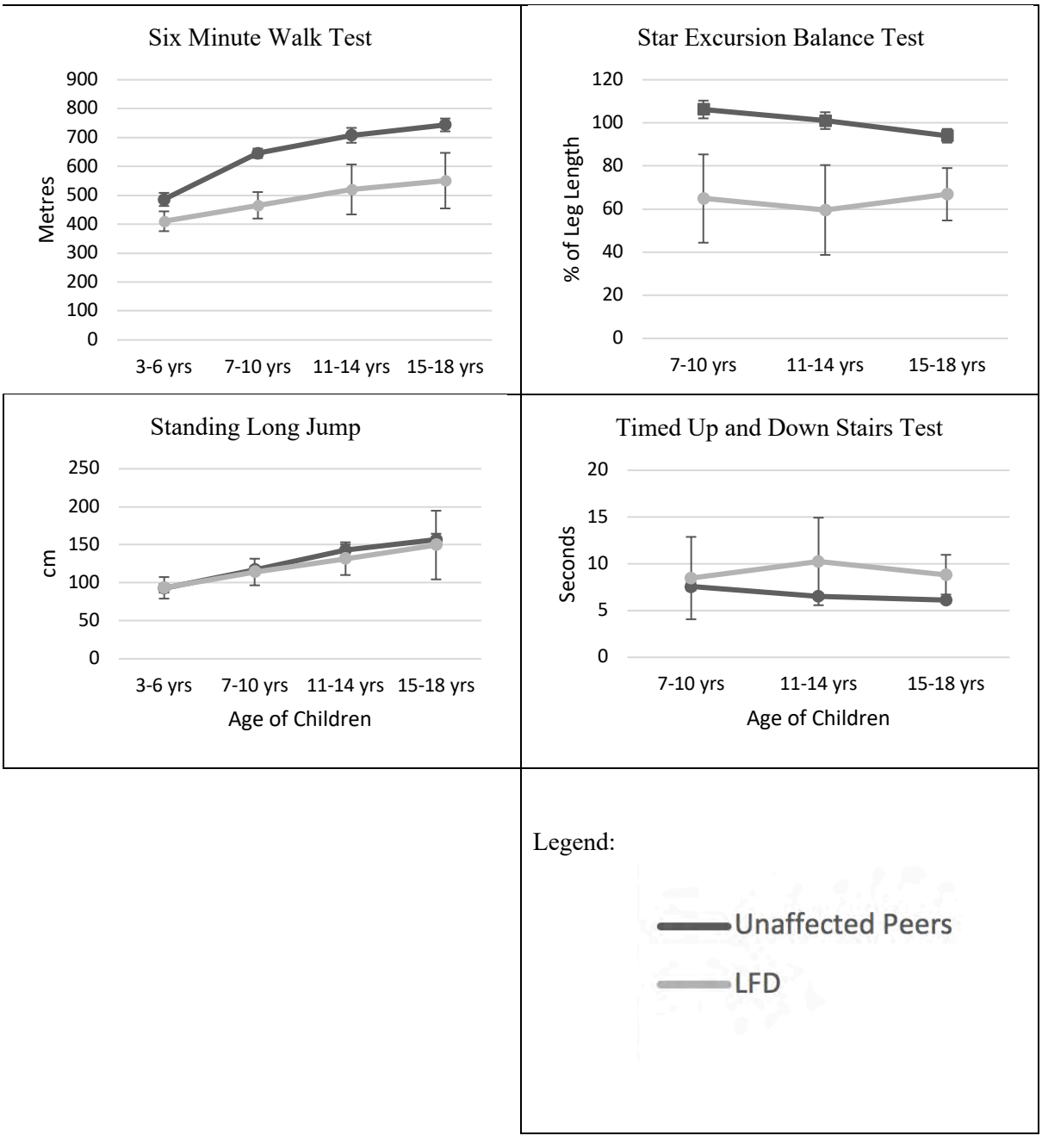


Lower Limb Functional Performance

In the six minute walk test the significant difference in the linear trend component indicated that the slope of the rise with age was steeper in unaffected children. ($F_{(1,309)} = 5.9$, $p = 0.015$). The significant quadratic component reflected a slowing rate of rise ($F_{(2,215)} = 4.9$, $p = 0.027$). No other tests were significant ($p > 0.141$). Thus, similar to the strength measures, children with LFD performed worse at the six minute walk test than their unaffected peers, and the performance difference was greater in older children (Figure 6).

In contrast, there was no significant difference in the trend components between children with LFD and unaffected peers across age on any other measures (Figure 6) ($p = 0.139$-0.826), with the exception of a significant quadratic interaction on the timed up and down stairs test ($F=4.2$, $p=0.042$), reflecting the observed worse performance by children with LFD in middle childhood.

Figure 6. Lower Limb Functional Performance of Children with LFD compared to Unaffected peers by Age. *Means indicated by data points. 95% confidence intervals indicated by error bars.*



Lower Limb Functional Performance in LFD Subgroups

There was no significant difference on any functional measure between children with a prior amputation or not (p = 0.182-0.89), between those with Paley fibular classifications 1 & 2 compared with classifications 3 & 4 (p = 0.059-0.788), or between children with unilateral vs bilateral LFD (p = 0.333-0.976).

Children who had undergone lengthening performed worse than those who had not in the six minute walk, where they walked significantly less distance ($F_{1,35} = 8.655$, p = 0.006), with power of 67% for the test on this effect. However, the two groups were similar across all other measures (p = 0.179-0.846). Children with a co-diagnosis of PFFD performed significantly worse in the Standing Long Jump compared to those without ($F_{1,35} = 4.366$, p = 0.046) but not on other functional performance measures (p = 0.120-0.658). Post hoc power analysis showed that the tests for this effect had 32% power. (Statistics provided in Supplementary Tables.)

Discussion

In this first study assessing children with LFD using standardised objective measures of strength and function and comparing values to unaffected peers, the findings demonstrate that children with LFD are significantly weaker and have poorer walking endurance than their peers, and that this difference is greater in older children compared to younger children. Whilst acknowledging the cross-sectional nature of these findings, this reveals a likely picture of children with LFD falling further behind their unaffected peers as they enter adulthood and is consistent with a recent study that found that 30 young adults with congenital limb deficiencies, including LFD, performed significantly worse than their unaffected peers on objective measures of function.[20]

Individuals with LFD overall performed on par with their peers in the standing long jump. However, children with concurrent PFFD performed worse than those without PFFD at this

functional task. This suggests that explosive power is less affected in individuals with LFD, and the impact of femoral deficiencies impedes performance more so than fibular deficiency. This is potentially the result of a relatively shorter quadriceps muscle and hence worsened length-tension relationship of this muscle or reduced hip range of motion.[14]

The relationship between strength and functional performance of children with LFD is unclear, as is the magnitude of other potential contributing factors such as muscle endurance, joint instability and proprioception which were not measured directly in this current study. It is interesting to note that the least affected limb was almost as weak as the most affected side and performed almost as poorly in the unilateral functional measure (the Star Excursion Balance Test). This may suggest that factors other than the underlying anatomy on the affected side alone are contributing to the weakness and poor functional performance demonstrated in this study. The only 2 previous studies to objectively measure lower limb strength in individuals with LFD reported only in terms of the affected limb compared to the unaffected limb. Given the findings of this study that both limbs are significantly weaker than normal values, this comparison may be of limited validity. Further research is required to examine the exact mechanisms causing poorer performance in individuals with LFD across different functional tasks.

The majority of the observed differences in strength and functional performance were displayed in all individuals with LFD, despite anatomical presentation or surgical intervention. Notably, children who had undergone lengthening surgery performed worse in the 6-minute walk test than children who had not had prior lengthening. Previous studies have demonstrated weakness following lengthening surgery, potentially due to intrinsic axonal neuropathy from the lengthening procedure rather than muscle disuse.[21] However, no consensus has emerged as to how long this weakness persists.[22,23] In the present cohort, the mean time since lengthening was 3.7 years, with

the shortest duration of one individual being 10 months. A Norwegian adult study[9] found no difference between adults who had or had not undergone lengthening surgery for LFD in their six minute walk test performance, suggesting that the difference in walk performance observed here may resolve as strength and other contributing factors improve with further post-lengthening recovery.

One weakness of this study is the relatively small sample sizes available for the sub-group analyses. The combination of this with the obtained small-medium effect sizes resulted in power limitations to detect these effects is significant. A larger cohort is required, with multi-centre participation, to provide greater statistical power to detect differences between subgroups and to make inferences regarding management and long-term prognosis. In order to maintain consistency in leg length measures between children with LFD who had and had not undergone an amputation, the "percentage of leg length reached" score in the Star Excursion Balance test was calculated using the leg length to the base of the foot rather than the malleoli as used in the 1000 Norms study. This will overestimate the difference in performance between those with LFD and their unaffected peers, however considering the large magnitude of difference it is unlikely to have altered the results in a significant way.

The findings from this study provide direction for further research. In such a heterogenous group, longitudinal data is required to examine in more detail the impact of LFD on strength and function in children of different ages, and how performance changes with age and with surgical and other interventions. In addition, randomised controlled trials are required to evaluate whether specific strengthening intervention, particularly at a young age, could alter long-term strength and functional prognosis. Finally, the relationship between previously reported subjective measures in this population and the reported objective measures in this study has yet to be investigated.[24,25,26,27]

Conclusion

Children with LFD are significantly weaker in both affected and non-affected lower limbs than their healthy peers, and this difference is greater in older children. While individuals with LFD performed on par with their unaffected peers in jump performance, functional performance was significantly worse in children with LFD for walking, performance on stairs and dynamic single leg balance. Regarding subgroups of children with LFD, those with PFFD performed worse than others in jump performance and those who had undergone lengthening had worse walking performance. Further research is needed to determine the relative contributions of the muscle weakness demonstrated in this study and the previously recognised anatomical consequences of the condition itself, including a stiffer and smaller foot, tarsal coalition and hypoplasia, ankle instability and knee instability on the functional performance and prognosis of children with LFD.

List of Tables and Figures

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Supplementary Material

Lower Limb Functional Performance in LFD Subgroups

Statistically significant results are highlighted in 'bold' text.

Supplementary Table 1. Children with Unilateral LFD vs Bilateral LFD

Functional Measure	Adjusted Mean Unilateral (95% CI)	Adjusted Mean Bilateral (95% CI)	Adjusted Mean Difference (95% CI)	SD	Cohen's D	p-value
Six minute walk test (metres (m))	N=31 474.0 (447.6 – 500.3)	N=6 452.7 (392.7 – 512.6)	21.3 (-44.2 – 86.9)	95.3	0.2	0.513
Standing long jump (centimetres (cm))	N=25 120.0 (109.7 – 130.4)	N=6 120.4 (99.2 – 141.5)	-.4 (-23.9 – 23.2)	33.5	0.0	0.976
Timed up and down stairs test (seconds)	N=15 9.5 (6.9 – 12.0)	N=3 9.6 (3.9 – 15.3)	-.1 (-6.4 – 6.6)	4.4	0.0	0.961
Star excursion balance test (% of leg length)	N=17 65.9 (54.6 – 77.1)	N=5 54.4 (33.3 – 75.5)	11.5 (-12.7 – 35.7)	21.5	0.5	0.333

Supplementary Table 2. Children with LFD alone vs PFFD and LFD

Functional Measure	Adjusted Mean Not PFFD (95% CI)	Adjusted Mean PFFD (95% CI)	Adjusted Mean Difference (95% CI)	SD	Cohen's D	p-value
Six minute walk test (m)	N=31 478.8 (453.1 – 504.5)	N=6 427.6 (368.0 – 487.1)	51.3 (-14.1 – 116.6)	95.3	0.5	0.120
Standing long jump (cm)	**N=25** **124.5** **(114.8 – 134.1)**	**N=6** **101.9** **(82.0 – 121.7)**	**22.6** **(.4 – 44.8)**	**33.5**	**0.7**	**0.046**
Timed up and down stairs test (seconds)	N=13 9.2 (6.5 – 11.9)	N=5 10.3 (5.9 – 14.7)	-1.1 (-6.3 – 4.1)	4.4	0.2	0.658
Star excursion balance test (% of leg length)	N=17 66.6 (55.6 – 77.5)	N=5 52.1 (31.8 – 72.3)	14.5 (-8.6 – 37.5)	21.5	0.7	0.205

Supplementary Table 3. Children with Paley Types 1 & 2 LFD vs Paley Types 3 & 4 LFD

Functional Measure	Adjusted Mean Paley 1&2 (95% CI)	Adjusted Mean Paley 3&4 (95% CI)	Adjusted Mean Difference (95% CI)	SD	Cohen's D	p-value
Six minute walk test (m)	N=20 473.7 (439.7 – 507.7)	N=17 466.8 (429.8 – 503.8)	6.9 (-44.9 – 58.7)	95.3	0.1	0.788
Standing long jump (cm)	N=14 126.1 (112.5 – 139.7)	N=17 115.2 (102.9 – 127.5)	10.9 (-7.5 – 29.4)	33.5	0.3	0.236
Timed up and down stairs test (seconds)	N=7 7.6 (4.1 – 11.0)	N=11 10.7 (7.9 – 13.4)	-3.1 (-7.5 – 1.3)	4.4	0.7	0.156
Star Excursion Balance Test (% of leg length)	N=8 74.9 (59.7 – 90.1)	N=14 56.6 (45.2 – 68.1)	18.3 (-.8 – 37.3)	21.5	0.8	0.059

Supplementary Table 4. Children with LFD who have undergone an amputation vs no amputation

Functional Measure	Adjusted Mean Non-Amputee (95% CI)	Adjusted Mean Amputee (95% CI)	Adjusted Mean Difference (95% CI)	SD	Cohen's D	p-value
Six minute walk test (m)	N=29 459.3 (432.6 –485.9)	N=8 511.3 (458.6 – 564.0)	-52.0 (-112.4 – 8.3)	95.3	0.5	0.089
Standing Long Jump (cm)	N=23 119.4 (108.5 – 130.3)	N=8 122.0 (103.2 – 140.9)	-2.6 (-24.7 – 19.5)	33.5	0.1	0.810
Timed Up and Down Stairs Test (seconds)	N=12 9.3 (6.5 – 12.2)	N=6 9.8 (5.7 – 13.9)	-.5 (-5.5 – 4.5)	4.4	0.1	0.838
Star Excursion Balance Test (% of leg length)	N=15 67.7 (56.0 – 79.4)	N=7 53.8 (36.6 – 71.0)	13.9 (-7.1 – 34.9)	21.5	0.6	0.182

Supplementary Table 5. Children with LFD who have not undergone lengthening surgery vs those who have.

Functional Measure	Adjusted Mean Not Lengthened (95% CI)	Adjusted Mean Lengthened (95% CI)	Adjusted Mean Difference (95% CI)	SD	Cohen's D	p-value
Six minute walk test (m)	**N=26 495.3 (467.7-523.0)**	**N=11 411.9 (365.0-458.0)**	**83.443 (25.8 – 141.1)**	**95.3**	**0.9**	**0.006**
Standing Long Jump (cm)	N=20 125.3 (113.4 – 137.2)	N=11 110.6 (93.8 – 127.3)	14.8 (-7.2 – 36.7)	33.5	0.4	0.179
Timed Up and Down Stairs Test (seconds)	N=7 9.2 (5.5 – 12.9)	N=11 9.650 (6.69 – 12.609)	-.4 (-5.2 – 4.3)	4.4	0.1	0.849
Star Excursion Balance Test (% of leg length)	N=11 62.3 (47.8 – 76.8)	N=11 64.2 (49.8 – 78.7)	-2.0 (-22.8 – 18.9)	21.5	0.1	0.846

Chapter Four:
Discussion

4.1. Overview

The following explores the findings of this thesis within the context of the current understanding of LFD and the physical performance of individuals with the condition, as discussed in Chapter 1 and 2. This exploration will be in more detail than was possible in the manuscript submitted to the Journal of Pediatric Orthopaedics (Chapter 3). Each finding shall be presented and discussed. The discussion will explore both clinical applications and implications for future research.

The key findings are:

1. Children with LFD are significantly weaker in measures of lower limb strength than their unaffected peers. The difference between these two groups of children is small in young children, and larger in older children.
2. Children with LFD perform significantly worse in walking performance than their unaffected peers. The difference between these two groups of children is small in young children, and larger in older children.
3. Children with LFD perform significantly worse than their unaffected peers in speed of stair ascent and descent and single leg balance, but not in jump distance performance. The performance in these tasks across ages is variable and does not follow a consistent trend.
4. There is no statistically significant difference in physical performance between the subgroups of children with LFD, with the exception of poorer walk performance in children who have undergone lengthening and poorer jump performance in children with a co-diagnosis of PFFD.

4.2. Thesis findings and implications for clinical practice and research

4.2.1. Finding 1: Children with LFD are significantly weaker than their unaffected peers. The difference between these two groups of children is small in young children, and larger in older children.

Children with LFD are significantly weaker than their unaffected peers in all lower limb muscle groups according to hand-held dynamometry measurements. This statistically significant difference held true for both the most affected limb and the least affected or non-affected lower limb. When adjusted for age and gender, the z-scores of mean strength values in children with LFD were between 1.7 and 3.4 standard deviations below the scores of their unaffected peers (as presented in Chapter 3, Figure 3). Furthermore, the difference in strength between children with LFD and their unaffected peers was smaller in younger children and larger in older children with LFD as they enter adulthood. The change in these differences was significant (Chapter 3, Figure 5).

4.2.1.1. Clinical Implications

These findings suggest clinicians may improve clinical care of children with LFD through integrating timely assessments of lower limb muscle strength. Hand-held dynamometry, as performed in this paper (Chapter 3), is a low cost, easily transportable, reliable and valid method of strength assessment in the clinical setting. The early assessment of lower limb strength may identify children with LFD performing particularly poorly in comparison to their unaffected peers, who may in turn benefit most from intervention.

Given that this was a cross-sectional study, it does not provide longitudinal data that would inform clinicians as to how a child is changing with age. Nevertheless, these findings suggest a progressive lack of improvement of strength performance in children with LFD as they grow older so that with age there is a "falling behind" effect relative to their peers. If this is the case, not only is early strength assessment important, but repeated assessments throughout childhood may also be helpful to identify timepoints where performance may be falling further behind the normative values of peers and intervene accordingly.

Currently there are no randomised controlled trials that assess the efficacy of interventions aiming to improve lower limb strength of children with LFD, such as specific lower limb strengthening programs. However, given the findings of significant weakness in this cohort it would be appropriate for clinicians to implement such interventions and monitor the results closely. If intervention is conducted in children at an early age and the benefits are maintained, this could potentially change the gradient of strength performance across childhood ages, resulting in the difference between strength performance of children with LFD and their peers being markedly reduced.

The findings of this study also suggest that routine assessment of the least affected or unaffected limb in children with LFD is indicated, given that this side was also significantly weaker than unaffected peers. The reason for this weakness on the least affected or unaffected side is unknown. There is some evidence to suggest that individuals with musculoskeletal conditions do less vigorous activity than unaffected peers, however this data relates to the adult population.[70] There is currently no such equivalent data available for children with musculoskeletal conditions. It is possible that children with LFD perform less physical activity and lower limb strengthening activity overall than their peers, resulting in both limbs being significantly weaker, but there is no current evidence to support or refute this theory. The clinician may consider assessing factors impacting on a child's level of strength or weakness including their level and type of physical activity.

It is well-established that surgical limb lengthening procedures cause lower limb muscle weakness.[67-69] It is unknown by exactly how much lengthening procedures affect strength and how long this takes to recover, however it appears likely that those with LFD who are already weaker than their peers, will be at risk of becoming weaker still when undergoing lengthening procedures

as discussed in Chapter 2. There is currently no available evidence that assesses the efficacy of specific strengthening interventions in children with LFD before, during or after lengthening procedures, however the clinician would be well-advised to monitor strength levels in these children and intervene accordingly.

4.2.1.2. Research Implications

While it is clear that children with LFD are weaker than their peers, it is unclear why. If their affected side alone was significantly weaker, one may assume the weakness is entirely the result of the hypoplastic limb. However, given the results presented in Chapter 3, the least affected side was also significantly weaker, which included an unaffected limb in the 82% of children with unilateral LFD. Further research is required to understand what other factors may be contributing to this weakness.

As identified above, the level of participation in physical activity including strength-based sports may have an impact on the overall lower limb strength of children with LFD. Research into levels of physical activity in this population would be highly beneficial, to understand if the type and magnitude of physical activity that a child with LFD is performing is directly related to their level of lower limb strength. Whilst a number of studies have assessed activity levels of children with LFD using validated participant-reported outcome measures, as outlined in Chapter 2, this has almost exclusively been in the context of post-operative management. The physical activity levels in a general cohort of children with LFD has not been assessed with validated participant-reported outcome measures or objective measures, nor have activity levels been compared to normative reference values. Such data would be helpful in understanding whether reduced physical activity is a possible cause of weakness in children with LFD.

It is also unknown whether the lower limb strength of children with LFD can be improved in order to reduce the difference between the strength values of children with LFD and their unaffected peers. There is no current literature examining if specific strength-training programs can improve the magnitude of lower limb strength in these children. While a randomised controlled trial would provide the highest level of evidence to support the effectiveness of strengthening programs, other trial designs would be informative prior to embarking on a large-scale study. For example, feasibility studies involving child and parent feedback on the acceptability of a short-term home-based, physiotherapist-led strengthening program would provide helpful information and practical guidance.

Longitudinal clinical research is required to confirm if the trend observed in the original research presented in Chapter 3 is true as an individual child ages, namely that they become progressively less strong in comparison to their peers throughout the childhood and adolescent years. If this is true, further studies examining the effect of implementing strengthening intervention at varying ages, but particularly programs that would be suitable for younger children with LFD may also be undertaken to inform best practice. Such programs may be designed to be incorporated into preschool and school settings to improve feasibility. Studies examining the effect of strengthening interventions before, during and/or after lengthening procedures would also be of great benefit in providing insight into the possible means by which additional detrimental weakness may be avoided in children with LFD who are undergoing limb lengthening.

4.2.2. Finding 2: Children with LFD perform significantly worse in walking performance than their unaffected peers. The difference between these two groups of children is small in young children, and larger in older children.

Children with LFD performed on average 1.7 standard deviations below unaffected peers in walking performance as measured using the 6-minute walk test (Chapter 3, Figure 4). The difference in distance walked between children with LFD and their unaffected peers was smaller in younger children and larger in older children with LFD, as they enter adulthood. The change in these differences was statistically significant (p=0.015) and of great clinical significance given that children with LFD aged 15-18 years walked almost 200 metres less than their unaffected peers in 6 minutes, as demonstrated in Chapter 3, Figure 6.

4.2.2.1.Clinical Implications

It is already established that adults with LFD walk significantly shorter distances than their peers in the same time frame.[59] These findings of the original research presented in Chapter 3 of this thesis suggest this is also true in children. Whilst this cross-sectional study cannot provide reliable prognostic data, it reveals a likely trend similar to strength performance in children with LFD, i.e. that their walking performance falls progressively further behind that of their peers.

It is unknown why children, or adults, with LFD have poorer walking performance. It is known that weakness can play a contributory role to performance in the six minute walk test in older adults.[71,72] This has not been demonstrated in children, however it appears possible that the poor performance seen in children with LFD in this measure may be in part due to the significant lower limb weakness already identified. Particularly since a similar trend across ages is seen in both outcome measures. If this is the case, interventions to improve lower limb strength as identified in the previous section, may serve to also improve the walking performance of children with LFD.

Foot position may also play a contributory role in walk performance in this population. As identified in Chapter 2, a plantigrade foot is a key treatment outcome that guides the clinician's

intervention. Good functional ability in children (including walking performance) has been demonstrated to be associated with greater ankle dorsiflexion flexibility.[72] Therefore, a non-plantigrade foot or a foot with a reduction in ankle range of motion may have a negative impact on walk performance. A number of studies identified in Chapter 2 report some reduction in ankle range of motion in children with LFD (both pre-operatively, and after surgical management). In our cohort 3 children were unable to achieve a plantigrade ankle position. (Chapter 3, Table 3). These children had all undergone lengthening surgery, and 2 of the 3 had also undergone some corrective foot/ankle surgery and were Paley type 3. The child who had not undergone any foot/ankle surgery was Paley type 1 but had undergone the greatest lengthening of any child in the study (10cm) (Chapter 3, Results). Specific analysis comparing these children and the remainder of the cohort was not undertaken due to the small number of cases.

4.2.2.2. Research Implications

Further research is required to understand the reasons behind the poorer walking performance in children with LFD and the variation seen in walking performance at different ages. Longitudinal data is again required to examine whether the trend observed in this study holds true over time, i.e. does walking performance of children with LFD fall progressively further behind that of healthy children, with increasing age? Studies that compare the relative contributions of weakness and ankle range of motion on walking performance in children with LFD would be of great benefit. This will require significantly large cohorts given the heterogeneity within the clinical spectrum of children with LFD. It would also be worthwhile to examine any effect that various surgical or other management pathways have on walking performance in this population.

Research assessing the efficacy of intervention aiming to improve walking performance in children with LFD would be beneficial. This may include interventions aimed at improving one of the

potential contributory impairments proposed above such as weakness or foot position. Task-specific training may also be of benefit and hence requires research to examine its efficacy.

4.2.3. Finding 3: Children with LFD perform significantly worse than their unaffected peers in speed of stair ascent and descent and single leg balance, but not in jump distance performance. The performance in these tasks across ages is variable and does not follow a consistent trend.

Children with LFD performed on average 2.45 standard deviations below peers in performance on stairs, 2.48 standard deviations below peers in single-leg balance of the most affected leg, 1.96 standard deviations below in single-leg balance of the least affected or unaffected leg. Only in jump performance was there no statistically significant difference between children with LFD and their peers, at 0.27 standard deviations below their unaffected peers.

4.2.3.1. Clinical Implications

Firstly, these findings provide helpful, practical information that may be included in the general counsel and education provided by clinicians to children with LFD and their families. Such education that may help families understand what to expect from this condition including prognostic information throughout childhood, can now include evidence-informed explanations that children with LFD are likely to have more difficulty than their unaffected peers with certain activities of daily life. Clinicians can in turn provide further support to children with LFD to facilitate equal participation and access, such as through environmental modifications or additional support in their homes, schools and communities. This new objective data, not previously available, allows both the clinician and family to better anticipate and understand these needs.

There are currently no studies that assess whether training at these tasks may improve performance in children with LFD, however given the significant difference between the performance of children with LFD in negotiating stairs and balance, it is appropriate that the clinician seeks opportunities to assist the child in improving this performance where possible. A number of studies have demonstrated improvement in adolescents with ankle instability by practicing balance tasks.[73,74] However this has not been evaluated in younger children or children with limb deficiencies. The star excursion balance test was used in these studies and found to be sensitive to changes with such training programs, and therefore may be a useful tool in the clinical setting to both assess balance and monitor improvement during interventions targeted at improving balance.[73,74]

The reason or reasons for the poor performance in the star-excursion balance test of single-leg balance is unknown. Weakness, poor foot/ankle position and reduced ankle range of motion, as identified above, may all have a significantly negative effect on the overall performance of single-leg balance.[25,75] In addition the presence of antero-posterior knee instability in children with LFD may also be playing a role in this poor performance. As identified in Chapter 1, Table 1, 95% of individuals with LFD do not have an ACL and 60% do not have a Posterior Cruciate Ligament (PCL). There has also been consistent reporting of objective knee instability and inconsistent reports of subjective knee instability in children with LFD (Chapter 2). While there is a paucity of data assessing the impact that congenitally absent cruciate ligaments have on single leg balance, in populations who have experienced traumatic cruciate ligament injuries it has been shown that single leg balance is significantly worse after cruciate disruption and improved with either physiotherapy or ligamentoplasty.[76] It is of great importance when considering balance and the contributory factors, to delineate between objectively identified joint laxity and functional instability. Joint laxity, such as the increased antero-posterior translation present in children with LFD who have an absent of hypoplastic cruciate ligaments is well-established. Less clear is the

presence of functional instability that may impact on an individual's ability to perform certain daily tasks or sporting activities, and the relationship between this functional instability and the previously acknowledged joint laxity. This distinction must be carefully considered when determining the timing and method of intervention. Implementing physiotherapy intervention or ligamentoplasty to improve single leg balance may be appropriate in this population if the functional instability is deemed significant. It may also be helpful to monitor such balance closely in conjunction with questioning children with LFD and their parents regarding symptoms of instability or pain in the knee, particularly if these symptoms are having a detrimental effect on function and activity participation. This will serve to guide both the potential physiotherapy intervention and surgical intervention as described above.

The poor performance demonstrated by children with LFD on stairs is likely to be influenced by all impairments already discussed, i.e. lower limb weakness, foot position, ankle range of motion, knee instability and overall lower limb balance. Hence, it is possible that interventions focus on one or all of these impairments may improve stair performance. Whilst it is clear from the research that children with LFD perform ascending and descending stairs slower than their peers, it is unclear to what extent the child with LFD should be supported in this activity by either attempting interventions that may improve stair performance or instead by modifying the environment to minimize the need to negotiate stairs and hence allowing children with LFD to better keep up with their peers. Again, it is possible that stair performance could be improved by task-specific training of this activity, but this has not been formally assessed in a paediatric population, LFD or other.

The children performed slightly worse in middle childhood in the timed up and down stairs test, than in early or late childhood. The reason for this "dip" in stair performance during childhood is unknown. A possible theory for this may include middle childhood being a "peak" period for

interventions such as lengthening procedures.[6,54] In this study, 60% of the "middle childhood" group had undergone lengthening procedures, whereas 50% of the "older childhood" group and 29% of the younger childhood group had undergone lengthening. However, without further data such theories remain conjecture alone.

Finally, the equal performance of children with LFD on the jump performance in comparison to their unaffected peers is worthy of note. The reason why children with LFD do perform on par with their peers in this functional activity compared to their poor performance in all other functional activities is unknown. The standing long jump assesses explosive power of the lower limbs. While, as this paper demonstrates, children with LFD have significantly weaker lower limbs than their unaffected peers, this was assessed with hand-held dynamometry that requires sustained muscle force for several seconds. This seems to suggest that children with LFD are able to achieve forces with their lower limb musculature equal to their peers for very brief, explosive moments, however they cannot sustain such forces for a "prolonged' period of multiple seconds during dynamometry testing or further prolonged periods such as during the six minute walk test or timed up and down stairs test. Furthermore, given there was no significant difference between jump performance when comparing different aged-groups of children with LFD (Chapter 3, Figure 6), it suggests that children with LFD are able to maintain their explosive power at all ages, despite the picture of progressive "falling behind" relative to their peers in strength performance. Therefore, when providing interventions to address the weakness in children with LFD, clinicians should focus on building sustained muscle force rather than brief explosive force.

4.2.3.2. Research Implications

Greater investigation is required to understand the impact of various impairments on the performance seen in these various tasks of physical performance. Specifically, studies that compare

the relative contributions of weakness, foot position, ankle range of motion, and knee instability in children with LFD on stair performance and single-leg balance performance would be of great benefit. This will require significantly large cohorts given the heterogeneity within the clinical spectrum of children with LFD.

Following this, further research is required to examine whether the performance in these functional tasks can be improved with physiotherapy training of strength, speed or balance to varying degrees relevant to each measure. Closer examination of strength performance, comparing explosive power, maximal power and sustained endurance power would also serve to inform the clinician as to the specific deficits of weakness in children with LFD and how these can best be addressed.

4.2.4. Finding 4: There is no statistically significant difference in physical performance between the subgroups of children with LFD, with the exception of poorer walk endurance in children who have undergone lengthening and poorer jump performance in children with a co-diagnosis of PFFD.

Children who had undergone lengthening procedures performed worse than those who had not in the six minute walk test, where they walked on average 83 metres less (Chapter 3, Supplementary Table 5). This was not only a significant finding (p=0.006) but considered a large effect size (Cohen's d = 0.9, Chapter 3, Supplementary Table 5) with 67% power (Chapter 3, Results). Children with a co-diagnosis of PFFD performed significantly worse in the Standing Long Jump compared to those without, with a mean difference of 23 centimetres (p=0.046). This was a medium effect size with low power (Chapter 3, Supplementary Table 2). There were no other statistically significant differences between subgroups of children with LFD.

4.2.4.1. Clinical Implications

These findings reveal that despite the large heterogeneity in the population of children with LFD, there is overall a small difference between them when dividing them into common clinical groups. This suggests that current classifications (including the Paley classification) or key anatomical features (such as bilateral presentation or major femoral involvement) are not useful predictors of functional performance in these children. It is possible that this is due to appropriate surgical intervention which has resulted in a "levelling of the playing field" in this condition where children with a more "severe" anatomical presentation can perform similarly on a functional level to those children who are classified as having a "mild" anatomical presentation. As identified in Chapter 2, the surgeon sets out to minimize leg length discrepancy, optimize foot position and optimize knee function when managing the child with LFD. Hence, these results may suggest that in aiming for these 3 goals, functional differences between children with LFD are minimized. It is also possible that functional performance is not impacted by anatomical variation, however given the preceding discussion regarding various impairments and the potential functional consequences this seems less likely.

The lack of difference between children with unilateral or bilateral LFD in physical performance is particularly interesting. As previously identified, children with LFD are significantly weaker in both lower limbs when compared to norms, regardless of whether they were unilaterally or bilaterally affected. This trend appears to be consistent across all physical performance measures since there was no statistically significant difference in any measure when comparing the children with unilateral LFD to those with bilateral LFD. Whether this lack of difference is due to altered activity, as explored in "Finding 1" or other reasons is unknown.

The poor walking performance in children who have undergone lengthening procedures may be due to the aforementioned weakness, since it is well established that those who undergo

lengthening procedures develop weakness. (Finding 2, and Chapter 2) A similar study in the adult population of LFD found no difference in performance of the six minute walk test between those who had undergone lengthening and those who had not.[59] Since it is unknown how long the weakness post lengthening procedures persists (Finding 2 and Chapter 2), it is possible that the children in our study were still recovering from this secondary weakness and hence their poor walk performance, however by adulthood full recovery had taken place to ensure an equal performance in the adult population. As identified above, this may suggest that children who undergo lengthening surgery would benefit from more intervention aimed at maintaining or improving lower limb strength. However, given the disappearance of this sub group difference in the adult population, it is possible the cause of this worsening performance resolves without specific intervention.

The poorer jump performance in children with a co-diagnosis of PFFD compared to those without is potentially due to the relatively reduced quadriceps muscle length associated with a shorter femur and the resulting poorer length-tension relationship causing a poorer explosive power. However, there is no current literature that has examined this theoretical possibility. This finding had low power to detect a statistically significant change and hence requires further examination before applying to the clinical context and management of these children.

Finally, it is of high importance to note that 11 of the 20 subgroup tests had a small or minimal effect size (Cohen's D 0.0 – 0.4, Chapter 3, Supplementary Tables) indicating at least half of the findings demonstrated no difference or were underpowered due to small sample sizes. Hence, there is a high risk of Type 1 error in these results. The remaining 9 subgroup tests had medium or large effect sizes, however the power of these effect sizes remained small with walking performance of lengthening vs not being the only result with greater than 50% power (67%, Results, Chapter 3).

4.2.4.2. Research Implications

Further subgroup analysis with a larger number of participants is required before there can be a clear understanding of the differences in physical performance between children of different LFD subgroupings. Sample size calculations should be performed prior to future research to ensure there will be sufficient power in the findings. These should focus on those subgroup tests that have been identified by this paper as having medium or large effect sizes to ensure an adequate sample size is possible. Given both the rare nature of this condition and the heterogeneity already identified, multi-centre trials will be required in order to achieve these sample sizes.

4.3 Conclusion

LFD is a rare and heterogenous condition. Whilst it affects multiple lower limb structures, it has been unclear, until now, what impact the condition has on the physical performance of children. The understanding of this physical performance in children with LFD has to-date relied almost exclusively on non-validated or subjective data. In adults with LFD, it is clear that whilst there is great variation in subjective reports of physical performance from no significant issues to much poorer performance than unaffected peers, the available objective data demonstrates adults with LFD perform much worse than their peers in measures of physical performance. This paper provides novel objective data demonstrating that children with LFD also perform much worse than their unaffected peers in measures of physical performance. Furthermore, this data suggests older children with LFD are performing much further below peers than younger children with LFD. These findings provide invaluable information to support clinical management, prognostic predictions and future research relevant to the child with LFD, their family, their treating clinicians, and future research investigators.

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Appendices

Appendix 1: Summary of Symptomatic and Functional Outcome Measures reported in Adults with LFD

Levels of evidence	Study	Type of Study	Participants	Intervention	Non-Validated Outcome Measures	Validated Clinician and Participant-Reported Outcomes	Validated Objective Measures
III	2017 Kaastad et al.[59]	Cross-sectional cohort	30 adults (18-35 years) with congenital limb deficiency. (20 with LFD).	Comparing amputation with limb salvage/lengthening and comparing both groups to norms.	(Nil reported)	Quality of Life: **SF36:**$^{\alpha}$ No difference between treatment groups. **EuroQOL:** No difference between treatment groups.	Walking Performance: **6MWT:**$^{\beta}$No difference between treatment groups, but adults with LFD significantly worse than norms. Stair Performance: **Stair Test:** No difference between treatment groups, but adults with LFD significantly worse than norms.
III	2012 Crawford et al.[47]	Cross-sectional case series	11 Adults with LFD and ACL deficiency	N/A	ADL's:$^{\chi}$ **Participant report of hobbies:** 9/11 adults with LFD reported relatively active hobbies. Occupation: **Participant report:** All employed in a broad range of occupations. Physical exertion not clarified.	Quality of Life: **SF36:**$^{\alpha}$ LFD participants had similar scores to control group but had lower scores in general health and higher scores in the physical role section compared to population with traumatic ACL injuries. **Co-Morbidity Index:** 5.63 on a scale of 0 = no co-morbidities and 100. Pain: **Hip & Knee Pain Questionnaire:** No	(Nil reported)

						difference between pain scores of unaffected and affected legs. Knee Function: **Tegner Lysholm knee score:** Mean score was 90.2 where 100 indicate best knee function and 0 worst.	
III	2011 Catagni et al.[16]	Retrospective cohort	32 Adults with LFD.	Limb Lengthening and Reconstruction procedures.	Activity Level: **Clinician report 0-3:** 4 mild restriction, 20 limitation of activity and 3 severe limitation of activity. Pain: **Clinician report 0-4:** 12 no pain, 12 pain at some time, 4 mild pain and 4 moderate pain. Range of Motion: **Clinician report (method not specified):** 8/32 full ROM of knee, 12 greater than 90 degrees of flexion and lacking less than 10 degrees of extension. 4 knee subluxation, 16 plantigrade foot and normal ROM. 16 residual foot deformities.	(Nil reported)	(Nil reported)
III	2009 Walker et al.[52]	Cross-sectional comparison study	62 Adults with LFD 28 Unaffected Adults for	Amputation or Lengthening Surgery	Social Status: **Non-validated Demographic questionnaire:** No difference between treatment groups in educational achievement, employment, income level, public assistance or disability payments.	Psychology: **Beck Depression Inventory II:** No difference the 2 treatment groups with LFD in depression scores. Unaffected norms had a higher mean score, but this remained	(Nil reported)

			comparison.		Symptoms/Comfort: **Non-validated Demographic questionnaire:** No difference between groups in reported limb pain, use of pain medicine, Sports and ADL's: **Non-validated Demographic questionnaire:** No difference between groups in sports participation and reported activity restriction.	within the scale of 'no indication for depression.' Quality of Life: **QLQ:**$^{\delta,}$ Adults with LFD who had undergone an amputation scored better than the lengthening group in job satisfaction, otherwise no difference was seen between groups with LFD overall. No difference overall between those with LFD and unaffected norms. **SF36:**$^{\alpha}$ No difference between treatment groups in health-related quality of life. Function: **AAOSLLM:**$^{\varepsilon}$ No difference between treatment groups. **AAOSFAM:**$^{\phi}$ Mean score was within 1 standard deviation of reference normative values.	
III	1999 Birch et al.[44]	Cross-sectional case series	12 Adults with LFD, 10 underwent physical	All had undergone Syme Amputations	Gait: **Report by clinician:** 9/10 reported as normal, 1/10 had an antalgic gait. Function: **Reported by participants:** no difficulty	Intelligence: **WAIS-R**:$^{\gamma}$ no significant difference between Adults with LFD and reference norms. Quality of Life:	Strength: **Cybex isokinetic dynamometer of knee flexion and knee extension:** Mean maximum torque strength of extension of the

			examination.		walking or running with prosthesis, 9/12 participation in recreational sports as children and adults, 5/10 could tolerate distal loading for walking without a prosthesis. <u>Range of motion:</u> **Report by clinician:** full and normal.	**QLQ:**$^{\delta}$, no significant difference between adults with LFD and reference norms. <u>Self-Concept:</u> **TSCS-R**$^{\eta}$**:** mean score of adults with LFD significantly lower than norms but within 1 standard deviation.	affected knee was 63% of the unaffected side, mean maximum torque strength of flexion of the unaffected side was 73%.

α Short Form 36

β Six Minute Walk Test

χ Activities of Daily Living

δ Quality of Life Questionnaire

ε American Academy of Orthopaedic Surgeons Lower Limb Module.

ϕ American Academy of Orthopaedic Surgeons Foot and Ankle Module.

γ Wechsler Adult Intelligence Scale-Revised

η Tennessee Self-Concept Scale-Revised (TSCS-R)

Appendix 2: Summary of Symptomatic and Functional Outcome Measures reported in Children and Adolescents with LFD

Levels of evidence	Study	Type of Study	Participants	Intervention	Non-Validated outcome Measures	Validated Participant or Clinician-Reported Outcomes	Validated Objective Measures
III	2018 Razak et al[62]	Retrospective case series	2 children with Type II (Achterman) LFD.	Ankle reconstruction and Lengthening	Range of Motion: **Clinician report:** 1 child full knee ROM after reconstruction and lengthening. ROM not documented in 2nd child. Nil method of measurement is provided.	(Nil reported)	(Nil reported)
III	2017 Sachlebe n et al.[49]	Retrospective case series	3 children with LFD (total 13 participants in study, predo-minantly children)	ACL Ligamentoplasty	AP stability: **Participant's report:** Improved knee stability (further detail not reported).	(Nil reported)	(Nil reported)
IV	2017 Kulkarni et al[38]	Retrospective cohort	29 children with LFD.	Ankle Reconstruction and Lengthening	(Nil reported)	Function/Healing/Pain: **ASAMI Score$^{\alpha}$:** 15 scored "excellent" post treatment 6 scored "good" 4 scored "fair" 2 scored "poor"	(Nil reported)
IV	2017 Hefny et al[47]	Prospective case series	8 children (10 limbs) with Type 3	Surgical hindfoot realignment.	Range of Motion: **Clinician report:** a "stable plantigrade foot" was achieved in 9 limbs, there was equinus in 1 ankle.	(Nil reported)	(Nil reported)

			(Paley) LFD.				
III	2017 Calder et al.[41]	Cross-Sectional Cohort	32 Adult and child Participants with Type 2 LFD (Achterman) who had not undergone lengthening.	Amputation (23) compared to use of an extension prosthesis (9)	(Nil reported)	Quality of Life: **PedsQL:**β No significant difference between groups. Pain: **Verbal Pain Scale:** Amputee group had less pain than extension prosthesis group. Mobility/Ambulation: **SIGAM**χ **Scale:** No significant difference between the groups. **K-Level:** Amputee group had higher levels of community ambulation than extension prosthesis group.	(Nil reported)
IV	2014 Mascarenhas et al.[61]	Retrospective Case Report	Adolescent with LFD and ACL deficiency.	ACL Ligamentoplasty	Sport Participation: **Participant report:** Returned to football without incident. ROM: **Clinician report:** post-operatively the participant had 130 degrees of flexion and full extension. And after revision surgery 120 degrees of flexion and full extension. The method of measurement was not detailed. Strength:	(Nil reported)	Strength: **Straight Leg Raise:** no extensor lag after either operation.

					Thigh atrophy: had improved to 15% when compared to the uninjured limb (method of measurement not detailed.		
III	2014 Shabtai et al.[57]	Prospective case series	18 individuals (13 with LFD)	Lengthening via an 122ataloguing 122ry nail.	(Nil reported)	(Nil reported)	Range of Motion: **Goniometer:** ROM of hip, knee and ankle was not statistically different between pre and post-treatment measures except ankle plantarflexion which was slightly improved.
III	2013 Oberc et al[12]	Retrospective case series	31 children with LFD	Amputation (22) or Lengthening/ Epiphyseodesis procedures (9)	(Nil reported)	Function/ADL's: **SMFA:**$^{\delta}$ (2 components: dysfunction and bother, both on 0-80 scale where higher score is worse):[G] Children with amputations: 12.5 dysfunction, 6.25 bother. Children post-lengthening alone: dysfunction 32, bother 31 Children who underwent epiphyseodesis alone: dysfunction 51, bother 52, Combination of lengthening and epiphyseodesis dysfunction 11, bother 2.	(Nil reported)
IV	2011 Figueroa et al.[60]	Retrospective case report	16-year-old with LFD and knee	Simultaneous surgical correction of	Gait: Clinician reported: normal gait without instability. Range of Motion:	(Nil reported)	(Nil reported)

			instability.	genu valgum and ACL construction.	Clinician reported: -5 – 110 degrees. (Method not described)		
III	2011 Alaseirlis et al.[54]	Retrospective Case Series	7 children with LFD	5/7 underwent bone lengthening surgery	Strength/Atrophy: **Clinician report:** all children reported to have calf atrophy but normal strength (No method of measurement provided). Limp: 5/7	ADL's: **LEFS:**$^{\varepsilon}$ Improved score 70.9 to 89.4%	(Nil reported)
III	2010 El-Sayed et al.[56]	Retrospective cohort	119 children with Achterman type 2 LFD	Limb Reconstruction & Lengthening	Range of Motion: **Clinician report:** Plantigrade foot in 78.3% of cases. Mild residual equinus or valgus in 21.6% of cases. Mobility: **Clinician report:** All individuals walking independently and without crutches at final review. Pain: **Participant report:** before treatment 44/119 reported ankle or knee pain.	General Function/ADL's: **MFA Questionnaire:**$^{\phi}$ All showed favourable results with satisfaction. Excellent: 70 Good: 49	(Nil reported)
III	2010 Changulani et al[51]	Retrospect Case Series	8 children with LFD	Limb Lengthening	Range of Motion: **Clinician report:** At last follow-up: 3/8 able to fully extend the knee, 5/8 had a fixed flexion contracture ($<10^0$) Mobility/walking: **Clinician report:** All participants 'ambulant and mobile'.	Quality of Life: **PedsQL:**$^{\beta}$ mean score 61/100, compared to health score of 83 (no statistical comparison performed).	(Nil reported)
III	2005 Kocher et al.[66]	Retrospective cohort	1 child with LFD (part of cohort of 44	ACL Reconstruction (physeal	Sports Participation: Clinician report: had not returned to cutting/pivoting sports but unclear if child was performing these pre-operatively.	Function: **Lysholm II:** unclear particular score for child with	(Nil reported)

			children)	sparing).		LFD, mean score 95.7 **IKDC:**[γ] unclear particular score for child with LFD, mean score 96.7	
IV	2005 Gabos et al.[50]	Retrospective case series	4 Adolescents including 1 with LFD and 2 with PFFD and LFD.	ACL Construction	ADL's and Sport: **Participant report:** Pre-operatively 1 participant was unable to continue playing sport due to knee instability and locking episodes. Post-operatively this participant reported he returned to basketball. Range of Motion: **Clinician report (method not specified):** Post-operatively there were no restrictions in knee flexion, but 1 participant had lost 10 degrees of extension. Walking: **Participant report:** Pre-operatively, all participants reported knee instability with walking despite bracing and strengthening exercises.	Knee Function: **Lysholm II:** Pre-operatively 38 mean and post-operatively 81.	(Nil reported)
III	2000 McCarthy et al[53]	Retrospective cohort.	25 children with LFD	Syme amputation (15) compared to lengthening via Wagner or Ilizarov	Activity Level: **Participant report on scale 0-3:** Group undergone amputation had mean score of 0 (no limitation), Group that had undergone lengthening had a mean score of 1.2 (mild restriction with strenuous activity). Pain Level: **Participant report on scale 0-4:** Amputation group: mean	(Nil reported)	(Nil reported)

				method (10).	score of 0.2 (no pain), lengthening group mean score of 1.2 (any pain).		
III	1999 Roux et al.[23]	Cross-sectional cohort	66 children with LFD	Nil Intervention. (Assessment of knee pathology)	Instability Symptoms: **Participant report:** 11/66 reported some instability and 2 of these (3%) reported the frequency of instability as troublesome. Functional Impact/Sports Participation: **Participant Report:** Some of the children played sports. Specific frequencies or method not reported.	(Nil reported)	(Nil reported)
	1998 Johnston et al[63]	Cross-sectional case series	10 children with LFD	Syme amputation (6) compared to limb lengthening/salvage (4)	(Nil reported)	(Nil reported)	Strength: **Cybex isokinetic dynamometer of ankle plantarflexion, knee flexion and knee extension:** Ankle plantarflexion 50% weaker in affected limb compared to unaffected limb of children who had undergone lengthening (21 vs 45 lbs). Knee flexion and knee extension significantly greater in unaffected limb than affected limb in all children with LFD (values not reported). Knee flexion was stronger in those who had had lengthening procedures, no difference in knee extension strength. Gait Analysis: **Kinematic and Kinetic Gait Analysis** (further detail of method not provided): Children post-

							lengthening: foot drop in affected limb, loss of dorsiflexion during stance, mild hyperextension of knee in stance. Children post-Syme amputation: no unusual sagittal plane kinematics in affected limbs, increased plantarflexion at toe-off on unaffected side. Increased knee valgus on affected side in coronal plane. Both groups had mild increase in stance phase pelvic obliquity, caused by a residual shortening, on the affected side. Power generation (ankle push-off) on the affected side was significantly less than on the normal side in Syme's limbs, in lengthened limbs there was less difference. Affected ankle in patients with lengthened limbs also did significantly more work than the ankles in patients with Syme's. The affected hip performed more work than the normal hip in those with a Syme amputation. The normal hips in patients with lengthened limbs produced more power and performed more work than the hip on the affected side.
III	1997 Naudie et al[15]	Retrospe ctive comparis	22 children with LFD	Amputation (12) vs Lengthening	<u>Walking Performance:</u> **Clinician report:** 6/12 who had undergone amputation were reported as 'ambulating well.' No clarifying detail was	(Nil reported)	(Nil reported)

		on case series		(10) by Ilizarov method	provided, and it was not stated whether or not the remaining 6 were ambulating to some degree. Of the 10 children who had undergone lengthening it was commented that 1 walked with a limp. No further detail regarding walking performance was provided on any of the remaining children. <u>ADL's and Sport Participation:</u> **Clinician report:** Of 12 children who had undergone amputation, 1 child was noted to be running and climbing, and another swimming but no additional or clarifying information provided other than to state "all functioning well." Of the 10 children who had undergone lengthening, 1 was commented as "doing sports". No detail provided on remaining 9 children. <u>Range of Motion:</u> **Clinician report:** 3/12 children were noted to have 'good ROM'. No detail or method of measurement provided.		
IV	1992 Miller et al[55]	Retrospe ctive case series	11 children with LFD (12 limbs)	Tibial lengthening	<u>Range of Motion:</u> **Clinician report:** Preoperative ankle range of motion was "normal" in 1 limb and "diminished" in 11 limbs. No method of measurement reported. At follow-up all limbs had regained "full" knee range of motion and all feet were plantigrade.	(Nil reported)	(Nil reported)
III	1990 Choi et	Retrospe ctive	43 individuals with LFD	Amputation (32) vs	<u>ADL's and Sport:</u> **Participant questionnaire (non-validated):** 6/11	(Nil reported)	(Nil reported)

	al[17]	cohort	(some adults were included in this cohort).	Lengthening by Wagner methods (11)	participants post lengthening able to participate in sports, 3 limited participation and 2 unable. 28/32 participants post amputation were able to participate in sport, 4 had limited participation. Pain: **Participant questionnaire:** Participants post lengthening: 4/11 had mild pain, the remaining had no pain. Participants post amputation: 4 reported mild pain, the remaining 28 reported no pain. Limp: **Participant questionnaire:** Participants post Lengthening: Only 1/11 reported no limp with reporting a moderate limp and 1 a severe limp. Participants post amputation: 8/32 had no limp, 20 reported a mild limp, 3 had a moderate limp and 1 a severe limp.		

α Association for the study and application of methods of Ilizarov

β Paediatric Quality of Life Inventory 4.0 Short form 15.

χ Special Interest Group in Amputee Medicine Score

δ Short Musculoskeletal Functional Assessment

ε Lower Extremity Functional Scale

ϕ Musculoskeletal Functional Assessment Questionnaire

γ International Knee Documentation Committee Score

Appendix 3: Analysis of strength and functional performance in children with LFD and their unaffected peers, comparing different age groups.

Statistically significant results indicated by 'bold' text in tables.

Strength and functional performance were compared across the different age groups of both the LFD population and normal population to examine the change in performance throughout childhood and adolescence.

Each diagnostic group (LFD and Norms) were divided into 4 age groups: Age Group 1 (AG1): 3-6 years, Age Group 2 (AG2): 7-10 years, Age Group 3 (AG3): 11-14 years, and Age Group 4 (AG4): 15-18 years.

Dependent variable (measure): **Ankle dorsiflexion**

Below is the summary Table for the 2 x 4 Analysis of Variance, with factors Condition Group (normal, LFD) and Age Group (AG1, AG2, AG3, AG4), arising from the use of planned orthogonal polynomial trend contrasts across the levels of AgeGroup that were conducted to examine the data for the presence of linear, quadratic and cubic trend components in the overall plot of the means across age, and for any difference between groups (ie. with or without the LFD condition) in terms of the shape of the functions across age. Because there are 8 independent groups, there are 7 possible independent contrasts that can be written and tested using the common error term from the ANOVA.

Contrast 1 Tests for Ankle Dorsiflexion differences between the mean scores of the two conditions

Contrast 2 Tests for linear trend across the levels of AgeGroup (ignores Condition grouping)

Contrast 3 Tests for differences between Conditions in linear trend (slope) over AgeGroup

Contrast 4 Tests for overall quadratic trend across the levels of AgeGroup

Contrast 5 Tests for differences between Conditions in quadratic trend (concave or convex)

Contrast 6 Tests for overall cubic trend (two turning points in the function, S or backward S)

Contrast 7 Tests for differences between Conditions in cubic trend

Note: Contrasts 1, 2, 4 and 6 are main effects (that involve only one factor in the ANOVA) and Contrasts 3, 5 and 7 are interaction contrasts that involve both factors.

Ankle Dorsiflexion

	df	$F_{(1,309)}$	p
[1] Group (Condition) main effect	**1**	**$(9.91)^2$ 98.2**	**.000**
[2] AgeGroup Linear main effect	**1**	**$(7.03)^2$ 49.4**	**.000**
[3] Group x AgeGroup Linear interaction	**1**	**$(4.7)^2$ 22.1**	**.000**
[4] AgeGroup Quadratic main effect	1	$(-.5)^2$ 0.3	.616
[5] Group x AgeGroup Quadratic interaction	1	$(-.5)^2$ 0.3	.596
[6] AgeGroup Cubic main effect	1	$(.3)^2$ 0.1	.762
[7] Group x AgeGroup Cubic interaction	1	$(-.9)^2$ 0.8	.396

Similarly, for ankle plantarflexion, knee flexion and extension, hip internal and external rotation, and hip abduction, as displayed below.

Ankle Plantarflexion

	df	$F_{(1,309)}$	p
[1] Group (Condition) main effect	**1**	**$(12.405)^2$ 153.9**	**.000**
[2] AgeGroup Linear main effect	**1**	**$(7.394)^2$ 54.7**	**.000**
[3] Group x AgeGroup Linear interaction	**1**	**4.685^2 22.0**	**.000**
[4] AgeGroup Quadratic main effect	1	$(-.659)^2$ 0.4	.510
[5] Group x AgeGroup Quadratic interaction	1	$(-.956)^2$ 0.9	.340
[6] AgeGroup Cubic main effect	1	$(.347)^2$ 0.1	.729
[7] Group x AgeGroup Cubic interaction	1	$(-1.282)^2$ 1.6	.201

Knee flexion

	df	$F_{(1,309)}$	p
[1] Group (Condition) main effect	**1**	**$(8.220)^2$ 67.2**	**.000**
[2] AgeGroup Linear main effect	**1**	**$(10.508)^2$ 110.3**	**.000**
[3] Group x AgeGroup Linear interaction	**1**	**$(4.983)^2$ 25.0**	**.000**
[4] AgeGroup Quadratic main effect	1	$(0.417)^2$ 0.2	.677
[5] Group x AgeGroup Quadratic interaction	1	$(-0.021)^2$ 0.0	.983
[6] AgeGroup Cubic main effect	1	$(0.023)^2$ 0.0	.982
[7] Group x AgeGroup Cubic interaction	1	$(-0.701)^2$ 0.5	.484

Knee Extension

	df	$F_{(1,309)}$	p
[1] Group (Condition) main effect	**1**	**$(8.628)^2$ 74.5**	**.000**
[2] AgeGroup Linear main effect	**1**	**$(10.698)^2$ 114.5**	**.000**
[3] Group x AgeGroup Linear interaction	**1**	**$(6.582)^2$ 43.3**	**.000**
[4] AgeGroup Quadratic main effect	1	$(1.733)^2$ 3.0	.080
[5] Group x AgeGroup Quadratic interaction	1	$(0.166)^2$ 0.0	.870
[6] AgeGroup Cubic main effect	1	$(-0.398)^2$ 0.2	.690
[7] Group x AgeGroup Cubic interaction	1	$(-0.888)^2$ 0.8	.380

Hip Internal Rotation

	df	$F_{(1,309)}$	P
[1] Group (Condition) main effect	**1**	**$(9.380)^2$ 88.0**	**.000**
[2] AgeGroup Linear main effect	**1**	**$(8.885)^2$ 79.0**	**.000**
[3] Group x AgeGroup Linear interaction	**1**	**$(5.594)^2$ 31.3**	**.000**
[4] AgeGroup Quadratic main effect	1	$(0.653)^2$ 0.4	.514

[5] Group x AgeGroup Quadratic interaction	1	$(-0.483)^2$ 0.2	.630
[6] AgeGroup Cubic main effect	1	$(0.370)^2$ 0.1	.711
[7] Group x AgeGroup Cubic interaction	1	$(-0.782)^2$ 0.6	.435

Hip External Rotation

	df	F	P
[1] Group (Condition) main effect	**1**	**$(7.068)^2$ 50.0**	**.000**
[2] AgeGroup Linear main effect	**1**	**$(9.615)^2$ 92.4**	**.000**
[3] Group x AgeGroup Linear interaction	**1**	**$(4.866)^2$ 23.7**	**.000**
[4] AgeGroup Quadratic main effect	1	$(0.960)^2$ 0.9	.338
[5] Group x AgeGroup Quadratic interaction	1	$(-0.001)^2$ 0.0	.999
[6] AgeGroup Cubic main effect	1	$(0.117)^2$ 0.0	.907
[7] Group x AgeGroup Cubic interaction	1	$(-0.477)^2$ 0.2	.634

Hip Abduction

	df	F	p
[1] Group (Condition) main effect	**1**	**$(8.870)^2$ 79.2**	**.000**
[2] AgeGroup Linear main effect	**1**	**$(10.405)^2$ 108.2**	**.000**
[3] Group x AgeGroup Linear interaction	**1**	**$(5.068)^2$ 26.0**	**.000**
[4] AgeGroup Quadratic main effect	1	$(-0.139)^2$ 0.0	.890
[5] Group x AgeGroup Quadratic interaction	1	$(0.294)^2$ 0.1	.769
[6] AgeGroup Cubic main effect	1	$(-0.462)^2$ 0.2	.644
[7] Group x AgeGroup Cubic interaction	1	$(-0.003)^2$ 0.0	.997

Similarly, for the functional performance measures as outlined below.

Dependent variable (measure): **6 minute walk test**

Summary Table for the 2 x 4 Analysis of Variance, with factors Group (Normal, LFD) and AgeGroup (AG1, AG2, AG3, AG4), using planned orthogonal polynomial trend contrasts across the quantitative variable AgeGroup to examine the data for the presence of linear, quadratic and cubic trend components in the function across age, and for any difference between groups (with or without the LFD condition) in terms of the shape of the function across age.

Because there are 8 independent groups, there are 7 possible independent contrasts that can be examined using the common error term from the analysis.

Six minute walk test

	df	$F_{(1,309)}$	p
[1] Group (Condition) main effect	**1**	**$(9.492)^2$ 90.1**	**.001**
[2] AgeGroup Linear main effect	**1**	**$(8.903)^2$ 79.3**	**.001**
[3] Group x AgeGroup Linear interaction	**1**	**$(2.435)^2$ 5.9**	**.015**
[4] AgeGroup Quadratic main effect	**1**	**$(-2.215)^2$ 4.9**	**.027**
[5] Group x AgeGroup Quadratic interaction	1	$(-1.474)^2$ 2.2	.141
[6] AgeGroup Cubic main effect	1	$(.305)^2$ 0.1	.761
[7] Group x AgeGroup Cubic interaction	1	$(.624)^2$ 0.4	.533

Contrast 1 Tests for 6MWT differences between the mean scores of the two conditions

Contrast 2 Tests for linear trend across the levels of AgeGroup (ignores Condition grouping)

Contrast 3 Tests for differences between Conditions in linear trend (slope) over AgeGroup

Contrast 4 Tests for overall quadratic trend across the levels of AgeGroup

Contrast 5 Tests for differences between Conditions in quadratic trend (concave or convex)

Contrast 6 Tests for overall cubic trend (two turning points in the function, S or backward S)

Contrast 7 Tests for differences between Conditions in cubic trend

Note: Contrasts 1, 2, 4 and 6 are main effects (that involve only one factor in the ANOVA) and Contrasts 3, 5 and 7 are interaction contrasts that involve both factors.

Similarly, for the remaining functional measures.

Standing Long Jump

	df	F	p
[1] Group (Condition) main effect	1	$(1.019)^2$1.0	.309
[2] AgeGroup Linear main effect	**1**	**$(8.792)^2$ 77.4**	**.000**
[3] Group x AgeGroup Linear interaction	1	$(0.685)^2$ 0.5	.494
[4] AgeGroup Quadratic main effect	1	$(-0.655)^2$ 0.4	.513
[5] Group x AgeGroup Quadratic interaction	1	$(-0.365)^2$ 0.1	.716
[6] AgeGroup Cubic main effect	1	$(-0.217)^2$0.0	.829
[7] Group x AgeGroup Cubic interaction	1	$(-0.379)^2$ 0.1	.705

Dependent variable (measure): **Timed Up and Down Stairs Test**

Summary Table for the 2 x 3 Analysis of Variance, with factors Group (Normal, LFD) and AgeGroup (AG2, AG3, AG4), using planned orthogonal polynomial trend contrasts across the quantitative variable AgeGroup to examine the data for the presence of linear and quadratic trend components in the function across age, and for any difference between groups (with or without the LFD condition) in terms of the shape of the function across age.

Because there are 6 independent groups, there are 5 possible independent contrasts that can be examined using the common error term from the analysis.

Timed Up and Down Stairs Test

	df	F	p
[1] Group (Condition) main effect	**1**	**$(-4.9)^2$ 24.0**	**.000**
[2] AgeGroup Linear main effect	1	$(-0.816)^2$ 0.7	.416
[3] Group x AgeGroup Linear interaction	1	$(-1.36)^2$ 1.9	.175
[4] AgeGroup Quadratic main effect	1	$(-1.37)^2$ 1.9	.173
[5] Group x AgeGroup Quadratic interaction	1	$(2.05)^2$ 4.2	.042

Star Excursion Balance Test Affected

	df	F	p
[1] Group (Condition) main effect	**1**	**$(9.8)^2$ 96.0**	**.000**
[2] AgeGroup Linear main effect	1	$(-1.1)^2$ 1.2	.285
[3] Group x AgeGroup Linear interaction	1	$(-1.5)^2$ 2.3	.139
[4] AgeGroup Quadratic main effect	1	$(0.713)^2$ 0.5	.476
[5] Group x AgeGroup Quadratic interaction	1	$(0.959)^2$ 0.9	.339

Appendix 4: National Health and Medical Research Council Levels of Evidence

Reprinted with permission from Coleman K, Norris S, Weston A, et al. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines STAGE 2 CONSULTATION Early 2008-end June 2009, viewed 26 March 2011. *Canberra, Australia.* 2009.

NHMRC Evidence Hierarchy: designations of 'levels of evidence' according to type of research question (including explanatory notes)

Level	Intervention [1]	Diagnostic accuracy [2]	Prognosis	Aetiology [3]	Screening Intervention
I [4]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among consecutive persons with a defined clinical presentation[6]	A prospective cohort study[7]	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among non-consecutive persons with a defined clinical presentation[6]	All or none[8]	All or none[8]	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial[9] ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study[10] ▪ Interrupted time series without a parallel control group	Diagnostic case-control study[6]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[11]	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

NHMRC Evidence Hierarchy Explanatory notes **Source:** Hierarchies adapted and modified from: NHMRC 1999; Bandolier 1999; Lijmer et al. 1999; Phillips et al. 2001.

[1] Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b*)*.

[2] The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002).

[3] If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (ie. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

[4] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

[5] The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

[6] Well-designed population-based case-control studies (eg. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

[7] At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in *both* arms of the trial would also meet the criterion for this level of evidence.

[8] All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

[9] This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).

[10] Comparing single arm studies ie. case series from two studies. This would also include unadjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).

[11] Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Appendix 5: Journal of Pediatric Orthopaedics Submission Guidelines

Journal of Pediatric Orthopaedics

Online Submission and Review System

SCOPE

The *Journal of Pediatric Orthopaedics* promotes communication of information on pediatric orthopedic problems and advances in patient care. We urge authors to comply with ethical principles as outlined in the Declaration of Helsinki (see J Pediatr Orthop editorial 1998;18:7012).

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Journal article

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Book chapter

2. Todd VR. Visual information analysis: frame of reference for visual perception. In: Kramer P, Hinojosa J, eds. *Frames of Reference for Pediatric Occupational Therapy.* Philadelphia, PA: Lippincott Williams & Wilkins; 1999:205-256.

Entire book

3. Kellman RM, Marentette LJ. *Atlas of Craniomaxillofacial Fixation.*Philadelphia, PA: Lippincott Williams & Wilkins; 1999.

Software
4. *Epi Info* [computer program]. Version 6. Atlanta, GA: Centers for Disease Control and Prevention; 1994.

Online journals
5. Friedman SA. Preeclampsia: a review of the role of prostaglandins. Obstet Gynecol [serial online]. January 1988;71:22-37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

Database
6. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 1996. Updated March 29, 1996.

World Wide Web
7. Gostin LO. Drug use and HIV/AIDS [*JAMA* HIV/AIDS Web site]. June 1, 1996. Available at: http://www.ama-assn.org/special/hiv/ethics. Accessed June 26, 1997.

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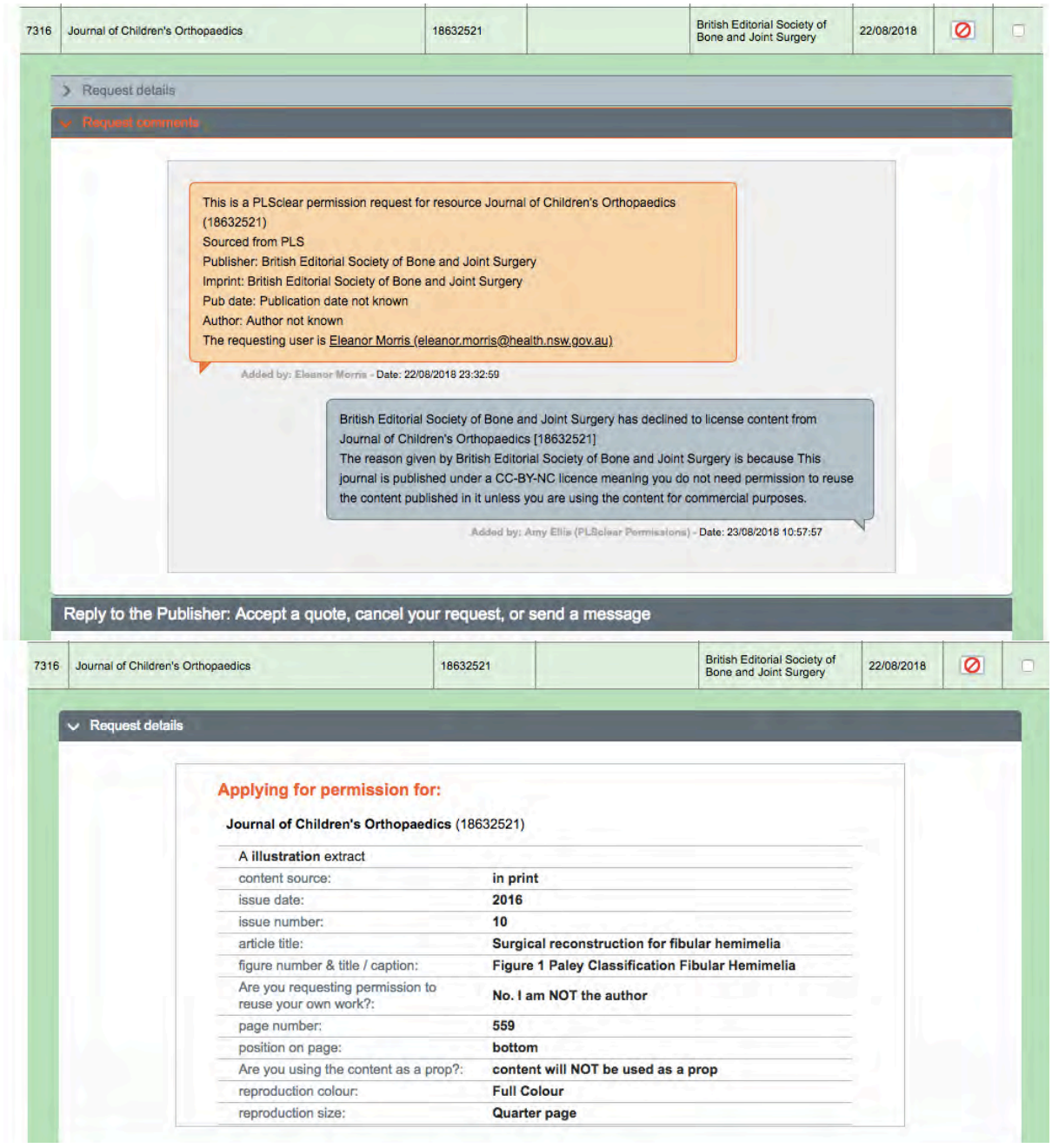

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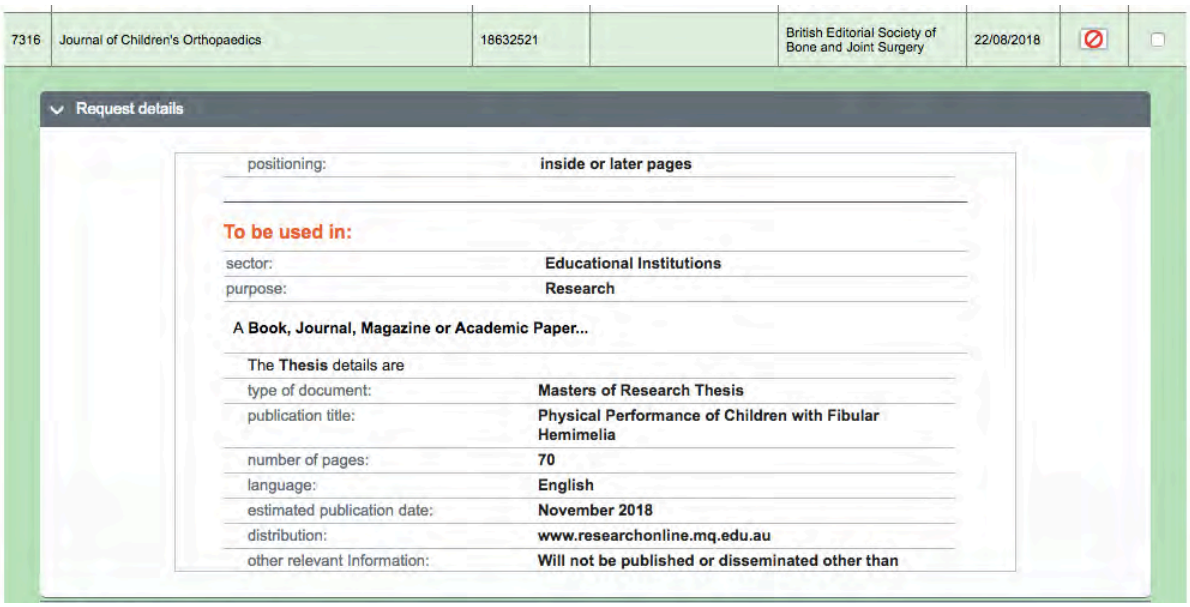

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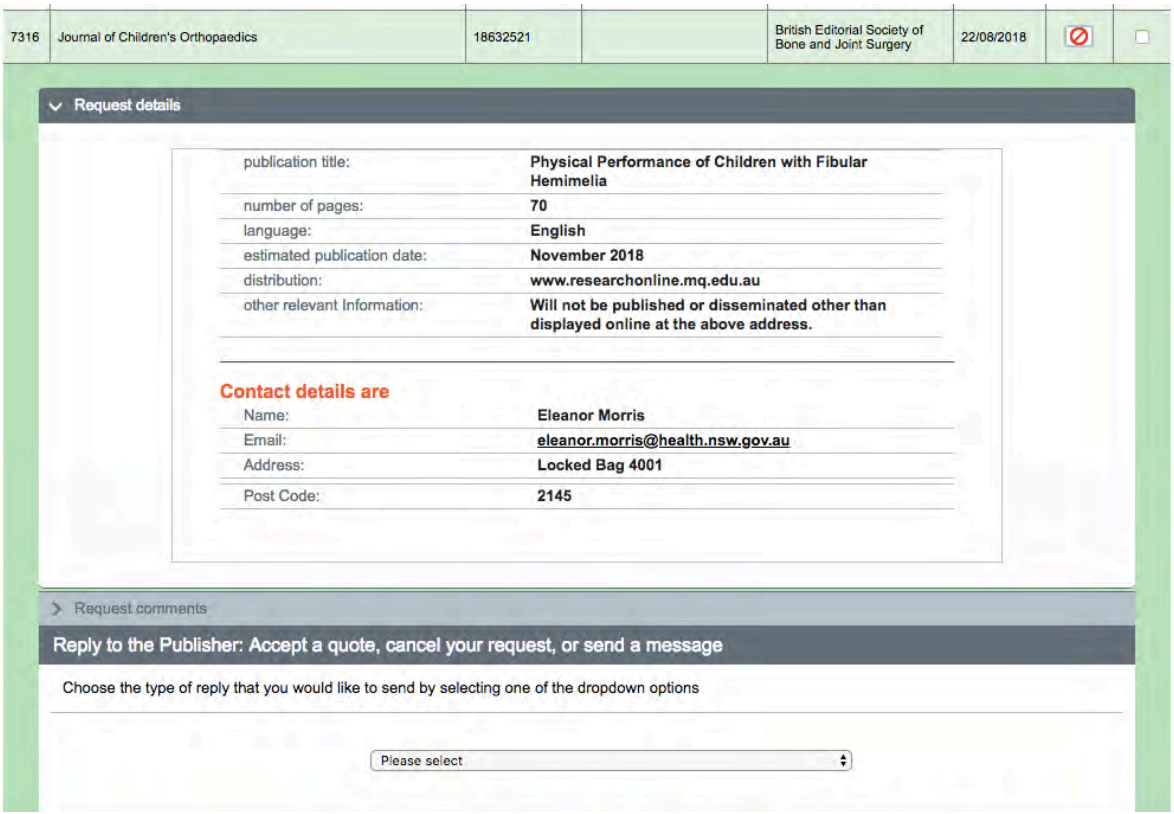

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5.2 This Licence contains the entire understanding and agreement of the parties relating to its subject matter and supersedes in all respects any previous or other existing arrangements, agreements or understandings between the parties whether oral or written in relation to its subject matter.

5.3 Licensee may not assign this Licence or any of its rights or obligations hereunder to any third party without Licensor's prior written consent.

5.4 This Licence is governed by and shall be construed in accordance with the laws of England and Wales and the parties hereby irrevocably submit to the non-exclusive jurisdiction of the Courts of England and Wales as regards any claim, dispute or matter arising under or in relation to this Licence.