From DEPARTMENT OF PAEDIATRICS AND CHILD HEALTH,
MAKERERE UNIVERSITY, KAMPALA, UGANDA
AND
DEPARTMENT OF WOMEN'S AND CHILDREN'S HEALTH
Karolinska Institutet, Stockholm, Sweden

CEREBRAL PALSY IN MULAGO HOSPITAL, UGANDA: COMORBIDITY, DIAGNOSIS AND CULTURAL ADAPTATION OF AN ASSESSMENT TOOL

Angelina Kakooza-Mwesige

Makerere University

Karolinska Institutet

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Front cover photo: A seventeen-year old boy with cerebral palsy at a health facility in Uganda.
Back cover photo: A mother with her child with cerebral palsy during a physiotherapy session
at a health facility in Uganda.

Cerebral Palsy in Mulago Hospital, Uganda: Comorbidity, Diagnosis and Cultural Adaptation of an Assessment Tool

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Angelina Kakooza-Mwesige

Principal Supervisor:
Prof. James. K. Tumwine
Makerere University College of Health Sciences
Department of Paediatrics and Child Health

Co-supervisor(s):
Prof. Ann-Christin Eliasson
Karolinska Institutet
Department of Women's and Children's Health
Neuropediatric Research Unit

Prof. Hans Forssberg
Karolinska Institutet
Department of Women's and Children's Health
Neuropediatric Research Unit

Opponent:
Assoc. Prof. Kate Himmelmann
University of Gothenburg
Department of Pediatrics

Examination Board:
Assoc. Prof. Joan Kalyango
Makerere University College of Health Sciences
Department of Clinical Epidemiology

Assoc. Prof. Lena Wettergren
Karolinska Institutet
Department of Dept. Neurobiology, Care Sciences
and Society

Assoc. Prof. Lena Westbom
Lund University
Department of Clinical Sciences
Division of Paediatrics

"Being Deeply Loved by A Child with Special Needs Gives You Strength, While Loving A Child With Special Needs Gives You Courage"---https://scrapperjudedesigns.files.wordpress.com

This work is dedicated in memory of my beloved brother,

Jude Matendo Kakooza

who suffered from cerebral palsy, epilepsy and autism and died at the youthful age of 30.

You will always be remembered for your quiet, beautiful spirit with a kind and tender heart.

Jude, may your soul rest in peace.

ABSTRACT

Background and aim: Cerebral palsy (CP) is the most common form of chronic motor disability that begins in early childhood and persists throughout life. The clinical features, including motor function, comorbidities and nutritional status, have not been investigated in Uganda. In addition, no assessment tool to measure functional skill development and the level of independence performance in activities of daily living has been developed for these children. The overall aim of this thesis was to describe the neurological, anthropometric and brain imaging findings of Ugandan children with CP and to develop a culturally relevant assessment tool for measuring their functional performance.

Methods and participants: Five cross sectional studies (I-V) were carried out at the Mulago National Referral Hospital in Kampala and in varied rural and urban districts within Uganda. Three studies were conducted at the health facility (I-III), while two were conducted in the community (IV-V). Study I investigated the clinical types, motor function and comorbidities of children with CP. In Study II, this same cohort had their anthropometric measurements taken, as well as information about their clinical, feeding and perinatal history to determine their nutritional status and associated factors. Study III, performed on a sub sample of the original cohort, investigated the brain computed tomography (CT) scans and associated features. In Study IV, the Pediatric Evaluation Disability Inventory (PEDI) was translated and cross-culturally adapted to the Ugandan environment to create the PEDI-UG instrument. The psychometric properties of the new PEDI-UG instrument was validated in Study V.

Results: Bilateral spastic CP was the main clinical subtype (45%). Severe gross and fine motor function levels were more common in the bilateral spastic and dyskinetic CP subtypes. Signs of learning disability (75%) and epilepsy (45%) were the most common comorbidities. Speech and language impairments were associated with bilateral spastic CP and severe gross and fine motor dysfunction (Study I). More than half (52%) of the children with CP were malnourished, with being underweight (42%) presented as the most common form. Malnutrition was associated more with children 5 years of age or older, and those with a history of complications during the neonatal period (Study II). The distribution of brain image patterns differed from that seen in high income countries with more primary grey matter injuries (PGMI) (44%) and normal scans (31%) and very few primary white matter injuries (4%). PGMI were more common in children with a history of hospital admission following birth (Study III). In the culturally adapted PEDI-UG, overall 178 of the original 197 PEDI items (90%) were retained, with a number of modifications in the remaining items, to create the final 185-item PEDI-UG. (Study IV). Most activities of the culturally adapted PEDI UG (95%) showed acceptable fit to the Rasch model. In addition, the caregiver assistant rating scale was changed from a six-point to four-point rating scale (Study V).

Conclusions: There was a large proportion of severely affected children with CP in this cohort, with frequent malnutrition and more PGMI. These results suggest a different etiology of CP in infants born full-term between sub-Saharan Africa and high-income countries. Our findings could imply a higher occurrence of birth asphyxia, postnatally acquired infections or other varied insults around the last trimester period which may possibly benefit from improved emergency obstetric and postnatal care. The culturally adapted PEDI-UG instrument with a four categories caregiver assistant rating scale is appropriate, providing a valid measure of the functional performance of typically developing children from the age of 6 months to 7.5 years in Uganda and other similar African contexts.

Keywords: cerebral palsy, child, brain injuries, malnutrition, disability evaluation, Uganda.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers, which will be referred to by their Roman numerals (I-V):

I.   **Kakooza-Mwesige A**, Forssberg H, Eliasson AC, Tumwine JK. Cerebral palsy in children in Kampala, Uganda: clinical subtypes, motor function and co-morbidities. BMC Research Notes 2015. 8: 166.
     doi: 10.1186/s13104-015-1125-9.

II. **Kakooza-Mwesige A**, Tumwine JK, Eliasson AC, Namusoke HK, Forssberg H. Malnutrition is common in Ugandan children with cerebral palsy, particularly those over the age of five and those who had neonatal complications. Acta Paediatrica 2015, 104: 1259–1268.
     doi: 10.1111/apa.13089

III. **Kakooza-Mwesige A**, Byanyima RK, Tumwine JK, Eliasson AC, Forssberg H, Flodmark O. Grey matter brain injuries are common in Ugandan children with cerebral palsy suggesting a perinatal etiology in full-term infants. Acta Paediatrica. 2016.
     doi: 101111/app.13352.[Epub ahead of print]

IV. **Kakooza-Mwesige A**, Tumwine JK, Forssberg H, Eliasson AC. Uganda cross-cultural adaptation of the Pediatric Evaluation Disability Inventory (PEDI) *(Submitted to the Journal of Disability and Rehabilitation)*

V.   Amer A, **Kakooza-Mwesige A**, Hermansson L, Tumwine JK, Forssberg H, Eliasson AC, Jarl G. Psychometric Properties of the Ugandan Version of the Pediatric Evaluation of Disability Inventory (PEDI-UG) *(Manuscript)*.

CONTENTS

LIST OF ABBREVIATIONS

CP	Cerebral Palsy
CT	Computed Tomography Scan
ICF	The International Classification of Functioning, Disability and Health
IRT	Item Response Theory
LMIC	Low and Middle Income Country
MNRH	Mulago National Referral Hospital
MRI	Magnetic Resonance Imaging
PEDI	Pediatric Evaluation of Disability Inventory
PGMI	Primary Grey Matter Injury
PWMI	Primary White Matter Injury
SCPE	Surveillance of Cerebral Palsy in Europe
WHO	World Health Organization

1 OPERATIONAL DEFINITIONS

Cerebral Palsy- this diagnosis is made when a child has a permanent, but not unchanging, disorder of movement and/or posture and of motor function, which is due to a non-progressive interference, lesion, or abnormality of the developing/immature brain.

Disability- any deficits in the performance of integrated daily activities.

Functional limitations- deficits which affect the child's ability to perform normal activities of daily living independently and safely.

Gross National Income per capita- is the gross national income, converted to U.S. dollars using the World Bank Atlas method, divided by the midyear population.

Impairment- any limitation or abnormality in anatomical, physiological or psychological processes.

Malnutrition- a child with a Z-score of -2.0 or lower in any of the nutritional indicators of weight, height/length, mid-upper arm and/or head circumference for age according to the World Health Organization (WHO) Standards.

Neurological condition- is any disorder of the brain, spinal cord and nerves.

Postnatal period- from birth until 2 years of age.

Prenatal period- from conception until birth.

Progressive disorders of motor function- when a child loses previously acquired skills during the first 5 years of life.

2 PREFACE

"Musawo, njagala ompandiikire ebbaluwa ensemba okutwaala omwana wange mu ssomero eddala. Omwana yayisibwa okugenda mu P.2 ku myaka kkumi egy'obukulu gyalina wabula abaana abalala tebaagala kuzannya naye. Nate era ku ssomero, eriyo amaddaala galina okulinnya okusobola okutuuka mu kibiinaakye, ekintu ekizibu gyaali. Ndi mukakafu nti omwana yalogebwa Mugya wange, y'ensonga lwaki tasobola kutambula yadde okwogera obulungi. Newankubadde kiri bw'ekityo njagala asome." (Doctor, I need you to write me a letter of recommendation enabling me to take my child to another school. He was promoted to primary 2 at the age of 10 years, but other children do not want to play with him and there are stairs he has to climb to reach his class which is difficult for him. I am certain he was bewitched by my co-wife, which is why he cannot walk or talk well. Despite this, I want him to get an education) *[Mother of 10yr old boy, Kampala district]*

"Musawo, omwana wange taseka, antunuulira butunuulizi, tasobola kutuula era y'esika emirundi mingi naddala ekiro. Mu butuufu, tasobola kukozesa mubiri ggwe kintu kyonna. Nyamba onfunire eddagala erinaamuwonya." (Doctor, my child does not laugh, she just stares at me, she cannot sit, she has many convulsions especially at night, and really she is unable to perform any bodily functions. Please help me with medicine to heal her). *[Adolescent mother of 18 month girl, Kiboga district]*

"Musawo,omwana wange yafuuka ekisekererwa ku kyaalo era ayitibwa 'mugogo' olw'okuba nti emikono gye wamu n'amagulu bikakanyavu nnyo. Newankubadde kiri bw'ekityo Musawo, mbulira, omwana wange alisobola ddi okutambula?" (Doctor my child is a laughing stock in the village and he is referred to as the 'wooden board', because his hands and legs are very stiff. However doctor tell me, when will my child be able to walk?) *[Mother of 4yr old boy, Wakiso district]*

"Musawo, ebyafaayo by'omwana ono ssi bimanyi. Yasuulibwa nnyina(eyali mukyala wa muganda wange) ewa Jajja ffe omukyala mu kyaalo nga wa myaka 2. Kitaawe tamufaako, yafuna omukyala omulala era kati abeera Kampala. Bye manyi byokka kwe kuba nti talaba, tawulira, tatuula, tatambula oba okwogera ku myaka 3. Takula bulungi era emikono n'amagulu ge agittambuza nnyo ekiseera kyonna, ekimuleetera okuba n'amalusu amangi mu kamwa." (Doctor I have no history regarding this child, she was abandoned by the mother (my brother's ex-wife) at our grandmothers place in the village at the age of 2 years. Her father is not bothered about her, he got another wife and now stays in Kampala. All I know is she is unable to see, hear, sit, walk or talk at 3 years. She is not growing well and also has abnormal limb movements from time to time that make her bring a lot of saliva in her mouth). *[Paternal aunt of 3yr old girl, Luweero district]*

These statements characterize some of the typical opening remarks made by the anxious mothers/caregivers who bring their children with cerebral palsy (CP) for consultation at the Paediatric Neurology Clinic in Mulago National Referral Hospital (Kampala, Uganda), where I have worked for the past 17 years. Moreover, they highlight four important aspects regarding disability in Uganda: i) myths about its cause, ii) the motor and associated limitations creating physical barriers that limit accessibility in the environment, iii) related stigma and discrimination, and iv) the lack of support from either family members or within the community.

Disability is a major public health concern worldwide and the situation for children with disabilities is even more deplorable. Children with disabilities comprise approximately one-

third of the world's disabled population, and in view that they now have a more enhanced likelihood to survive, require to have suitable services to cater for their various needs [1-3]. A multi-site study carried out in Africa by the World Health Organization (WHO) reported that the leading cause of disability was infections [4]. More recent studies, however, indicate that the causes of disabilities in children have shifted away from some of the communicable diseases, such as polio, malaria, tuberculosis, meningitis and parasitic disease to CP and other conditions that cause multiple disabilities [1].

The information available about children with disabilities in Uganda is scarce and unreliable, but the prevalence has been estimated at approximately 12 % [5]. Disabled children are a particular vulnerable group in Uganda because the population's attitude to disability is influenced by ignorance and superstition, among other things. Consequences from this situation ranging from social isolation, rejection, vulnerability and powerlessness exemplify the experience of many of these disabled children, hence their reference as "invisible" children [1].

CP is a common cause of childhood disability and is associated with abnormal development of movement and postural control. Research in developed countries on children with CP have shown that:1 in 3 cannot walk; 1 in 4 cannot talk; 1 in 2 have a cognitive impairment; 1 in 4 suffer from epilepsy; 1 in 25 are deaf and 3 in 4 experience pain [6].

Regrettably there is lack of national and accurate data relating to CP in Uganda and sub-Saharan Africa as a whole. CP is associated with a mixture of motor and non-motor impairments but these have never been described in Ugandan children. It is not clear what subtypes of CP are present or the level of motor function these children exhibit. The feeding practices of these children and their nutritional status has not been documented. The prevalence of HIV seropositivity status has never been studied in these children. To date, the possible etiologies of CP in Uganda remain poorly understood. Studies examining the pattern of brain injury in these children, which could furnish us with these answers as well as information from their past pre and postnatal history, is non-existent. There is also no available assessment tool to measure functional skill development and level of independence performance in the activities of daily living in these children.

This thesis attempts to address these gaps by enhancing our knowledge regarding CP in Uganda, and to provide future directions for the management and rehabilitation of this vulnerable population. It is hoped that the results from this research work will assist to shed more light on this neglected topic, and serve as the basis for informing policy and setting up larger epidemiological and community based intervention studies to improve the quality of life of children with CP and their caregivers in Uganda.

3 BACKGROUND

3.1 BACKGROUND OF CHILD DISABILITY IN UGANDA

Children with disabilities are one of the most marginalized and disadvantaged groups in our society and confer a large burden on child development. Statistical data relating to children with disabilities in Uganda is limited and rather inconsistent with conflicting reports from varied sources. Approximately 80% of the 100 million children with disabilities worldwide are under the age of five and live in developing countries [7], with the majority found in sub-Saharan Africa [8]. Based on estimations, the prevalence of childhood disability in Uganda is about 7-13%, which infers that about 2.5 million children live with some form of disability in Uganda. However, the prevalence of childhood disability varies across the country, being highest in the Northern region and lowest in the Eastern and Central regions [5], and also depending upon the sources of data utilized.

According to earlier information from the Uganda National Housing and Population Census, the highest proportion of disabilities is seen in those with physical impairments (34%), followed by the impairments of vision (24%) and hearing (15%) [9]. This trend has remained the same even with more recent studies. The African Child Policy Forum performed a multisite country study investigating the lives of children with disabilities in Africa and reported physical impairments contributing a quarter of the burden observed (See Figure 1) [1]. A growing problem in the health situation of Ugandans concerns non- communicable diseases (NCDs), which include disabilities. Despite this growing public concern, there is a lack of nationally representative data and NCD policy with a clear strategic plan and guidelines for their management.
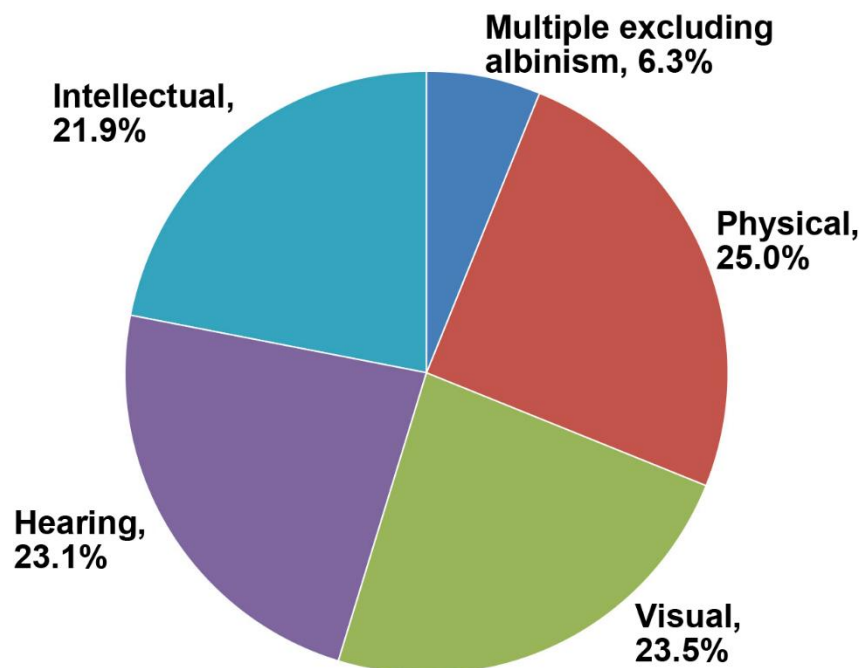
Figure 1. Children with disabilities in Uganda per types of impairment in percentage [1]

Regardless of the government of Uganda's pledge to provide treatment and care for individual NCDs at all levels of care within the health care system there is often scarcity of adequately trained health workers to provide NCD screening, early diagnosis, and treatment services. Rehabilitation services are in desperate need with less than 10% of people with disabilities having access. Furthermore, assessment tools for appropriate screening and diagnostic equipment are generally missing at the health facilities. In addition, there is insufficient supply of medicines and assistive care devices for the management of NCDs at the lower level health facilities (see section 3.13). All these issues present a draw back in the access of the Ugandan population to quality NCD care.

3.2 DEFINITION OF CEREBRAL PALSY

CP is a well-known neurodevelopmental disorder commencing in early childhood and persisting throughout life. The history of CP dates back to the times of ancient Egypt as illustrated in drawings from the 5th century BC [10]. Exploiting his own childhood disability as an inspiration, orthopedic surgeon Dr. John William Little wrote the initial medical reports of this condition in 1861, and was originally called 'Little's disease'. Later in 1889, Sir William Osler, built on Little's work, and coined the term "cerebral palsy" on the Latin words for "brain" and "paralysis" [11]. The definition of the current term 'cerebral palsy' has been the focus of debate over the years as illustrated by the varied number of concepts and descriptions of CP that have been put forward [12-16].

With the advent of advanced technology (modern brain imaging techniques) aiding our understanding of CP with respect to the developmental neurobiology and the changing concepts regarding impairments, functional status and personal 'participation', leaders in the preclinical and clinical services felt it important to reassess the definition of CP. To achieve this an International Workshop on the Definition and Classification of Cerebral Palsy was held in Bethesda, Maryland (USA) in July 2004. The aim of the workshop was to come up with international consensus definition that would provide a wide range of audiences with a common understanding about the cerebral palsy concept.

According to the consensus definition proposed by the International Executive Committee for the Definition of Cerebral Palsy, cerebral palsy describes "*a group of permanent disorders of the development of movement and posture causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behaviour, and/or by a seizure disorder*" [17]. Despite this all-encompassing definition, it is still challenging to define CP precisely given that other neurological conditions can present with similar motor symptoms. These include diseases specific to the peripheral nerves of the spinal cord (e.g. spinal muscular atrophy, myelomeningocele) or to the muscles (e.g. poliomyelitis, muscular dystrophies).

3.3   CEREBRAL PALSY AS A DISABILITY

The International Classification of Functioning, Disability and Health (commonly known as ICF) is an important framework from WHO for measuring health and disability that can help guide modern thinking about management of children with CP [18]. The ICF is an attempt to move away from the view that disability is simply a medical issue. It encourages health professionals and others working with disabled people to look beyond the health condition of an individual and consider other factors that may prevent or hinder them from participating in all aspects of life. The ICF consists of two parts: part one is directly related to an individual's health condition while the second part is linked to the circumstantial facets of the environment and personal factors. These circumstantial facets though not directly related to the patient's health condition may impact on how he/she views or accepts the disability, the consequences of the disability and how they cope in their day to day lives. Figure 2 illustrates this concept, with CP as the example. In this framework, disability is not solely due to the end result of a health condition, but also ensues as a result of the interaction between an individual's health condition and his/her external environment and is influenced by an individual's characteristics.
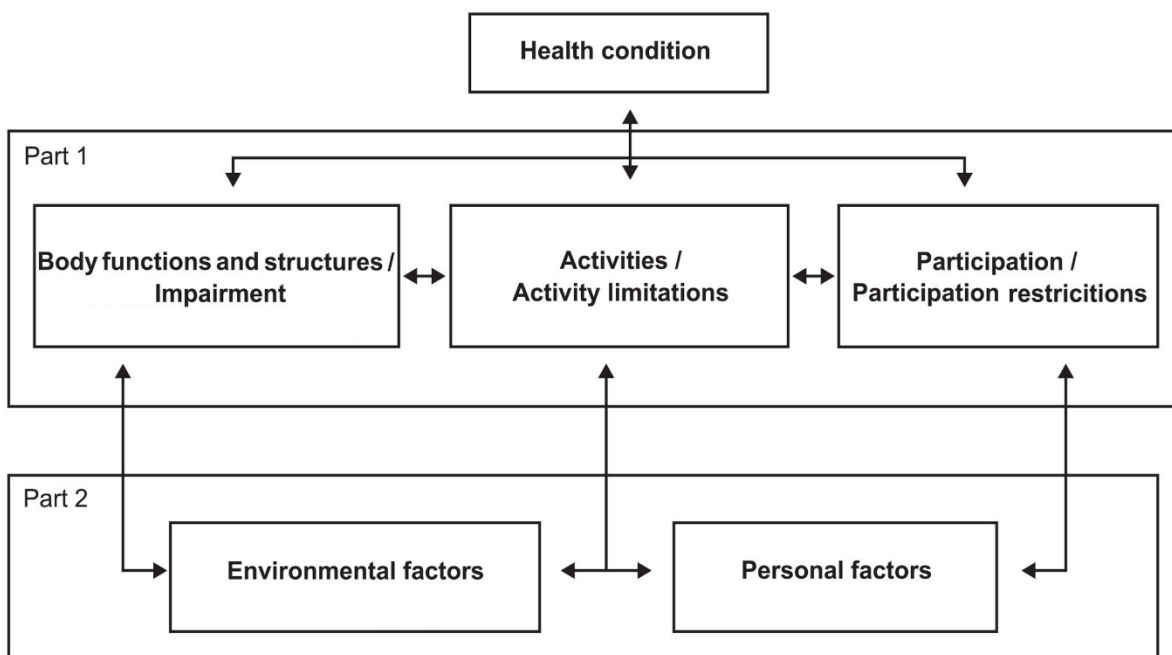
Figure 2. The ICF Model and its application in children with cerebral palsy. Adapted from WHO [18]

As illustrated by the ICF, most disabilities are the result of a medical condition which affects 'human functions or structure' as well as a person's ability to carry out 'activities'; it follows that doing less will lead to reduced 'participation'. Someone with severe quadriplegic CP, for example, is likely to have reduced mobility and be less able to participate in his/her chosen activities. Planning good access to buildings and public transportation may help, but unless 'participation' is also addressed, solving access to the activity is only part of the solution.

3.4   EPIDEMIOLOGY OF CEREBRAL PALSY

CP is the most common neurological disability in childhood and is more prevalent in more deprived socio-economic populations [19]. It is estimated to have a prevalence of 2 to 3.5 cases

per 1,000 live births in the developed world [20-23]. While the prevalence in the developing world is not well established, it estimated to have a more broad range at 1.5 to 5.6 cases per 1,000 live births [24]. The prevalence of CP is substantially higher among preterm and extremely preterm infants (< 28 weeks) and infants with low birth weight (< 2.5 kg) [25-27]. However, data from studies looking at the trends of CP in Europe show a decreasing prevalence of CP among low birth weight infants, while that in children born with a birth weight of 2500g or more has remained stable [28].

Population–based prevalence estimates for motor disabilities and its subtypes are lacking in Sub-Saharan Africa. A study done in a rural South African District (Kwazulu Natal) noted that CP was one of the most prevalent disabilities at 10/1000, however this study was only conducted in children below the age of 10 years from a single district (i.e., Manguzi sub-district) [29]. An earlier study by Boyo [30] on the prevalence and types of serious childhood disabilities in Kaptanya, Kapchorwa district in Uganda screened a total of 1,789 children of the age group 2-9 years, using the Ten Question Screen [31]. He identified 29 children with serious disabilities, giving a prevalence of 1.64%. The most frequent disability was motor (20.8%) with most cases associated with either CP or some non-specific global motor delay. The numbers of children identified in this study were few and this could have been affected by the study case definition of serious disability, in addition the screen utilized was not validated for the population. On the other hand, a pilot epidemiological study done in two districts of Uganda representing both urban and rural communities, utilized a validated screen for children with moderate to severe neurodevelopmental disabilities (NDDs) including CP. This study found a high burden of NDDs with an estimated population prevalence of 10–13/100 children for all seven investigated NDDs including CP [32]. This prevalence is three times higher than previously reported in Pakistan (4.4/100) [33], and twice that in South Africa (6/100) [29], thus highlighting the growing burden of NDDs among children in the sampled communities.

In Uganda, the prevalence of CP is not well established but it is suspected to be high in view of the high maternal and infant mortality rates inferred from the fact that annually, approximately 141 000 children die before their fifth birthday and 5000 women die due to complications of pregnancy and childbirth. It is believed that this situation, coupled with poor newborn care practices [34], exposes these children to further risk of development of CP. This postulation needs verification.

3.5   RISK FACTORS FOR DEVELOPING CEREBRAL PALSY

Human brain development begins from the 3rd week of gestational life and continues through early adulthood [35]. It progresses through a cascade of developmental stages (e.g., neurulation, neurogenesis, neural migration, apoptosis, synaptogenesis, myelination and synaptic pruning). It is reported that the fastest developmental phase of brain growth occurs during the 2nd and 3rd trimesters of pregnancy and the first 2 years of the child's life [36]. Evidence from neuroimaging data indicate that CP results from interactions of multiple risk factors generating a series of causal pathways that leads to brain injury during the prenatal, perinatal and/or postnatal periods [37]. Although we are still lacking data from large scale

epidemiological studies on CP from low-and middle-income countries (LMIC), the available information from the few community and hospital based studies report that amongst the major risk factors identified include neonatal infections, kernicterus and birth asphyxia [38-41]. Previously it was thought that birth asphyxia was the dominant culprit in the development of CP, however with refinement in its definition to include signs of encephalopathy [42], birth asphyxia may now account for approximately 10-20% of cases [43] when the strict definition is used. Other researchers recommend that there is still a lot more research needed to verify the exact estimated proportion of cases of CP attributed to birth asphyxia due to the existing wide inconsistencies in reported figures (3-50%) from the literature [44]. This may be as a result of the methodological limitations, challenges in identifying birth asphyxia, differences in the definition of CP used, and misunderstanding of the proximal effects of the study results with likely causes of CP in the various studies. Currently, there is no information on risk factors for CP from Uganda. Conversely, in the high income countries (HIC) the top ten risk factors enumerated to be associated with CP include placental abnormalities, major and minor birth defects, low birth weight, meconium aspiration, emergency caesarean section, birth asphyxia, neonatal seizures, respiratory distress syndrome, hypoglycaemia, and neonatal infections [45]. It is worthwhile to note that a number of the factors claimed to be responsible for the development of CP such as intrapartum asphyxia, birth injury, infections and kernicterus are amenable to prevention, raising the critical question of whether the incidence of CP may be reduced in the future with their prevention.

Genetic factors have been implicated in CP with a number of single gene Mendelian disorders inherited as autosomal dominant, autosomal recessive, or X-linked pattern [46]. For example, the GAD1 gene, which encodes the brain-expressed isoform of glutamate decarboxylase that is responsible for the production of the major inhibitory neurotransmitter γ-amino butyric acid (GABA), was the first identified gene responsible for a Mendelian form of CP [47]. Studies using advanced sequencing techniques have shown that in sporadic CP cases approximately 14% are a result of causative single-gene mutations and up to 31% are due to clinically relevant copy number variations [48]. Another study by McMichael and colleagues performed a whole-exome sequencing of 183 cases with CP and their parents when available and found that 14% of the cases had a potentially disease-causing gene variant [49]. It is hoped that in the near future it will be possible to identify new novel genes implicated in CP.

3.6 DIAGNOSIS OF CEREBRAL PALSY

The observation of slow motor development, abnormal muscle tone, and an unusual posture are common initial clues to the diagnosis of CP. The clinician must consider multiple aspects such as the overall clinical picture, the pattern of development of symptoms, the clinical history of the mother and infant and the pediatric and neurological examination of the infant. Furthermore, it includes a detailed family history, the history of fetal and maternal health and illness during pregnancy, the health status of the newborn, the infant's postnatal development (developmental milestones), postnatal illnesses and dysfunctions during the child's early years of life [16]. To date, there is no single test to diagnose CP. However, when considering that CP may arise from multiple risk factors, several tests are performed to identify potential causes of CP. These tests are useful diagnostic tools and include targeted laboratory and neuroimaging. Some of the common targeted laboratory examination includes: i)

chromosomal microarray analysis, which is a high-resolution method of chromosome analysis that can detect a genetic anomaly [50], ii) hemoglobin electrophoresis to rule out sickle cell anemia for those with recurrent anemia and cerebral vascular accidents [51], iii) metabolic work–up for children with developmental regression, periods of emesis/dehydration or failure to thrive [52], and iv) an evaluation for clotting dysfunction should also be considered in children with unilateral CP [52,53]. Neuroimaging tests such as computed tomography (CT) and magnetic resonance imaging (MRI) are helpful diagnostic tools to identify potential brain structural abnormalities, and tumors. Although CT can show congenital malformations, hemorrhage, and periventricular leukomalacia in infants, the resolution of MRI techniques is superior and provides a more detailed high-resolution images of the brain. MRI technology can readily detect abnormalities of both grey and white matter more clearly than CT. However, MRI scans are more expensive than CT scans and that limits its availability in LMICs. This neuroimaging information directs the clinician to determine the child's long-term prognosis as well as identify causes amenable to treatment that could reduce on the child's burden of disease.

3.7   CLASSIFICATION SYSTEMS IN CEREBRAL PALSY

In the past decades in many CP studies, the classification of cases was basically addressed from a clinical perspective based on neurological findings [54-57]. Some examples of these classification systems focused on topography (which parts of the body are involved), the anatomical site of the brain lesion, clinical symptoms, the accompanying impairment(s), the degree of muscle tone, severity of involvement (usually characterized as mild, moderate, or severe) and therapeutic requirements. The Swedish classification by Hagberg has been used for more than four decades in many international CP studies and describes three neurologic categories of spastic, ataxic, and dyskinetic [16]. The spastic group was further characterized into spastic hemiplegia, spastic diplegia and spastic tetraplegia. The ataxic group into either diplegia or congenital (simple), whereas the dyskinetic group as either mainly chorioathetotic or mainly dystonic (see Table 1).

Table 1. A comparison of the Hagberg and SCPE CP classifications

Group of CP classification	Hagberg	SCPE
SPASTIC		
	Hemiplegia	Unilateral Spastic CP
	Tetraplegia	
	Diplegia	Bilateral Spastic CP
ATAXIC		
	Diplegia	Ataxia
	Congenital (simple)	
DYSKINETIC		
	Mainly dystonic	Dystonic
	Mainly choreoathetotic	Choreo-athetotic.

Unfortunately, few of these traditional classifications of CP were shown to be either reliable or valid and proved confusing in terms of comparability of results across studies. This

dilemma, coupled with the growing interest in monitoring CP prevalence among populations and the desire to compare the rapidly changing neonatal care, prompted the need to develop a reliable standardized way for classifying people who have CP. The Surveillance of Cerebral Palsy in Europe, (SCPE) published standardized procedures for ascertaining and describing children with CP for registers and databases [2]. The emphasis was placed on diagnosis by the dominant syndrome and adopted a simple classification of four CP subtypes: unilateral spastic, bilateral spastic, dyskinetic, and ataxic. Later, SCPE and other researchers established that the addition of an account explaining the degree of functional ability markedly improved the reliability of diagnosing children with CP [58].

The Gross Motor Function Classification System (GMFCS) is recommended and was developed in order to provide a standardized system for classifying the severity of movement disability among children with CP [59]. The GMFCS (extended and revised version) includes descriptions of children's abilities for each level across five age bands: less than 2 years, 2 to 4 years, 4 to 6 years, and 6 to 12 years, and 12 to 18 years [60]. The Manual Ability Classification System (MACS) was developed based on a method comparable to the GMFCS, to classify how children 4 to 18 years with CP use both their hands together, when handling objects in daily activities across five levels [61]. The MACS has shown excellent reliability between family and professional assessments. Since communication difficulties are often experienced by children with CP, the Communication Function Classification System (CFCS), or the Functional Communication Classification System (FCCS) [62] is recommended for the wider assessment of communication difficulties during epidemiological surveillance studies. The skillfulness in eating or drinking is another area in which impairments linked to CP can restrict the child's ability to eat, drink and swallow safely and efficiently. The Eating and Drinking Ability Classification System for people with cerebral palsy (known as EDACS) was developed as a standardized system to classify eating and drinking ability for people with CP [63]. Each of these systems classifies the full range of ability for each function namely how CP affects the ability: to move (sit, stand and walk), to handle objects, to communicate with others and to eat and drink, using five levels, where Level I indicates least limitations, and Level V indicates the most limitations. All these classification systems are acceptable to parents, a range of healthcare professionals, and researchers, because of their provision of a common language that is easy to understand, the ease of use, and high reliability in the findings by parents and professionals.

3.8 BRAIN IMAGING IN CEREBRAL PALSY

There is scant information on brain structural features in children with CP in LMIC, especially where MRI is still relatively unavailable. This creates a significant gap in information since neuroimaging investigations are recommended in CP management as they may provide useful information regarding the timing and potential cause of the brain injury [64,65].

The few studies performed in other LMIC mainly used CT as the modality of brain imaging considering the cost and availability. Results from these studies [66,67] have been inconsistent in view of differing terminology used in the classification and timing of brain injury. Furthermore, there is hardly any information on the pattern of brain injury and its relation to

etiology or timing of the brain injury. Information regarding the correlation of the pattern of brain injury with phenotype, motor function and co-morbidities is also lacking.

From the varied neuroimaging studies performed in the high-income countries, the vast majority of children with CP (80% - 90%) have atypical neuroanatomical findings found more often identified with MRI than with CT [67]. From the population-based studies white matter damage and malformations are the more commonly reported findings while isolated grey matter damage is rare. Based on the findings from a neuroimaging study performed in a LMIC, 4 out of 10 were as a result of complications around the birth period, 3 out of 10 from prenatal insults and the remainder due to postnatal insults [67]. Overall, MRI neuroimaging findings in children with CP have been very instructive in providing explanation of the timing of the brain insult and whether the observed finding could be attributed to the motor impairment [68]. Broadly the first trimester insults are associated with cerebral maldevelopment, whereas periventricular white matter injury (PWMI) and cortical and deep grey matter damage occurring during the 2nd and 3rd trimester, respectively [37]. It is not known what the neuroimaging patterns in Ugandan children with CP are, when the brain injury occurs and their relation with phenotype, motor function and co-morbidities which could give us possible clues about the timing and etiology of the CP children we manage.

3.9   COMORBIDITIES IN CEREBRAL PALSY

It is estimated that dependent on the classification type of CP, about 25-80% of children with CP have additional non-motor impairments [19]. The more severe the CP, the more the likelihood of having comorbidities including visual and hearing impairments, epilepsy, behavioural and intellectual impairments, feeding and swallowing problems, poor nutrition and growth and high rates of infection . Many children with this development disorder may also experience communicative impairments and may have complex limitations in self-care functions. Intellectual impairment occurs in about two-thirds of patients with varying degree and profile [69]. Intellectual impairment may be either generalized (cognitive impairment) or specific to one area (learning difficulty). The more subtle sensory anomalies such as abnormal touch and/or pain perception and cognitive problems become apparent at school age [70]. Though the evidence of pain in CP is often under-researched it is estimated to occur in 75% of children making it one of the most frequent comorbidities [71]. The occurrence of epilepsy is dependent on the type of CP being most common among the unilateral and bilateral spastic cases [19,72]. The proportion of CP patients with severe bilateral involvement that have epilepsy ranges from 50 to 94% [72]. Children who have epilepsy have higher rates of other comorbidities including intellectual impairment and gross motor dysfunction [73]. Psychosocial and behavioural problems have been reported in 20% of CP patients with 9% having an autism spectrum disorder diagnosis [74]. Severe visual and hearing impairments (80) may be possible to detect at an early age. The occurrence of visual abnormalities varies from 10 to 39% [73,75]. The most common disorders being strabismus, visual field defect, myopia, or hypermetropia. Hearing impairment on the other hand ranges from 4 to 15% [73,75]. Impairments in hearing are often reported in patients with a past history of kernicterus, congenital infections, VLBW, or severe hypoxic ischemic injury.

Other co-existing health complications include feeding impairment that is very common and is reported in CP patients with frequencies ranging from 58 to 86% [76,77]. Markedly reduced bone mass in non-ambulatory children can cause osteopenia, osteoporosis fracture, scoliosis or pain [78]. Spasticity and contractures prevents the stretching of muscles and tendons and child may require assistive devices to cope. Urinary incontinence may occur caused by impaired control of the bladder muscles, this may require prescription medications, surgery or special exercises for management [79]. It is hence recommended that children with CP should be screened for all possible co-existing conditions as part of their evaluation [40,80].

3.10 NUTRITION IN CEREBRAL PALSY

Growth is a fundamental and integral marker of health and well-being in children. Children with CP frequently grow poorly with a reported high incidence of short stature and growth failure [2,22]. Poor linear growth in CP has been attributed to nutritional factors as well as non-nutritional factors such as those involving the neurologic or endocrine systems [81]. The inadequate intake of calories to meet their metabolic demands is cited as the most significant factor affecting the nutritional status of children with CP [82]. The significant reduction in nutritional intake largely results from problems with oropharyngeal incoordination, which is associated with slow rates of feeding, prolonged feeding times, excessive spillage of food and difficulties in swallowing. Furthermore, the co-existence of gastrointestinal states like gastroesophageal reflux disease, constipation, vomiting, or the presence of poor dentition, early satiety, communication defects and behavioral disturbances are all contributory [81,83,84]. Not only macronutrients are deficient in children with CP, but also electrolytes and micronutrients. Low levels of iron, zinc, essential fatty acids and vitamins C, D and E were noted in 15- 50% of these children [84].

Several children with CP are at risk of malnutrition, especially those with severe gross motor impairment and oropharyngeal dysfunction [76,81,85]. The severely affected CP patients are unable to communicate hunger and solely depend on the caregiver for feeding with the risk of either, over or underestimating his/her caloric needs. Furthermore, the more severe the motor impairment the more the likelihood of more feeding dysfunction, which is strongly associated with malnutrition [81]. It is reported that the energy requirements of CP children who are able to walk and have athetosis are higher than those unable to walk [84]. Assessment of the feeding and nutrition in children with CP requires a multidisciplinary team approach which involves the services of the neurodisability paediatrician, paediatric gastroenterologist, paediatric dietician, clinical nurse specialist, speech and language therapist, and occupational and physiotherapists. A detailed feeding and dietetic history should be recorded and in addition a detailed anthropometric analysis of the nutritional status [86].

Nutritional assessment includes the measurement of the anthropometric variables: weight (W), length (H), weight for height or length (W/H) and body mass index (BMI). In addition, the mid-upper arm/ head circumference and triceps skin fold thickness may be taken. The WHO 2006 child growth standards and the WHO 2007 growth reference charts provide gold standards for assessing and monitoring the growth of children and adolescents [87]. Children with CP can now be assessed for malnutrition by using the WHO standard deviation scores (Z-scores) [88].The consequences of malnutrition in CP children are diverse and include

interrupted growth and developmental potential, impaired immune function (which increases the risk of infection), reduced circulation time (which increases the risk of poor wound healing), presence of pressure sores, and diminished respiratory muscle strength (which is associated with weak cough and further chest infections).

The purpose of nutritional management is to enhance nutritional status by providing dietary advice and counselling and, if the nutritional needs of the child cannot be met by normal foods alone or by the use of oral nutritional supplements. The severity of oropharyngeal dysfunction, may dictate the use of nasogastric tube feeding as a short term solution. In the long-term, gastrostomy feeding may be employed and has been shown to lead to improved weight gain. Gastrostomy is recommended in children with CP with a functional gastrointestinal tract who have a clinically unsafe swallow, are unable to maintain a satisfactory nutritional state by oral feeding alone, have exceedingly long oral feeding times and are nasogastric tube dependent [89].This procedure is not without its shortcomings which involve causing peritonitis or secondary gastroesophageal reflux since it is a surgical procedure, skin excoriation and granulation at the tube site and the risk of overfeeding.

3.11 ASSESSMENT INSTRUMENTS IN CHILDREN WITH CEREBRAL PALSY

Rehabilitation is an important component in the management programs for children with disabilities like CP. It is a process aimed at enabling them to reach and maintain their optimal physical, sensory, intellectual, psychological and social functional levels [90]. The process of rehabilitation involves identification of the child's problems and needs, relating these problems to relevant factors within the child's environment, defining specific rehabilitation goals, planning and implementing these measures, and assessing their effects. The early commencement of rehabilitation programs not only produces better functional outcomes for almost all health conditions associated with disability [91,92], but also increases the educational and developmental gains especially in children with, or at risk of, developmental delays as seen in CP [93,94]. The implementation of these rehabilitation programs is critically dependent on assessment tools to evaluate child's level of disability and assess their improvements as well as in research. These tools are equally useful to monitor improvements in individualized functioning that assists the child to be independent in daily living. Regrettably, there is a deficiency of such validated tools for disability in children in the LMICs [95].

On the other hand, in the developed countries several measures are available for measuring functional performance in daily activities in children. Among the commonly used and researched functional measures in pediatric clinical practice include the School Function Assessment, the Pediatric Evaluation of Disability Inventory (PEDI), the Vineland Adaptive Behavior Scales, and the Functional Independence Measure for Children (WeeFIMTM) [96-99]. The WeeFIMTM and the PEDI provide information about independence in daily activities. The advantage of using the WeeFIMTM, is the few number of items (i.e., 18-items) it contains, making it efficient as a screening tool [98,100]. In contrast, the PEDI, which consists of a total of 237-items, offers a more comprehensive workup regarding a child's functional performance and the level of assistance required in daily activities [101].

3.12 THE PEDIATRIC EVALUATION OF DISABILITY INVENTORY

The Pediatric Evaluation of Disability Inventory (PEDI) is a clinical assessment tool specifically developed in the United States, with the objective to evaluate the functional performance of children with disability aged 6 months to 7.5 years. The PEDI consists of 197 functional skill items, and 20 items each that assess caregiver assistance and modifications, respectively. The PEDI measures both functional performance and capability within the three domains: (1) self-care, (2) mobility, and (3) social function. The PEDI assessment is based on a detailed, structured interview with parents, professionals and/or other caregivers who know the child well, and can be used in hospitals, outpatient clinics, kindergartens and schools. Considering that the PEDI follows the International Classification of Impairments, Disabilities and Handicaps conceptual model of activity and participation [102], using the PEDI for measuring functional performance of a child with CP provides the clinicians with a thorough understanding of the functional performance as well as how much assistance a caregiver provides in a child's daily activities. A main use of the PEDI is to detect whether a functional deficit or delay exists in children with respect to the functional status development, and if so, the extent and content area of the delay or deficit. It is also an evaluative instrument to monitor individual or group progress in pediatric rehabilitation programs and as an outcome measure for program evaluation of pediatric rehabilitation services or therapeutic programs. The increasing use of the PEDI in multinational studies has resulted in its translation into many languages [103-112], but never for an African population.

In Uganda, there is lack of an adapted paediatric clinical assessment tool for measuring everyday functional performance in children with CP or disability. Whereas the PEDI is reliable, valid and sensitive to change, it is not advisable to wholeheartedly embrace such a western developed tool to identify children with functional delay in our environment. This is because it may fail to identify children in need of assistance, in spite of a proper translation of the instrument into the local language. Furthermore, the diminished ability to detect a child in need may occur as a result of the PEDI's variability [103,104,106-108]. It is therefore of scientific and practical importance to evaluate the applicability of adapted instruments in the recipient country's cultural and practical context before they can be validly and reliably utilized. Normative PEDI data has been validated for American children, to reflect the racial, ethnic, and socio-economic distributions of the U.S. population. However, there is currently no published literature of any normative African data on the PEDI. In view of the cultural and environmental differences among countries, age norms for the Ugandan population is urgently needed to create a database, which can be used to evaluate the progression of independence at home and in the community of children with CP/disability.

A clinically useful assessment tool should possess sound psychometric properties. Reliability and validity are two criteria used to assess the accuracy of an instrument. Reliability or reproducibility refers to the extent to which a measure is able to measure something in a consistent and reproducible manner and validity indicates whether a measure is assessing what it intends to assess [113,114]. The PEDI has never been culturally adapted for the African population. It is hence important and warranted that the PEDI be culturally adapted to the Ugandan population and its reliability and validity be fully established before it can be used for assessment in children with CP.

3.13 PROFILE OF THE COUNTRY UGANDA

The Republic of Uganda is a land locked country located in the Nile Basin of Eastern Africa. The Democratic Republic of Congo is its neighbour to the west, Rwanda to the southwest, Kenya to the East, Southern Sudan to the North and Tanzania to the south. The country has a total surface area of 241,550.7 square kilometers, 83% is occupied by land mass, 15.3% and 1.9% taken up by open water bodies and wetlands, respectively. Its landscape ranges from tropical rain forest vegetation in the south to savannah woodlands and semi-arid vegetation in the north [115].

3.13.1 Demographic and socio-economic context

Uganda has a population of over 35 million, approximately 1.5 million of whom live in the capital city, Kampala, with the remainder living in rural communities and a few small towns [116]. On the whole, the country is mainly rural with about 18.4% of the population living in the urban areas [115]. Uganda's population is dominated by a young age structure with more than half (56.1%) of the total population aged below 18 years. The sex ratio is 94.5 males per 100 females [115]. The median age for both males and females is ~15 years; life expectancy at birth is 48.8 years for males and 50.2 years for females. On average, 6.2 children are born to each woman [115]. The Ugandan population includes many different ethnic groups, none of whom are a majority. English is the official language of the country, although local languages are frequently used, Swahili less frequently. In the more populated part of the country including and surrounding Kampala, *Luganda* is the predominant local language.

Uganda is a low income country, the gross national income per capita was 670 U.S. dollars in 2014 [117]. The economy is largely dependent on agriculture which employs over 80% of the work force; with the major economic activity being subsistence agriculture. More than 75% of the population live on less than two dollars a day [118]. Uganda is currently administratively divided into 112 districts which are further subdivided into lower administrative units namely counties, sub-counties and parishes. Each district has a decentralized system of government; the central government retains the role of policy making, setting standards and supervising implementation of national directives [115].

### 3.13.2 Uganda child and maternal health indicators

There has been slow progress registered over the last twenty years in the reduction of child and maternal mortality rates in Uganda. The child mortality is uneven across the country and is much higher among the poor, those living in rural areas and those with less educated mothers [118]. The available information from the current neonatal, infant and under-five mortality rates shows 27 deaths, 54 deaths and 90 deaths per 1,000 live births, respectively (see Figure 3) [115]. This implies that one in every 37 babies born in Uganda does not live beyond the age of 1 month, one in every 19 babies born in Uganda does not live to the first birthday, and one in 11 children will die before their fifth birthday. The trends in Uganda child mortality statistics over the past twenty years are shown in Figure 3.
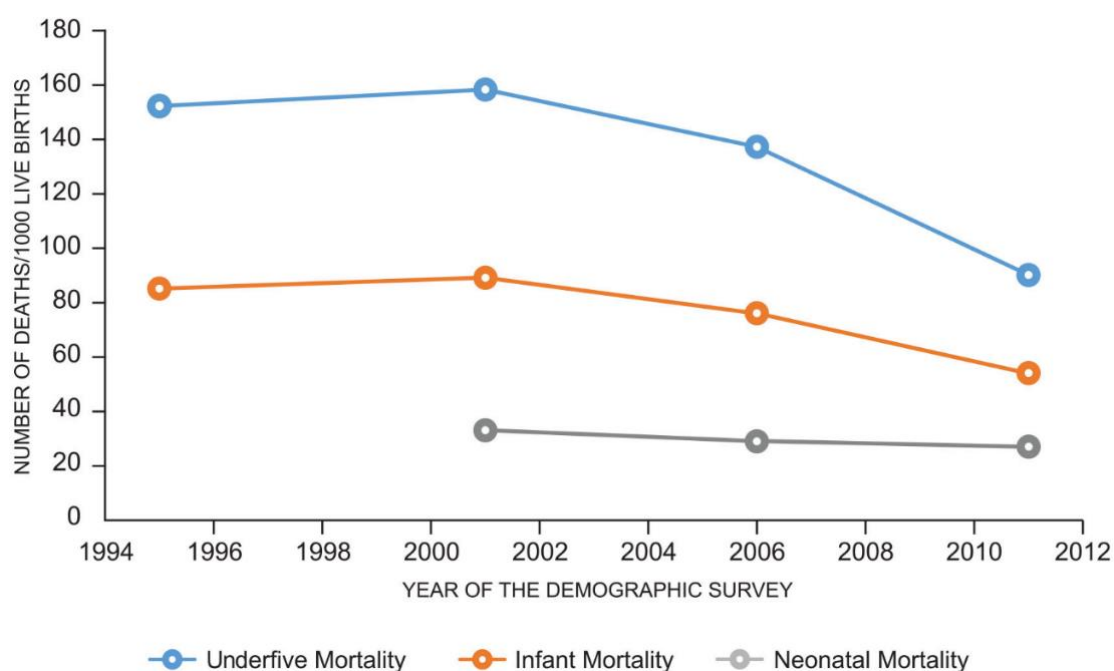
**Figure 3.** Trends in Uganda Child Mortality Statistics 1995-2011

The three main causes of death among children under five years of age are pneumonia, malaria, diarrhoea and infections such as HIV/AIDS which are associated with more than 70% of deaths in this age group [118]. Notably, the biggest proportion of the causes of deaths from the under-fives is neonatal in origin (see Figure 4) [118]. Newborn complications often occur in the first 24 hours around labour, during childbirth and within the first week of life which are the critical periods. It has been noted that one in every 100 babies born in Africa has the risk of dying during the first day of life [119].

In Uganda, newborn babies are dying from complications related to prematurity, birth asphyxia and infection (see Figure 4) [118]. Therefore, it is of great importance to lower the number of children dying before their first birthday and the neonatal deaths need to be curtailed by focusing on the prevention and management of complications of the mother-baby pair during these life–threatening sensitive periods of life.
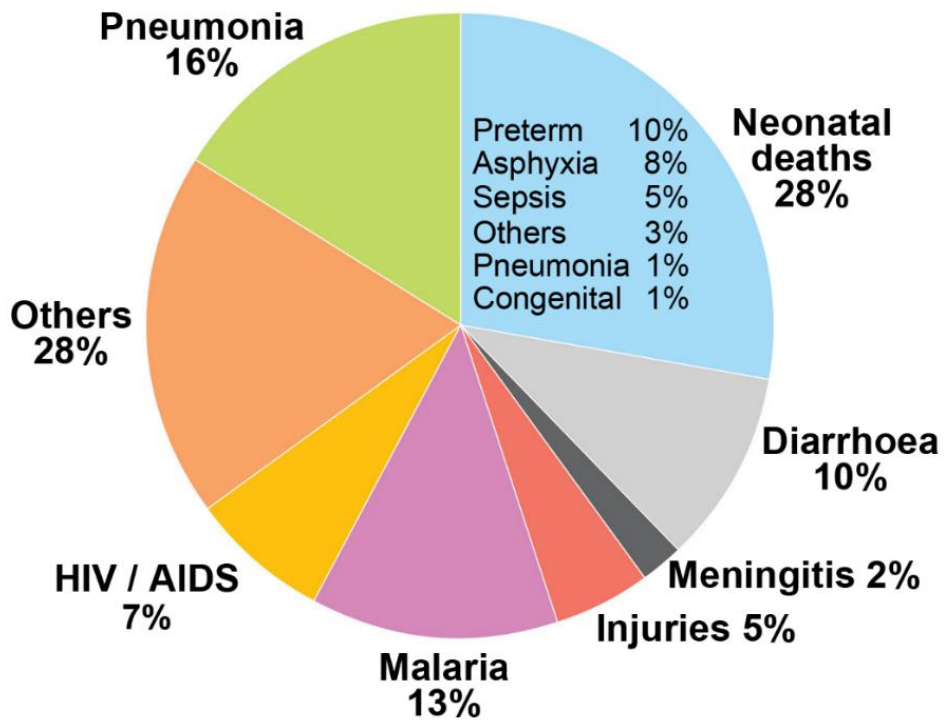
Figure 4. Causes of death among under-fives in Uganda 2010

The trends in maternal mortality ratio are shown in Figure 5. On average 18 women die every day from pregnancy related complications in Uganda with over 60% of deaths occurring 23-48 hours after delivery. The causes for this are both direct and indirect in nature. Regarding the direct causes: haemorrhage (42%), obstructed or prolonged labour (22%) and complications from abortion (11%) are the most common. The indirect causes are due to complications of malaria (36%), anaemia (11%) and HIV/AIDS related problems (7%) [118]. From the previous information it is evident that Uganda was unable to meet the Millennium Development Goals 4 and 5 by 2015 namely, reducing child mortality by 2/3 and reducing maternal mortality ratio by 3/4. Among the reasons for this is the poor use and quality of the health care systems from pregnancy, to child birth and the post child birth period resulting in reduced access to quality emergency and obstetric care to prevent these deaths [34,118].
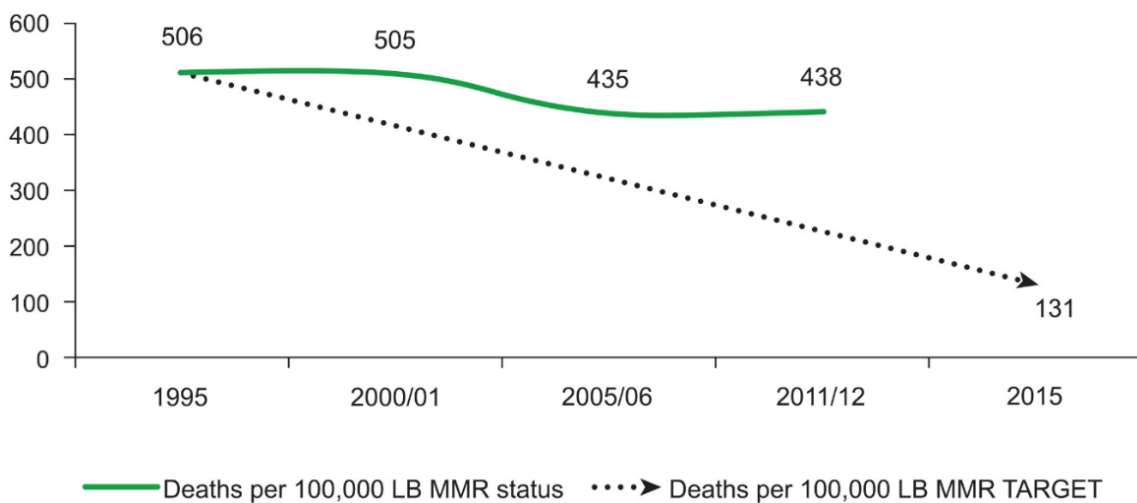
Figure 5. Trends in Uganda Maternal Mortality Ratio Statistics 1995-2011

3.13.3 Health service delivery in the Ugandan health care system

There are four sources from which the health care services are provided to the Ugandan population and comprise of the public, private not for profit, private health practitioners, and traditional and complimentary medicine practitioners. The public sector is made up of the central government and the district and sub-district health services provided under the decentralized system of governance, while the private sector is made up of the three other sources. There is a fairly equal contribution from both the private and the public sectors at 50%. The central government serves as the overall supervisor to ensure that proper health policies are drafted and standard of care of the patients is maintained. The Health System in Uganda consists of a seven tiered construct of health facilities (see Table 2).

Table 2. Structure of the Health care system in Uganda

Administrative structure			Corresponding Health Structure
Description	Local Council Level	Population Served	
Village	I	1000	Health Centre I
Parish	II	15,000	Health Centre II
Sub county	III	85,000	Health Centre III
County as sub-district	IV	190,000	Health Centre IV
District	V	260,000	District/General hospital
Region	Not applicable	2,300,000	Regional Hospital
National	Not applicable	30,000,000	National Referral Hospital

The functional capacity of each facility depends on the local administrative structure that it represents, ranging from villages to districts, and population coverage (e.g., 1,000 for health center II to 1,000,000 for health center IV). The functions assigned to each of these health facilities also differs with the Heath Center I comprising of teams of select lay members of the community who volunteer to ensure health promotion, prevention and utilization of health services. The Health Centre II serves as the bridge between the formal health sector and the local community, here outpatient services such as immunization, outreach services and treatment of common ailments is offered. The Health Centre II is supposed to be led by an enrolled nurse, working with a midwife, two nursing assistants and a health assistant. Both Health Centre III and IV provide outpatient, maternity, general ward and laboratory services. However, Health Centre IV has a theater for carrying out emergency operations (minor surgeries and caesarean sections) and provide blood transfusions. The district hospital provides all the previously mentioned services in addition to radiological investigations. The regional hospitals serve the various country areas they are assigned to and provide specialized care, conduct health services based research, teach paramedical, medical and nursing students. The National Referral Hospital in addition to what is provided at regional level provides more comprehensive super specialist care and training.

4 CONCEPTUAL FRAMEWORK

A conceptual framework explaining the key theories that supported and informed the studies in this thesis are briefly discussed. The biomedical model/theory is one of the most widely used principal model in modern medical practice. In this model, the assumption is that illness occurs as a result of a single main cause (disease-pathology), which is always the root cause of the illness and once this basis is repaired (treated), the body resumes a normal health state.

Regarding CP, the biomedical model has been used to explain how intrauterine *Cytomegalovirus* infection is transmitted from the mother to the baby resulting in CP. This has been reported both in studies conducted earlier [120] and more recently [121]. This relationship and that of several other congenital infections has been fronted to explain the link between the ill health of a mother being transferred to her child [122]. The biomedical model with respect to CP infers that the good health of the mother will mean the good health of the child. Therefore, the promotion of a healthy state that prevents and reduces the risk of illness in the mother before and during the pregnancy or during and after delivery of her baby, are crucial in the enhancement of the mother and child's health

The biomedical model has been very helpful in advancing the progress of medicine by explaining the occurrence of disease as an interplay between the host and the agent, but its effects are not always true. For example, in one study not all infected pregnancies developed infected fetuses, neither did all the infected fetuses that survived, have neurodevelopmental impairment. Furthermore, there are instances of patients with symptoms that cannot be associated with any specific disease [123] or the presence of laboratory evidence of a disease agent, but with missing symptoms of the disease [124].

Although the prevailing knowledge regarding the factors that enhance the risk for CP is still evolving, it is highly unlikely that a single factor acting on the brain is sufficient to produce irreversible cerebral damage [125]. The viewpoint of considering single-cause attribution of perinatal brain damage has thus been considered as a very simplistic way of thinking and it is recommended that it should be treated with caution [126]. It is argued that the biomedical model does not take into consideration the multidimensional nature of disease causality since it focuses on purely biological factors, and excludes psychological, environmental, and social influences, which have been noted to be contributory in the pathogenesis of health related conditions, including CP [127,128].

In the biopsychological model of health, illness is said to result from the interaction between physical factors and behaviour of individuals. While in the social model of health, in addition to focusing on the individual's biological attributes, it also takes into account several other aspects such as gender, family, social class, patient's environment, employment, education, level of income, culture, and government policies dealing with these inequalities.

George L. Engel proposed the biopsychosocial model of health that embraces the patient's biological, social, psychological, and behavioural background to determine the illness and path of treatment [124]. This model also explains the relation between the diagnosis of disease subject to the patients' clinical history and the way they behaviorally express themselves. In the biopsychosocial model of health, it is the interplay between the individual's genetic

makeup (biology), mental health and behavior (psychology), and the sociocultural environment (social world) that determines the course of their health-related outcomes.

In view of the complex and multifactorial etiology of CP, some aspects of biopsychosocial model of health were adapted in the conceptual framework employed in this study. It is believed that the interplay of several risk factors present during the antenatal, perinatal, and/or postnatal periods interact with other social and environmental factors through converging pathophysiologic pathways to cause CP. Theoretically, the WHO's ICF can also be viewed as the biopsychosocial model of disability helping to appreciate disability from diverse perspectives, including physical, psychological and social aspects. The WHO's ICF incorporates the biomedical model, which supposes that the impairment is directly responsible for the manifested disability [129], and the social model, which ascribes social circumstances as contributory to the disability, rather than as a result of a biological factor [130].

An assessment test can be studied from various viewpoints and the items in the test can be evaluated according to different theories. Two such theories include the Classical Test Theory (CTT) and Item Response Theory (IRT). The assumptions in the CTT are an examinee has an observed score and a true score. When a particular test is applied, the observed score of the examinee is often seen as an estimate of the true scores of that examinee plus/minus some unobservable measurement error [131,132]. These assumptions in CTT, however, are flawed, and have featured as one of its weaknesses. For example, the true score is not an absolute characteristic of the examinee since it also depends on the content of the test. In situations of examinees with varying ability levels, a simple or more difficult test would result in different scores. Secondly, the ability of the test to discriminate between higher and lower ability examinees (item discrimination) and the item difficulty could also differ depending on the sample of examinees that take a particular test. As a means to surmount the problems with CTT, the IRT was developed [133,134] and is still a work in progress [135].

One of the principal assumptions in IRT is that the latent ability of an examinee's item responses during a test is influenced by characteristics of both the individual and the item [136]. The fundamental theory is that there is a differential effect of item 'difficulty' on individuals at different characteristic levels [136]. This implies that as the subject's ability to perform a certain task increases, the probability of a correct response increases. The association between the probability of answering an item correctly and the ability of an examinee can be displayed in diverse ways depending on the nature of the test [137]. Often the concept of unidimensionality is assumed, i.e. that the items in a test measure one single latent ability.

In adapting, translating and evaluating the PEDI-UG instrument's psychometric properties, including the latent structure, we made use of the IRT. The IRT models that we utilized were the unidimensional rating scale Rasch models. By endorsing each task item using Rasch models, you specify the definite information about individuals with differing levels of ability in the underlying content area you are investigating. The use of IRT models, which have been the preferred technique in standardized testing since the advancement of computer programs [138], assists in improving the scoring accuracy of a test, as well as guiding the researcher in which items to use by selecting only the discriminative items.
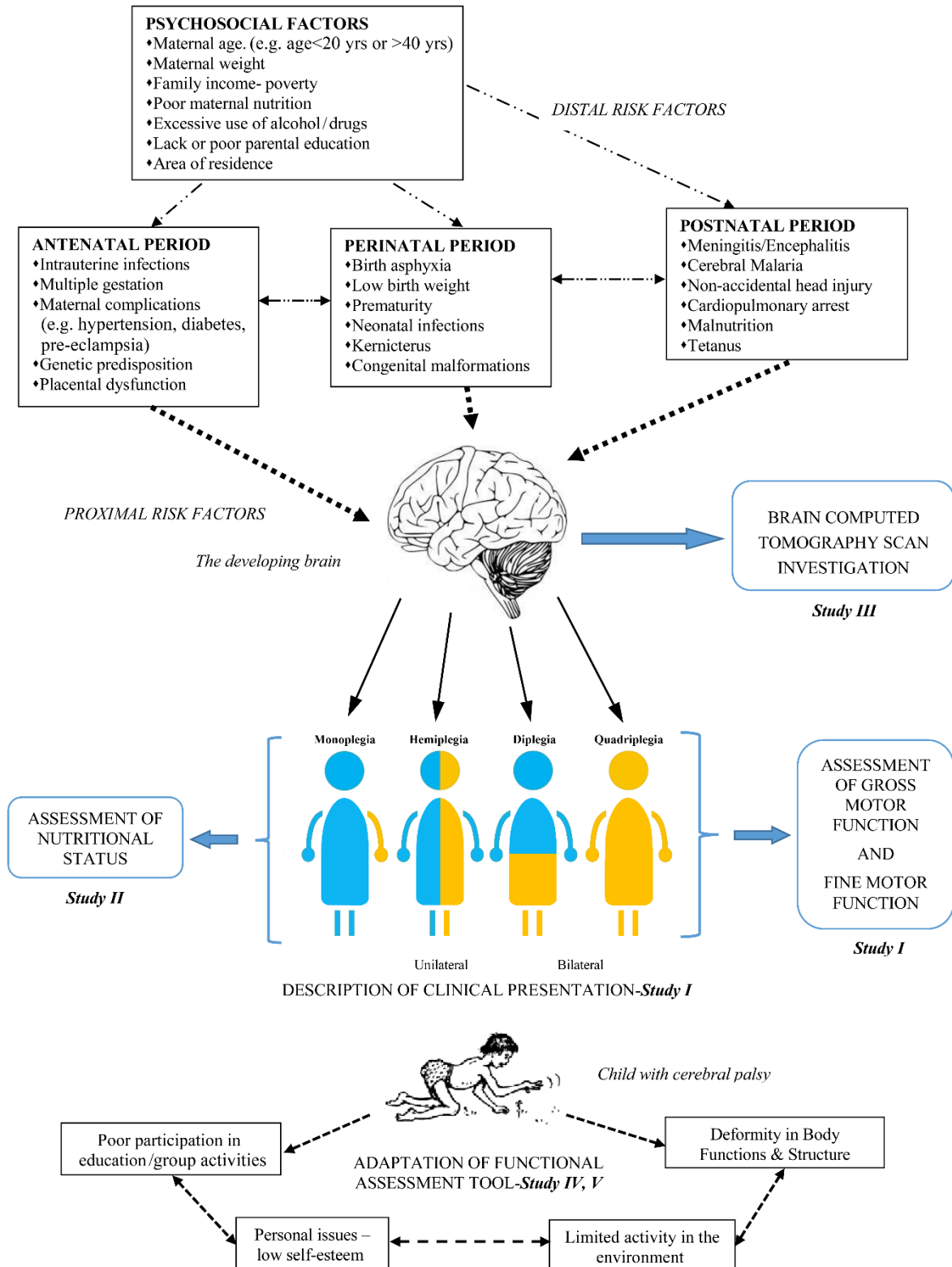
Figure 6. Simplified conceptual frame work of the cerebral palsy studies

5 RATIONALE FOR THE STUDIES

CP is the most common physical disability in childhood and yet there is an enormous lack of health related information regarding this condition amongst the Ugandan pediatric population. Within this context, there is no literature on the neurological comorbidities, brain imaging findings or nutrition status of these children. Furthermore, there is no adapted pediatric clinical assessment tool for measuring everyday functional performance in children with CP.

The studies in this thesis extend the knowledge and understanding of CP in Ugandan children by filling in these gaps. The provision of this important information will contribute to enabling the Uganda Ministry of Health use this data in planning, developing strategies for prevention and implementing specific intervention programs for this group of children.

In rehabilitation it is important to identify culturally pertinent assessment tools that facilitate comparisons between intervention groups and also aid in future longitudinal analyses. The valid pediatric clinical assessment tool that has been adapted for use in the management of the Ugandan children with CP will measure the functional skill development and the level of independent performance in the activities of daily living. This will serve to facilitate the research capacity of Ugandans working with children with CP and at the same time assist health workers to introduce interventions aimed at improving the quality of life of CP children and their caregivers.

In the use of the adapted tool, there will be training of allied health workers from the schools of physiotherapy and occupational therapy at various health units within Uganda. Amongst other previously mentioned functions, this tool will also improve their assessment skills, assist them to set realistic measurable goals during the individual rehabilitative management plans, and support them in working together with the family members.

The findings from this thesis could, together with future research in this field, be used to supplement the teaching content of the Ugandan Community Based Rehabilitative programs and make important contributions to improving clinical guidelines and treatment recommendations in this grossly neglected field.

6   AIMS AND OBJECTIVES

6.1   GENERAL AIM

To describe the neurological, anthropometric and brain imaging findings of Ugandan children with CP and to develop a culturally relevant assessment tool for measuring their functional performance.

6.1.1   Specific objectives

1. To describe the clinical subtypes, gross and fine motor functions and comorbidities in children with CP attending a specialized clinic at Mulago National Referral Hospital (**Study I**).

2. To investigate the nutritional status and the associated factors of poor nutrition in children with CP attending a specialized clinic at Mulago National Referral Hospital (**Study II**).

3. To describe the neuroimaging patterns in a clinical sample of children with CP attending a specialized clinic at Mulago National Referral Hospital and determine the associations with prenatal and postnatal risk factors (**Study III**).

4. To adapt a culturally relevant Pediatric Evaluation Disability Inventory Uganda (PEDI-UG) instrument and describe the translation and validation process (**Study IV**).

5. To investigate the psychometric properties of the culturally adapted PEDI-UG by testing the instrument's rating scale functioning and internal structure (**Study V**).

7   METHODS

7.1   DESCRIPTION OF STUDY SITES

The data for studies I-III was obtained from MNRH, while that for studies IV was from MNRH as well as districts in Kampala and the environs. Study V was from various districts within the country.

MNRH is located on Mulago hill in the Northern part of Kampala, the capital city and is one of three national referral hospitals in Uganda. The hospital serves as a primary, regional and tertiary health facility as well as Health Center IV, III for the Kampala metropolitan. MNRH also serves as a teaching hospital for Makerere University College of Health Sciences and a number of schools of nursing and allied health workers in and around Kampala. Most patients attending MNRH are self-referred from Kampala and the environs, the diverse health units countrywide as well as from the neighboring countries.

The MNRH Complex comprises several units including Lower Mulago, Upper Mulago, Uganda Heart Institute and the Uganda Cancer Institute. In Upper Mulago, a specialized clinic, the Cerebral Palsy Rehabilitation Clinic provides specialized services to children with CP. This clinic has a turnover of about 170 children annually, is operated by two physiotherapists and conducted thrice a week. The Pediatric Neurology Clinic with turnover
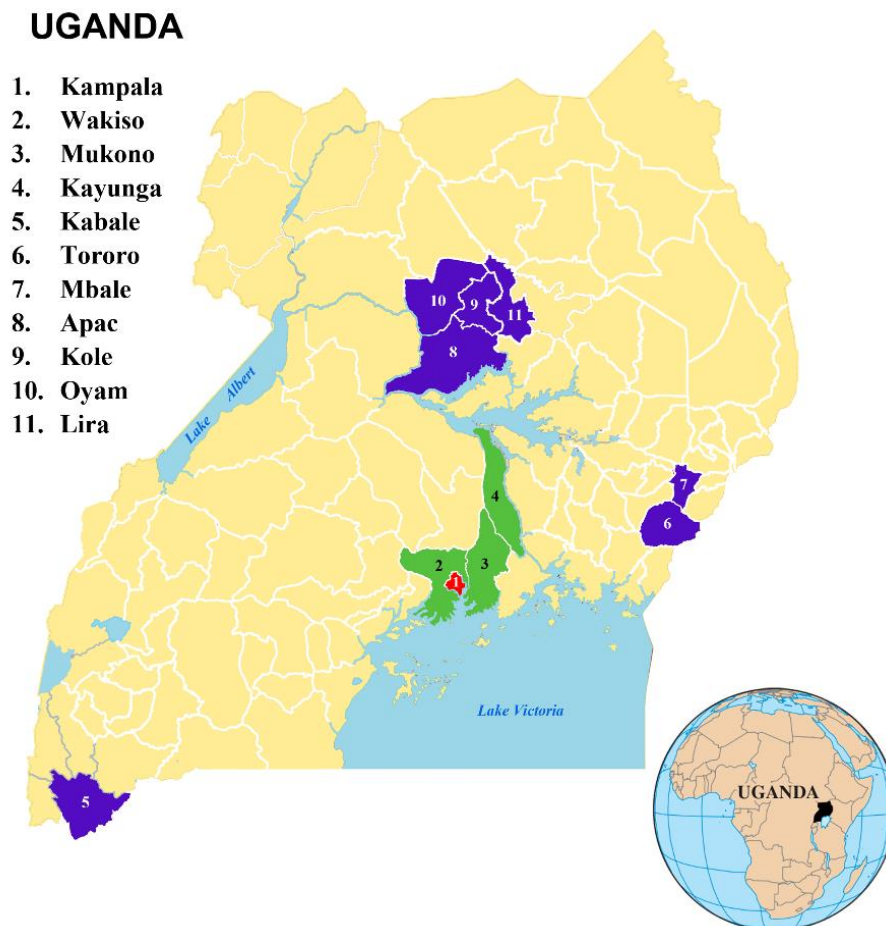
Figure 7. Map of Uganda showing the sites of the various studies. Red indicates sites for Studies I-V; Green indicates sites for IV and V; Purple indicates sites for Study V.

of about 400 children annually also reviews children with CP in addition to other neurological conditions such as epilepsy, autism and cognitive impairment. The clinic operates once a week with the support of pediatric neurologists, pediatricians, pediatric residents and nursing staff.

Study IV was carried out in Mulago Hospital, Kampala and neighboring districts. Study V was carried out in the rural and urban areas of the following Ugandan districts : Kampala , Mbale , Lira , Tororo , Wakiso , Mukono , Kabale , Kayunga, Apac , Oyam and Kole (see Figure 7).

7.1.1 Study participants

The thesis contains three studies that comprised of a CP population while the other two were made up of the non-disabled, typically developing Ugandan children.

7.1.2 Studies I and II

These studies included a sample of 135 children. The inclusion criteria were: attendance at the Cerebral Palsy Rehabilitation Clinic or Pediatric Neurology Clinic of Mulago Hospital, age between two to twelve years, a confirmed diagnosis of CP, and a written informed consent from parent/caregiver to participate in the study.

7.1.3 Study III

This study was nested in Studies I and II and was made up of 80 children with CP. The same inclusion criteria applied in addition to the caregiver returning to hospital for the performance of the CT scan examination.

7.1.4 Study IV

This study consisted of 75 children (aged 6 months to 7.5 years) who were attending MNRH for other reasons or were living within Kampala and the neighbouring districts. To be included: parental/guardian consent had to be obtained, children had to be developing normally with no evident disability or known diagnosed developmental disorders. An additional group of 10 parents/caregivers were involved in informal in-depth interviews.

7.1.5 Study V

This study involved 249 children living in the urban and rural areas of designated districts of Uganda. The inclusion criteria were: age 6 months to 7.5 years, absence of any known disability, and parental/guardian consent for child to participate in study.

7.2 STUDY DESIGN, SAMPLING AND DATA COLLECTION

7.2.1 Studies I and II

These were cross-sectional descriptive studies carried out between September 2009 and August 2010. For the sample size calculation we used the sample size formula of Cochran for proportions in large populations and adjusted this with the formula of finite population correction for proportions [132]. Given that a population of approximately 170 children with CP aged 2 to 12 years attend the MNRH in a one year period, we based our assumptions on the estimated epilepsy prevalence of 31%, noted in a chart review as the most common neurological comorbidity seen in children attending the Pediatric Neurology Clinic, at MNRH (Mugasha C, Pediatric Neurology Clinic chart review, 2007). At 80% power, 5% precision and 95% confidence interval, a sample size of 113 children was sufficient. However to cater for contingencies in terms of non-response or recording error, the sample was further increased by 10% to make a total of 124 children. The sample size for these studies of 135 children was therefore appropriate.

The assessments were conducted in a series of three steps performed on the same day by a team comprising of a specially trained physiotherapist, a study medical doctor and the principal investigator. In the initial two steps, screening of potential children with CP was performed by the physiotherapist, and in step three, the diagnosis of CP was verified by the principal investigator.

First step- screening of suspected cases

Questions 1 and 5 of the Ten Question Screen [31] that correlate with motor disability were utilized by the physiotherapist to screen the children for possible CP as follows:

1. Compared with other children, did the child have any serious delay in sitting, standing or walking?

2. Does the child have difficulty in walking or moving his/her arms or does he/she have weakness and/or stiffness in the arms or legs?

These questions were administered to the caregivers in either English or the local language *Luganda*.

Second step- inclusion of suspected CP cases

The children that screened positive to either one of the two questions were further assessed by the physiotherapist, with the aid of an observer flow chart, adapted from the SCPE 'DECISION TREE for identifying CP' [2]. Whereas the SCPE confirms the diagnosis of CP from the age of 4 years and above, in our study we were confident to recruit children from the age of 2 years and above. The reason behind this was based on the report that while at the age of 1 year more severe forms of CP can be identified, it is only after the age of 2 years onwards that those seemingly milder forms persist and a definitive diagnosis can be made [139]. Furthermore in this step any child exhibiting a history suggestive of a progressive motor

disorder, hypotonia as the only clinical feature or presence of an isolated spinal neural tube defect was excluded.

Third step- confirmation and assessment of cases

The confirmation of cases was made by the principal investigator using the consensus CP definition [140] and later assigned to the different clinical categories, as described by SCPE [2] into: (a) bilateral spastic; (b) unilateral spastic; (c) dyskinetic and (d) ataxic. Sixteen children were excluded at this stage due to either current caregiver's inability to provide a sufficient history or declined consent. A summary of the process entailed in the recruitment and inclusion of the children is shown in Figure 8.
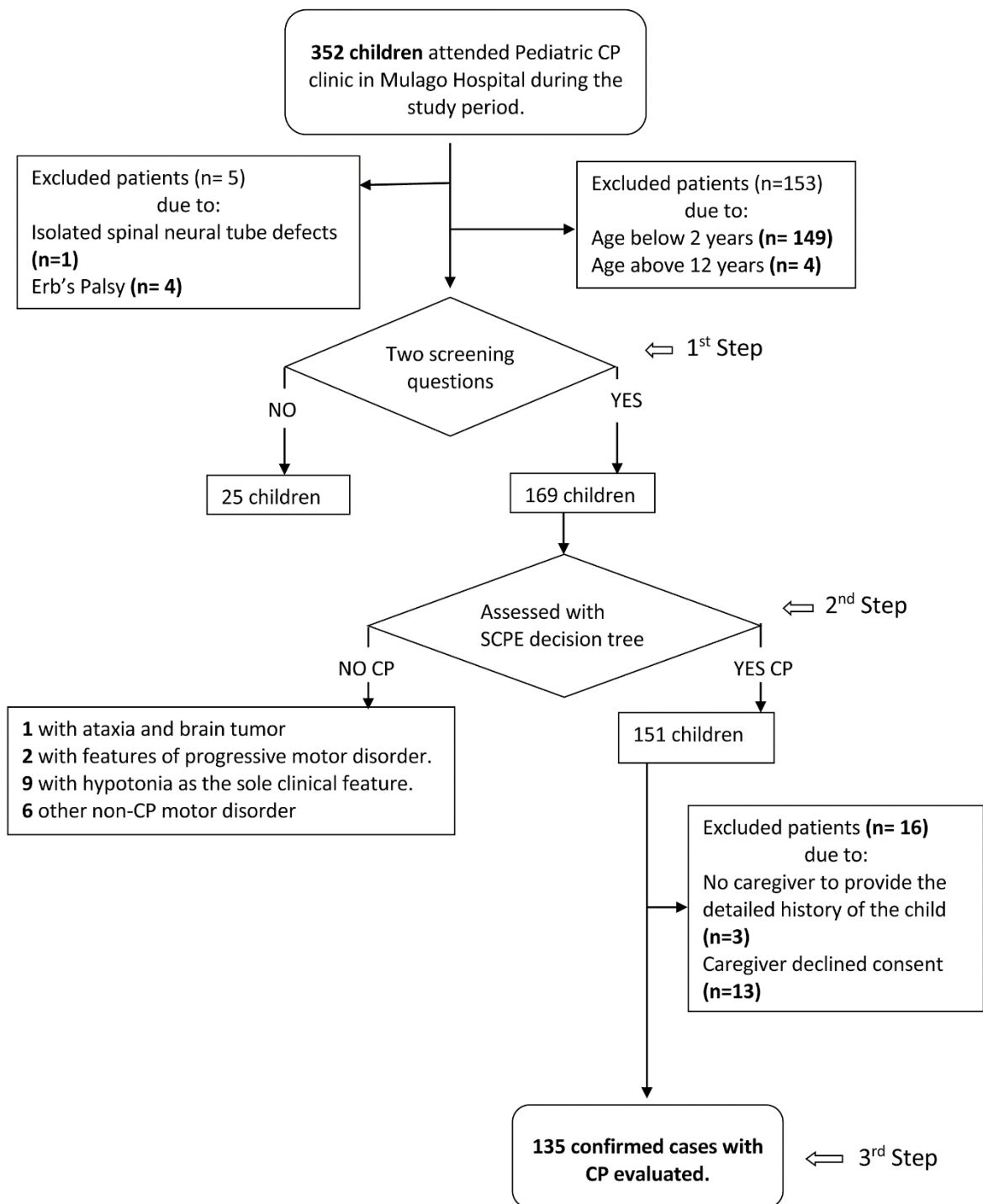
Figure 8. Flow chart depicting the selection of the subjects for studies I and II

Following the categorization of the children into the various clinical groups, the study doctor and the physiotherapist used a pretested and pre-coded questionnaire to interview the caregiver. Questions related to the child's medical history from pregnancy to the present, family history, the child's developmental milestones, past and present nutritional history and information on the existence of comorbidities. The history was followed by a detailed general clinical assessment with a standard neurological examination performed by the principal investigator and study doctor. The severity of motor impairment involving the children's

gross and fine motor function was assessed and the anthropometric measurements of weight, height/length, head and mid upper arm circumference taken.
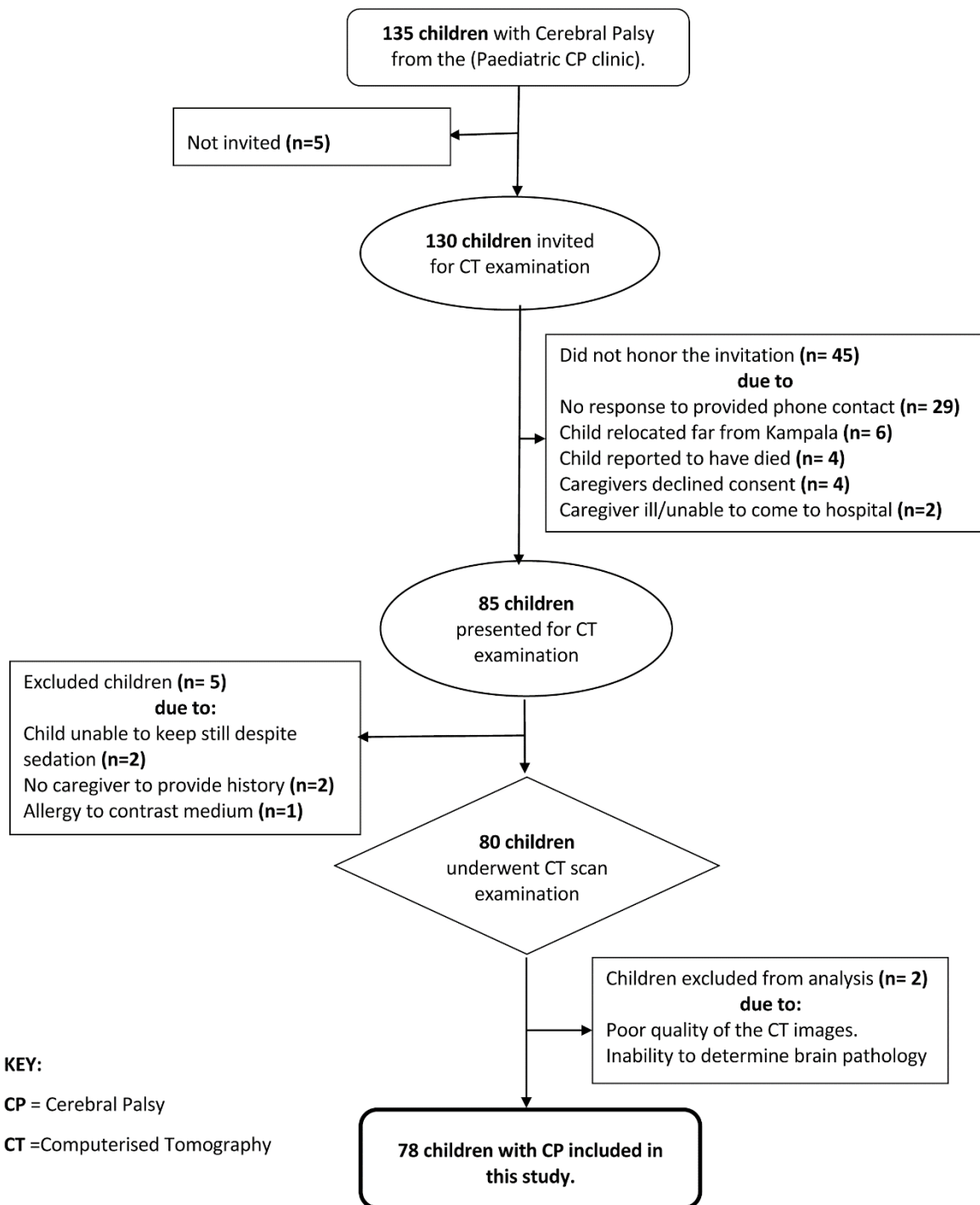
7.2.2 Study III

This was an observational cross-sectional study recruited from the original cohort of 135 children identified in studies I and II. A sample of 80 children was obtained based on the additional inclusion criteria of the parent/caregiver providing written informed consent and honoring the appointment of having the brain imaging done on the scheduled day. The excluded children included those lacking a reliable caregiver to provide adequate history, children who were unable to keep still in the CT scanner despite sedation and those with known allergies to the contrast medium.

A summary of the process entailed in the recruitment and inclusion of the children in study III is shown in Figure 9.

The risks and benefits of the procedure were explained to the parent/caregiver before obtaining their consent. The child was required to fast for a minimum of 6 hours before the procedure. Using a Philips MX 16-slice CT scanner, 2010 Model (Philips Medical Systems, Best, the Netherlands) the brain CT scan examination was performed with the aid of a radiology technician. Care was taken to ensure that the best output in the clarity of the images was achieved by removing all metallic materials and intrusive clothing around the child's body prior to the procedure. Initially the plain CT scan was performed using a protocol of 3mm slice thickness and then followed by the contrast CT scan. In the latter, IOPAMIRO contrast medium at a concentration of 76%, was administered intravenously at a rate of 2 mL/kg of body weight in all the children with the exception of 12 children in whom intravenous access was not possible. Using similar parameters as in the plain CT scans, the brain CT scan was performed after the contrast injection. Following the CT scan procedure the child was observed for any signs of delayed allergic reaction to the contrast medium such as itching, rash, vomiting, sweating or effects of the sedation such as stridor, wheezing or airway obstruction. Sedation was provided to sixty two children using intravenous diazepam (0.2 mg/kg body weight), however none of the children showed evidence of any side effects to the sedation or contrast medium.

The brain CT scan films were independently reviewed by two very experienced radiologists working in the tertiary hospitals of MNRH in Uganda and Karolinska University Hospital in Sweden. The accompanying clinical and demographic characteristics of the children were deliberately withheld from each radiologist prior to reporting on the CT scans. In a few instances of disagreement between the two radiologists, a re-evaluation was made by the radiologist based in Sweden and a consensus on the final image pattern drawn.

Figure 9. Flow chart depicting the selection of the subjects for study III

7.2.3 Study IV

A cross sectional study employing both quantitative and qualitative methods was carried out from April to June 2007 in eight steps using a convenience sample of a total of 75 typically developing Ugandan children and in line with the recommended WHO guidelines. The children were recruited during field tests performed in two stages. Following the first field test a random selection of 10 caregivers who had participated the field tests underwent informal in-depth interviews. The interviews were conducted by the principal investigator

and two members of the research team conversant with qualitative interviews. The purpose of this exercise was to inquire from the caregivers how they understood the questions and identify any inappropriate phrasing in the content of the questions. The notes from this exercise were recorded by the principal investigator verbatim and used to further clarify the adaptations made to the tool. The adaptation of the PEDI-UG was developed with the assistance of a technical advisory group consisting of two pediatricians, three occupational therapists, two physiotherapists, one speech and language therapist, and two mothers of children with no disability (above 7.5 years old) through a series of meetings to oversee the whole process. In addition, permission to make the adaptation of the original PEDI was obtained from the authors [101]. The summary of the methodology employed in the adaptation process is summarized in Figure 10.
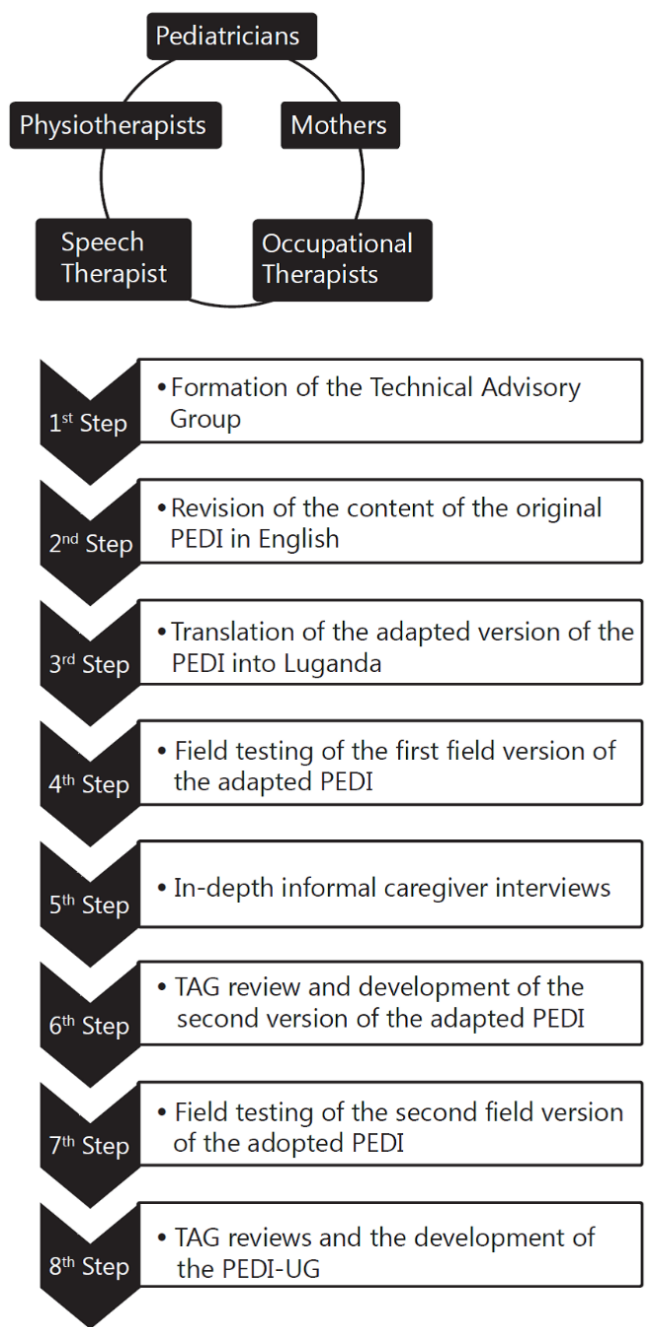
Figure 10. Summary of the procedure for adapting the Pediatric Evaluation of Disability Inventory- Uganda (PEDI-UG) tool.

7.2.4 Study V

A cross sectional observational study in which purposive sampling of typically developing children was employed. Study was carried out from July to September 2011. The sample size of a minimum of 200 children was estimated using the formula for reliability studies described in the book: 'Health measurement scales: a practical guide to their development and use' by Streiner and Norman [141].

Children were randomly selected from a stratified socioeconomic, urban/mixed/rural population and geographical neighborhood in the selected Ugandan districts. The inclusion criteria were: (i) age between six months and 7.5 years. (ii) no evidence of a disability as assessed by the Ten Question Screen [31], (iii) written informed consent from the parent/caregiver and (iv) a caregiver able to provide history of the child. Children with significant neuro-disability and signs of malnutrition (severe visible wasting) were excluded.

A total of 249 typically developing children (125 female) aged from six months to seven and a half years were included in this study. A minimum of 10 children per group using a 4 monthly age interval from the age of 6 months to 6.5years and having equal representation of boys and girls as well as urban/rural residence were recruited. The principal investigator, together with a team of 11 trained research assistants who included: 3 occupational therapists, 3 speech and language therapists; 3 social workers and 2 physical therapists administered the adapted PEDI-UG to the caregivers. The research assistants were trained about the administration and scoring criteria of the PEDI with each interviewing a minimum of 22 caregivers in the language of preference of the caregiver. English versions were administered to 163 (66%) of the caregivers.

The PEDI-UG (with 185 items) was administered to the caregivers by the research assistants at a convenient location within their home settings. More than half (57%) of the caregivers were mothers and were interviewed on one occasion between July and September 2011. On average each assessment took 30 to 45 minutes. Items were accepted on report if the mother/caregiver was very certain that the child could do the item in most situations, or the item had previously been mastered and functional skills had progressed beyond the queried level. Where possible, items were directly observed. We scored items as 0=unable and 1=capable.

7.3 MEASUREMENTS

7.3.1 Anthropometric measurements

The medical doctor and the principal investigator measured the weight and height of all children, using WHO standards for measurement (93). A high-precision 813 SECA® digital weighing scale (seca Vogel & Halke GmbH &Co., Hamburg, Germany) with readings recorded in kilograms (kg) to the nearest 0.1kg was used to measure the weight. Children unable to stand had their weights obtained as the difference between weights of caretaker as she/he held the child and the weight of the caretaker alone. Height and length measurements were carried out using a stadiometer and were recorded in centimeters (cm) to the nearest 0.1cm. Children (more or equal to 85cm) and able to stand flat-footed and straight had heights

measured while standing, while those less than 85 cm or unable to stand had their lengths measured while lying down using the stadiometer. The length of subjects with contractures was measured in segments by means of a flexible tape measure [142]. The Mid Upper Arm Circumference (MUAC) was obtained in children 2 - 5years and measured using a tape measure recorded to the nearest 0.1cm. In patients with a hemiplegia the unaffected side was used for taking measurements. The head circumference was measured by placing a tape between the occipital and frontal bones of the child's skull. Measurements were recorded to the nearest 0.1cm. To minimize errors there was daily validation of the instruments and measurements with random auditing by the principal investigator.

7.3.2 Laboratory tests

Under aseptic conditions, 5 mL of venous blood was drawn for hematological assays, which included a complete Blood Count, and serological tests for HIV. For the HIV testing, the ABOTT DETERMINE® test was used as the initial screen of the child's serostatus which if positive, was confirmed with a STATPACK® test. If the STATPACK® was negative the UNIGOLD® test was used as the tie-breaker. Post-test counselling was done for all patients prior to receipt of the test results.

7.3.3 Clinical examination for the comorbidities

The comorbidities that were investigated included epilepsy, hearing and visual impairments, autism spectrum disorder, speech and language disorders, behavioral disorders and cognitive impairment (learning disability). Epilepsy, was defined as two or more afebrile seizures in the last 5 years that were spaced 24 hours apart and were unrelated to acute infection, metabolic disturbance, or drugs [143,144]. Autism spectrum disorder was identified using the DSMIV-TR criteria [145], and cognitive/intellectual and behavioral disorders using the ICD-10 Classification of Mental and Behavioral Disorders [146], and visual impairments, for children less than 3 years were assessed by observation for eye contact, torch light or bright object, while a picture chart was used for those above 3 years [147]. Presence of a hearing impairment was acquired from the history and clinical judgement and further verified to determine whether severe or profound by audiometry testing. Children who were nonverbal, or lacking a recognizable vocabulary in the child's maternal language irrespective of the possible etiology (i.e., motor or cognitive limitations) were labelled as having a speech and language impairment. The information regarding the presence of these comorbidities was purposely inquired for during the parental interview. The interview was conducted at the time of recruitment of the child into the study and was coupled with results from the clinical examination conducted by the principal investigator, with a review of patient medical records (were available) to come to a diagnosis of the particular comorbidity.

7.3.4 Surveillance for Cerebral Palsy in Europe classification (SCPE)

The classification of the subtypes of CP was adopted from the SCPE checklist shown in Figure 11.
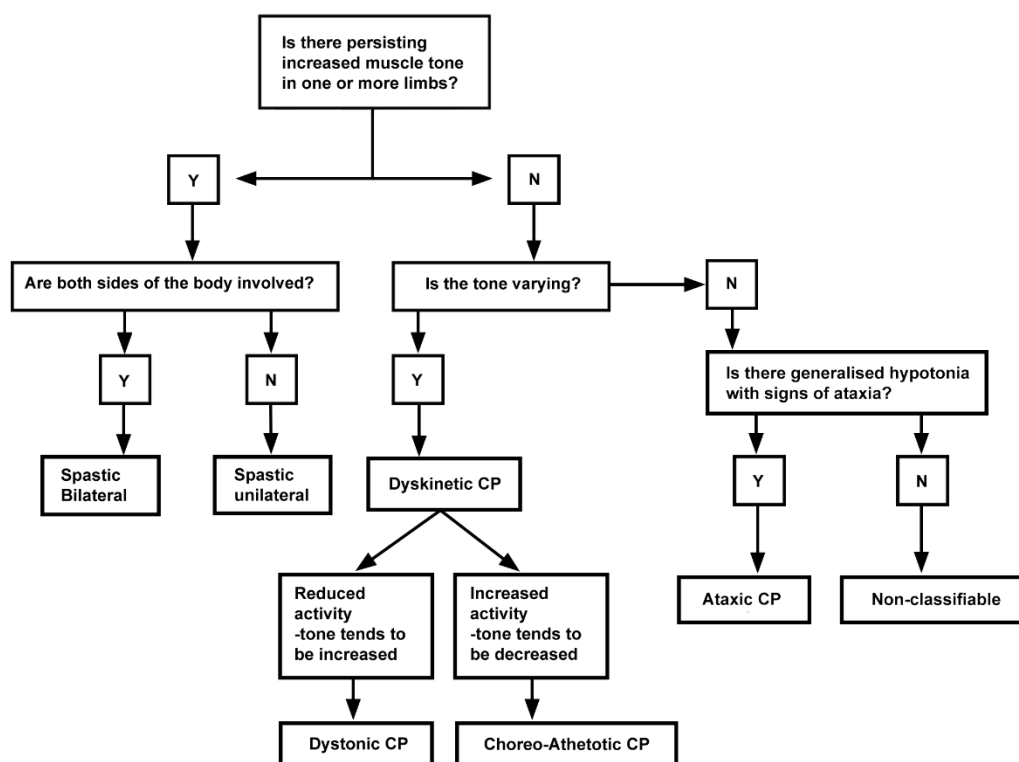
Figure 11. Classification tree for subtypes of cerebral palsy. This was adapted from SCPE [2]

7.3.5 Grading of motor function

The severity of gross and fine motor impairment was graded into three categories: mild, moderate and severe, this was determined by the child's ability to sit, initiate walking, and the capacity to grasp in fine motor skills. This summarized in Table 3.

Table 3. The levels of Gross and Fine motor function and differentiating criteria used to classify the children with CP

GROSS MOTOR FUNCTION		
LEVEL I	Mildly Affected	Sits without support, at best walks without restrictions indoors, with limitations in walking outdoors and in the community, no use of an assistive mobility device.
LEVEL II	Moderately Affected	Sits with external support or adult assistance, at best, walks short distances indoors with help of furniture or use of an assistive mobility device. Transportation is needed outdoors and in the community.
LEVEL III	Severely Affected	Unable to sit even with support, unable to walk. No means of independent movement. Transportation is needed both in and outdoors.
FINE MOTOR FUNCTION		
LEVEL I	Mildly Affected	Limitations in more advanced skills for either hands or one hand manipulates without restrictions, while other hand has only ability to grasp.
LEVEL II	Moderately Affected	Both hands can grasp but one hand has less functional ability or worse.
LEVEL III	Severely Affected	Both hands only the ability to hold or worse.

7.3.6 WHO growth standards

Based on weight, height/length, age and sex, anthropometric indices were constructed using the WHO growth standards used for children from low resource settings. The recordings were converted into Z-scores using the software 'WHO Anthro' [148] and 'WHO Anthroplus' [149] to calculate the different indices to assess the nutritional status namely; stunting, underweight, wasting and thinness defined when the Z-score was ≤ -2.0 accordingly (see Table 4) [87]. Children with extreme z-score values beyond the default flag limits for each indicator as set by the WHO standards and the WHO reference software were excluded in the statistical calculations after the first presentation. The indicators weight- for-age Z score was calculated only for children up to 120 months (10 years) and weight-for-height Z-score for those up to 60 months (5years) of age, according to WHO norms.

Table 4. Definitions of the different anthropometric indicators

Indicator	Definition
Stunting(HAZ)	Height- for- age Z-score of −2.0 or lower.
Underweight(WAZ)	Weight- for-age Z-score of −2.0 or lower.
Wasting (WHZ)	Weight-for-height Z-score of −2.0 or lower.
Thinness(BAZ)	BMI-for-age Z-score of −2.0 or lower.

7.3.7 Neuroimaging investigations

The experienced radiologists reviewed the CT scans and classified them into six categories, using a classification system comparable to that used in other studies [150], including the Pan-European Cerebral Palsy study [64], and the Australian population-based study [151] (see Table 5).

Table 5. Categories of CT scan neuroimaging pattern

GROUP	CLASSIFICATION	Imaging characteristics
1.	Congenital malformations.	Any abnormal brain development with cerebral dysgenesis
2.	Primary white matter injury	White matter damage of immaturity (WMDI) with loss of tissue, atrophy or gliosis in periventricular white matter.
3.	Primary grey matter injury	Cortical and central grey matter atrophy with dilatation of the lateral ventricles, dilated fissures and prominent sulci; bilateral or unilateral.
4.	Heterogeneous injuries	Combination of both primary white and grey matter damage. This includes postnatally acquired disorders such as: post-neonatal meningitis, cerebral malaria, encephalitis, infarcts or brain trauma.
5.	Focal cortical infarcts	Neonatal stroke following occlusion of one of the middle cerebral arteries or branches thereof.
6.	Normal	Normal findings – no brain damage detected

7.3.8 Procedure for scoring the PEDI

Part I, the functional skills scale, covers 40 diverse content areas that are assessed using 197 items scored ''unable'' [0] or ''capable'' [1]. The items are divided into three domains: (i) The self-care domain consists of 73 items and covers use of utensils, personal hygiene, grooming, toileting tasks, etc., (ii) The mobility domain has 59 items and covers transfers such as normal use of the toilet/potty, getting into and out of bed or a chair, as well as indoor and outdoor locomotion, and (iii) The social function domain has 65 items and covers word comprehension, communication, problem solving, playing with adults and peers, safety, etc. Each domain produces a total score. Part II, the caregiver assistance scale measures the amount of help provided by the caregiver and covers 20 diverse content areas in the domains self-care (n = 8), mobility (n = 7) and social function (n = 5) scored on a six-point scale ranging from independent, through supervision, minimal help, moderate help, and maximum help, to total help. In our study, Part III, the Modifications Scale section was not used due to the limited availability of technical aids in Uganda.

7.4 STATISTICAL ANALYSIS

Simple descriptive statistics to describe the frequency and distribution of the different study outcomes were utilized in all the five studies, however further statistical tests were carried out dependent on the aim of the study. The other statistical methods used for the analyses were:

i) Pearson's Chi-square test or Fisher's exact test was used to compare two groups of categorical data and determine the strength of association, such as proportion of children with a poor nutritional indicator and perinatal factors in Study II or pattern of brain injury with perinatal factors in Study III.

ii) Pearson's correlation coefficient assessed the correlations between different poor nutritional indicators.

iii) The Kruskal-Wallis H test and the Mann-Whitney U test were used to detect any differences between the comorbidity scores tabulated across CP subtypes and levels of gross and fine motor function in Study I.

iv) Multivariable logistic regression was used in Study II and III to determine the factors independently associated with poor nutritional indicators and pattern of brain injury respectively. In Study I, this test was used to determine the comorbidity independently associated with bilateral spastic CP and the severe levels of gross and fine motor function.

v) In Study V Rasch analysis was used to investigate the validity evidence for the PEDI-UG using the WINSTEPS 3.81 program. Two Rasch models were used based on the type of data; the Rasch dichotomous model was used for the Functional skills section, and the rating scale model was used for the Caregiver assistant section.

All p values were two sided with a probability level of $p < 0.05$ considered statistically significant. Data analysis was performed using IBM SPSS Statistics software, version 22.0 (IBM Corporation, Chicago, IL, USA) for Study I, II and III.

7.5 OVERVIEW OF THE METHODS

All the studies were cross sectional in design and Table 6 shows a summary of the methods employed in each study.

7.6 ETHICAL CONSIDERATIONS

The studies were performed according to the Declaration of Helsinki on research on human subjects and approved by the Mulago Hospital Ethics Committee, the Makerere University School of Medicine Research and Ethics Committee and the Uganda National Council of Sciences and Technology (reference HS 628). The purpose, risks and benefits of the study were explained to the parent/caregiver in a language they understood, following which if they accepted to participate in the study, were requested to sign a consent form. Well-written and informative consent forms were designed and administered for signed parental/caregiver consent in a language of preference of the caregiver (*Luganda*/English), before any child was recruited into any study. It was made clear to the parents/ caregiver that failure to participate in the study would not compromise the services they received at the referral hospital. In addition, they were free to withdraw from the study whenever they wished. All the data records collected from the children were kept under strict confidentiality. The data records were kept in a safe file cabinet with a key accessible by the principal investigator.

Notably, children with CP constitute a particularly vulnerable population by virtue of their often accompanying impaired intellectual capacity and delayed developmental achievement. While it was a requirement by the ethics board to obtain assent from the children above the age of eight years, it was not possible to do so in view of the severe learning disability in our sample with none of the children able to understand the information presented on the assent form nor make a reasoned decision about participation in the study. The ability to give assent requires not only cognitive ability but also the ability to engage in abstract thinking, which is dependent not on chronologic age alone but developmental achievement.

During the conduction of the CT scans we were justified to use sedation in our patients because it was necessary in some children who were unable to keep still and in addition, enabled us to fulfil our research objective.

Table 6. A summary of the methods in each of the studies included in the thesis

Study	Participants	Setting	Outcome measures	Study period
I	Children with CP, n=135; age 2 to 12 years	Mulago Hospital	CP subtypes; Comorbidity; Level of gross and fine motor function.	September 2009 to August 2010
II	Children with CP, n=135; age 2 to 12 years	Mulago Hospital	Poor nutritional indicator; and associated factors.	September 2009 to August 2010
III	Children with CP, n=80; age 2 to 12 years	Mulago Hospital	Brain imaging pattern; and associated factors.	September 2009 to August 2010
IV	Typically developing children, n=75; age 6 months to 7.5 years	Mulago Hospital & Kampala and neighbouring districts	Cross culturally adapted PEDI-UG tool	April to June 2007
V	Typically developing children, n=249; age 6 months to 7.5 years	Rural and urban settings of various Ugandan districts	Assessment of rating scale functioning and internal structure of the PEDI-UG.	July to September 2011

8 SUMMARY OF RESULTS

8.1 CLINICAL FEATURES AND COMORBIDITIES OF CHILDREN WITH CP

Study I aimed to describe the clinical subtypes, gross and fine motor functions and comorbidities of children with CP. One hundred and thirty five children with CP were enrolled (72 males, 63 females, median age 3 years 5 months, IQR-2 years 4 months-5 years 6 months) with a summary of the demographic and clinical characteristics depicted in Table 7.

More than two thirds of the cases seen in this study were below the age of five years with an apparent decline in the numbers of children with CP in the study with increasing age. Most children in our study were term babies (86%), delivered normally (76%) with 16% delivered by Cesarean-section and only 1.7% were positive for HIV.

The most frequent clinical subtype was bilateral spastic CP (45%) followed by unilateral spastic subtype (23%).There were more children with moderate impairment in gross motor function (43%), with comparable numbers (37%) in the mild and severely impaired fine motor function groups. The distribution of clinical subtypes and level of gross and fine motor function are shown in Figure 12.
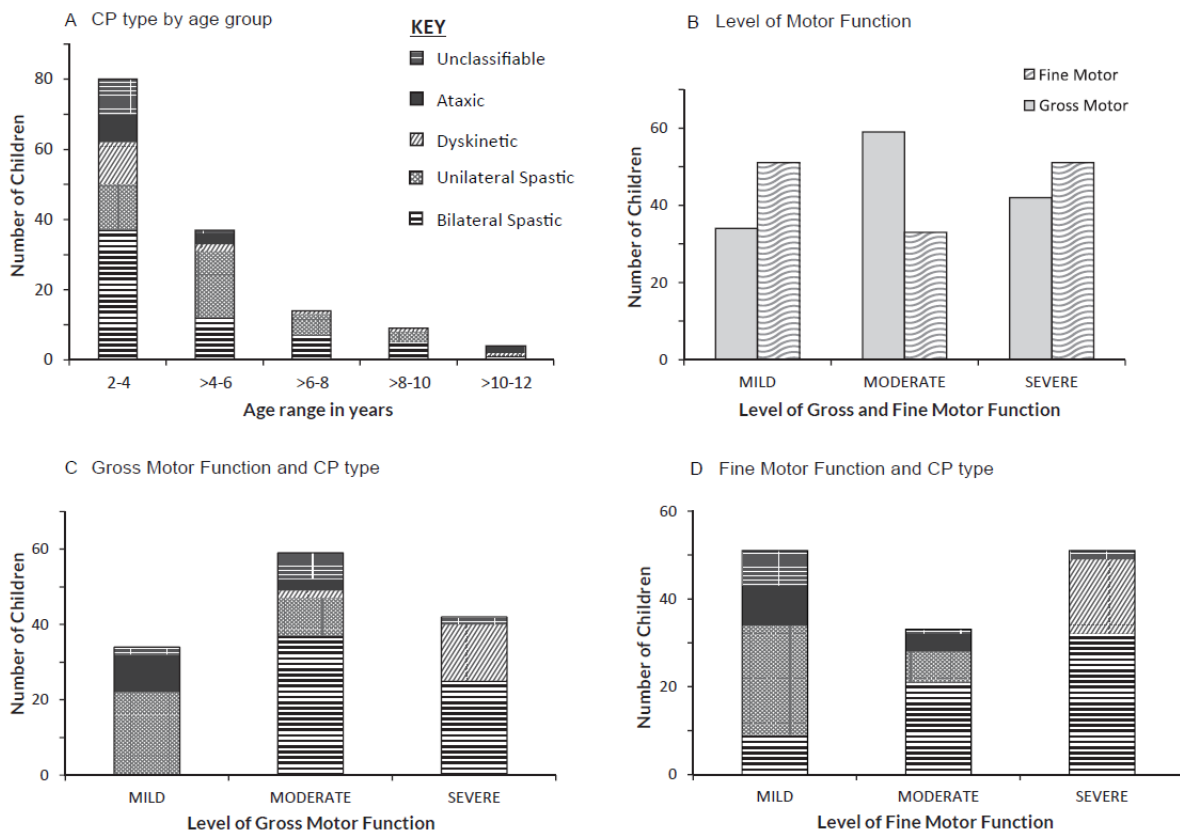
Figure 12. Distribution of age, clinical subtype and motor function in children with CP. Distribution of A) Clinical subtypes of CP by age; B) Levels of Fine and Gross Motor function; C) Clinical subtypes of CP by Gross Motor Function D) Clinical subtypes of CP by Fine Motor Function.

Table 7. Social Demographic Characteristics of Children with Cerebral Palsy (n=135) and their Caregivers plus Clinical Characteristics of the Children

	n (%) or median (IQR)
CHILD characteristics	
Sex M/F	72/63
Age at presentation(years) SD	3.5 (3.2)
Birth weight (Kg) n=113	3.2 (0.94;0.8-6.0)
Birth in Hospital	101 (74.8)
Residence (Urban/Rural)	95/40
CAREGIVER/PARENTAL characteristics	
Age of father at child's birth (years) n=121	30 (7.9;18-68)
Age of mother at child's birth(years) n=130	24 (5.4;14-45)
Marital status of caregiver	
1.Married	92 (68.1)
2.Single	35 (26.0)
3.Widowed	6 (4.4)
4.Separated/Divorce	2 (1.5)
Major source of income-caregiver	
1.Daily petty business	68 (50.3)
2.Salary earner	46 (34.1)
3 Consulting/commission fees	12 (8.9)
4.Fees from hiring rentals	9 (6.7)
Highest level of education attained by caregiver	
1.None/Unknown	12 (8.8)
2.Primary school	28 (20.7)
3.Secondary school	74 (55.0)
4.Diploma	3 (2.2)
5.Tertiary institution	18 (13.3)
Mother's health care during pregnancy	
Mother attended antenatal care	122 (90.4)
History of infection/fever during 1st trimester	58 (43.0)
Poor maternal nutrition during pregnancy	35 (25.9)
Perinatal factors[a]	
Vaginal delivery	103 (76.3)
Preterm birth (<37wks GA)	18 (13.3)
Prenatal complications	37 (27.2)
Neonatal complications	28 (20.6)
Post neonatal complications	25 (18.4)
CHILD CP subtype and comorbidity	
Type of Cerebral Palsy	
Bilateral Spastic	62 (45.9)
Unilateral Spastic	32 (23.7)
Dyskinetic	17 (12.6)
Ataxia	13 (9.6)
Unclassifiable	11(8.1)
Co-morbidity	
Signs of Epilepsy	61(45.2)
Signs of Speech and Language disorders	50 (37.0)
Signs of Visual Impairments	40 (29.6)
Signs of Hearing Impairments	21 (15.6)
Signs of Behavioral disorders	
▪Signs of Anxiety/ Depression	26 (19.3)
▪Signs of Attention Deficit/ Hyperactivity	46 (34.1)
Signs of Learning disability	102 (75.6)
Signs of Autistic Spectrum Disorders	32 (23.7)

M-Male; F-Female; GA-Gestational age **[a]Prenatal factors:** Prenatal period: From pregnancy until birth. ; Neonatal period: From birth up to day 28. Post neonatal period: From day 29 up to 2 years.

The majority (96%) of the children had more than one comorbidity. Signs of learning disability (75.6%) was the most frequent comorbidity followed by epilepsy (45.2%). There were much higher comorbidity scores noted in children with the dyskinetic subtype of CP and those with severely impaired gross and fine motor function. The only comorbidity associated with the bilateral spastic CP subtype and severe levels of gross and fine motor function was signs of speech and language impairments. ($P<0.05$).

8.2   NUTRITIONAL STATUS AND ASSOCIATED FACTORS OF MALNUTRITION IN CHILDREN WITH CP

The aim of study II was to investigate the nutritional status and the associated factors of poor nutrition in children with CP. We found that more than half (53%, 95% CI 44-46%) of the children with CP were malnourished, given that they had a Z-score of below 2.0 in at least one of the malnutrition indicators. Children with underweight (measured by weight for age-Z score) were the most common form of malnutrition, documented in 53/127 children (42%, 95% CI 33-51%), followed by stunting measured by height for age-Z score in 48/128 (38%, 95% CI 30-46%; see Figure 13). There were significant differences in the group of CP children that were malnourished compared to those that were not, with more severely impaired children, with cognitive impairments in the former group $p>0.05$. The poor nutritional status was observed in close to half of children 35/72 (49%) to be present in combination with another nutritional indicator, that is, underweight (low weight-for-age Z-score), stunting (low height-for-age Z-score), wasting (low weight-for-height Z-score) or thinness (low BMI-for-age Z-score).
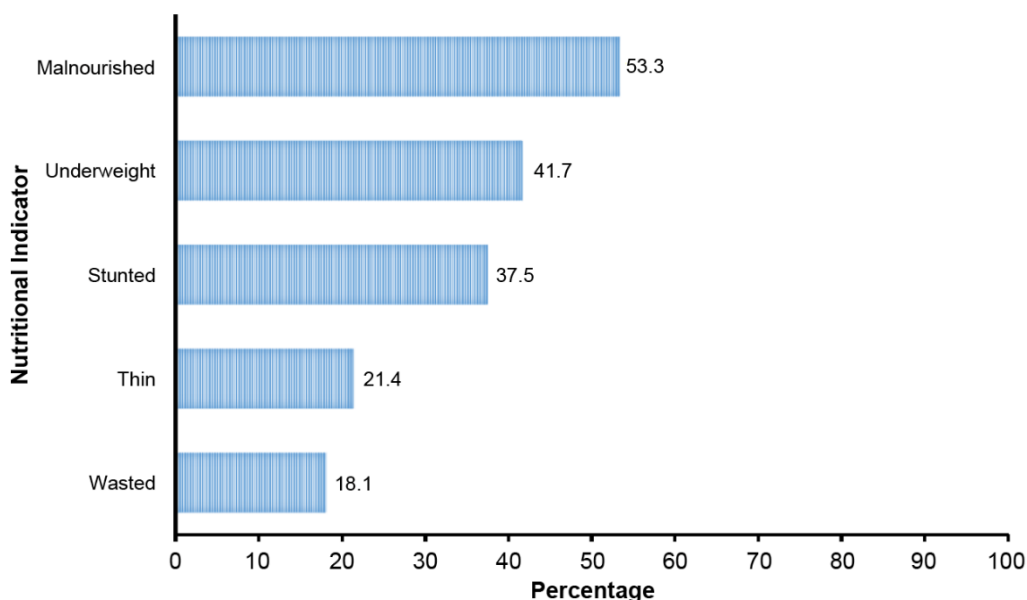
Figure 13. Distribution (%) of children with cerebral palsy by nutrition Z-scores

The frequency of feeding in these children was low with almost half 62/135 (46%) fed one to two times a day and only 11 (8%) fed more than four times a day. Feeding problems were present in 62/135 (46%) of the children with chewing difficulties 36/62 (58%) as the most dominant problem. Complications in the perinatal period were significantly associated with

the various forms of malnutrition. Malnourished children were three times more likely to have had a history of feeding difficulties in the perinatal period (95% CI: 1.3 to 7.9). Underweight children were three times more likely to have had a history of infection in the perinatal period (95% CI: 1.2 to 10.3). Stunted children were twice more likely to have been kept in hospital following birth (95% CI: 1.1 to 5.9), and wasted children were four times more likely to have had an infection during the neonatal period (95% CI: 1.0 to 15.7). The age of the child and presence of cognitive impairment were other noted associations. Children with malnutrition and underweight were three and six times more likely to be older than the age of five (95% confidence interval [CI]: 1.2 to 9.7) and (95% CI: 1.9 to 19.0), respectively. The presence of cognitive impairment (learning disability) was four times more likely in both the malnourished and underweight children, (95% CI: 1.6 to 12.5) and (95% CI: 1.5 to 15.8), respectively.

8.3 NEUROIMAGING PATTERNS IN THE CHILDREN WITH CP

The aim of study III was to describe the neuroimaging patterns in a clinical sample of children with CP and determine how they differed from studies reported from high income countries and their relationship with prenatal and postnatal factors. A sub sample of 78 children with CP had their brain CT scans examined. Abnormal brain neuroimaging findings were detected in 54/78 (69%) of the sample. Primary grey matter injury (PGMI) was the commonest neuroimaging pattern seen and identified in 34 children (44%) with very few white matter injury 3 (4%). Normal brain CT scans were noted in 34 (31%) of the children. A mixture of both grey and white matter injury (heterogeneous pattern) was seen in 13(17%) of the children. Severe gross and fine motor impairment was noted in more than half (59%) of the children with PGMI and half (50%) of the children with normal CT scans. Children with a history of having been admitted to hospital following birth were three times more likely to have primary grey matter injury than any of the other neuroimaging patterns [odds ratio (OR) 2.8; 95% CI 1.1–7.1; p = 0.026].

8.4 CROSS-CULTURAL ADAPTATION OF THE PEDIATRIC EVALUATION DISABILITY INVENTORY IN UGANDA (PEDI-UG)

The aim in study IV was to adapt a culturally relevant PEDI instrument in Uganda (PEDI-UG) and describe the translation and validation process. The purpose of this adapted tool was to aid in the future rehabilitative intervention programs for children with CP in Uganda. During the adaptation process the original PEDI was reviewed by the purposively selected Technical Advisory Group (TAG) through a series of sequential meetings. In addition to English (the official language of Uganda), the PEDI was translated by certified translators into Luganda, the most commonly used local language in Kampala where the study was carried out. Culturally inappropriate terms were deleted, ambiguous terms clarified, appropriate examples were provided for some items, and new items generated in the functional skills part. Uniquely, alternative items were created bearing in mind the different living conditions in rural and urban areas of Uganda in the matters of 'Type of Toilet' and 'Type of Bed' used. For Toileting tasks and Toilet transfers, two options were provided, either "flushing type" or "pit latrine". For Bed mobility/transfers, the two options provided

were, either "actual bed" or "floor bed" to indicate arrangements such as a mattress, papyrus reed mat, or pieces of cloth bundled together and placed on the floor to make a bed. There was no adjustment to the caregiver assistant part during this stage. Two field versions were developed and tested before the (PEDI-UG) instrument was created. In total, seven new items were inserted, ten alternative items created, and nineteen items deleted. In spite of 90% of the original 197 items being retained in the PEDI-UG, many of the remaining items were modified to conform to the local context in Uganda.

8.5   PSYCHOMETRIC PROPERTIES OF THE PEDI-UG

The aim of study V was to investigate the psychometric properties of the culturally adapted PEDI-UG by testing the instrument's rating scale functioning and internal structure. Regarding the functional skills part of the PEDI-UG, the initial analysis demonstrated that misfiting items accounted for 7% in the Self-care domain, 12.5% in the Mobility domain, and 3% in the Social function domain. A re-run during the secondary analysis in which three items each were deleted from the Self-care and Mobility domains reduced the misfiting percentage to the recommended value of $\leq 5\%$. In the final model, there were still a few misfit items detected, three (4%) in Self-care domain, four (7.4%) in Mobility domain and two (3%) in Social Function domain. Nevertheless these items were maintained in view of their Positive Point Measure Analysis correlation (PTMA) values being positive for all items indicating that they all influenced the total raw sum score.

There was good unidimensionality exhibited in the PEDI-UG domains in the functional skills part and all domains fulfilled the criteria for person and item reliability. For the caregiver assistance part, a preliminary analysis of the rating scales were performed initially to assess how best to improve the rating scale functioning. For the Caregiver assistance part the original 6-category rating scale, grouped as: 0= Total Assistance; 1= Maximal Assistance; 2= Moderate Assistance; 3=Minimal Assistance; 4=Supervise/Prompt/Monitor and 5=Independent was reversed to a four category rating scale. The new four point scale is now grouped as: 0=Total assistance, 1= Maximal assistance, 2=Minimal assistance, and 3=Independent. One item in the Self-care domain was underfit and one item in the Mobility domain was overfit to the model. The overfit item, D. Tub transfer, had a non-positive PTMA and was deleted resulting in resulting in 19 items for this section as opposed to the 20 in the original PEDI. There was good unidimensionality exhibited in the PEDI-UG domains in the caregiver assistance skills part and all domains fulfilled the criteria for person and item reliability apart from the Mobility domain that did not fulfil the criteria for person reliability.

9 DISCUSSION

This thesis attempted to answer three overarching questions regarding children with CP in Uganda and other similar contexts:

1) What is the clinical panorama (i.e. clinical and demographic features, clinical subtypes, gross and fine motor function, comorbidities, feeding practices, nutrition) of children with CP in Uganda in comparison with population norms and other previously published studies?

2) What are the possible etiologies of CP in the Ugandan children?

3) Can the Western developed assessment tool, the PEDI, be adapted to measure aspects of function in the activities of daily living of children in the Ugandan situation?

The findings from the studies designed to respond to these queries are henceforth discussed, focusing on the novel information generated, comparison with other studies, the clinical implications, methodological limitations and suggestions for future improved studies.

9.1 CLINICAL PROFILE, ASSOCIATED COMORBIDITIES AND NUTRITION IN CHILDREN WITH CP IN UGANDA

In this thesis, we show that there was a distinctly steady decline in the numbers of CP cases with advancing age, a fairly equal gender distribution and more severe case presentation with the bilateral spastic type of CP being most frequent. Little is known about the distribution of CP by age, sex, severity of motor function, or neurological subtype in children in Uganda or Africa as a whole. A study conducted 48 years ago (1968-69) which described the problems seen in children at Mulago Pediatric Neurology Clinic also noted fewer children from the age of five years onwards [138]. It was also found that tetraplegia (bilateral spastic CP) was a common presentation (with a male/female sex ratio of 1.6: 1), but no information about the severity of motor function was reported. Other clinical based studies conducted in other parts of Africa more than seven years ago found that spastic tetraplegia was the most frequent CP subtype [136,137,152]. However, detailed information on the age, distribution, or severity of the motor functions were not described. A recent study from Nigeria by Okike and colleagues reported fewer numbers of children with CP in the age group greater than 10 years (14.8%) as compared to those below this age (85.2%); however, spastic hemiplegia (unilateral spastic CP) was the most frequent subtype [139]. It is possible that the children in LMIC may not be surviving beyond the age of five years or do not seek medical services as frequently beyond this age. The reasons for this may be as a result of caregiver fatigue, increasing patient weight making accessibility more difficult, or a lack of services for them as they grow older [1]. In a retrospective study of a single pediatric neurology practice in Canada, 217 cases of children with CP were identified over a 10 year period. Although the age distribution was not described, it was reported that 129 of the children with CP were males (59.4%), and that spastic tetraplegia was the most common subtype (35.5%) [153]. The similarity with the subtype found in Canada and LMICs may suggest comparable risk factors at the time this study was

carried out. With regard to sex differences in CP cases, consistent data in both LMIC and developed countries is lacking. Some studies have shown more male preponderance [38,136,154], while others have reported more females [40], and there are also reports of no sex difference [139]. The male gender has been recognized as a risk factor for CP. Males are more prone to white mater brain injuries, especially if they are born very preterm [155].

The more severe form of CP, bilateral spastic CP (tetraplegia), still dominates the clinical presentation in some LMIC [39,40], whereas the milder form (spastic diplegia) of bilateral spastic CP is more prevalent in other LMIC [156,157]. The reasons for these clinical differences may be due to the small size of the studies, methodological issues (not case-controlled or population-based), and different aetiologies. In the developed countries, there are more cases of the milder form (spastic diplegia) reported [158], and this is thought to be due to an increased survival of the extremely preterm infants and those with low birth weight. In contrast, in LMIC where various challenges still exist in terms of lack of improved perinatal and neonatal care and increased rates of meningitis, jaundice, and asphyxia, this situation may play a part in the decreased survival of extremely preterm infants. Alternatively, inconsistencies in the identification of different CP subtypes which may also be related to the level of health worker training, the definitions employed, age at which the diagnosis was made, and challenges in detection of the milder cases, could be contributing factors [159].

A study comparing motor severity in a high income versus a low income country noted more cases with CP from the low income country having poorer motor function [160]. Further support of this finding is seen in two register based studies carried out in Sweden. One study conducted in Southern Sweden in a population of 4 to 11 year olds, identified 344 cases of CP over a 3 year period with spastic diplegia 130 (38%) as the most common subtype and close to half (48%) having the least severe level of gross motor function (GMFCS 1) [161]. However, prior to this finding, other researchers in Western Sweden had recorded more cases of spastic diplegia (44%) and less spastic hemiplegia (33%) [22]. While our study is not directly comparable to these register based population studies, since the age of diagnosis of CP they used starts at age 4 years and different ascertainment methodologies were used, the results from these studies suggest that children with CP in LMIC may have more severe functional compromise compared to those from the high income countries. Secondly, the findings from our results and those from other LMICs seem to suggest that the more frequently identified CP subtype in LMIC remains the same over time, as is the one seen in high income countries. The severity of impairment in children with CP in both regions also seems fairly stable. The more frequent occurrence of bilateral spastic CP in our setting may suggest difficulties happening around the time of birth such as severe birth asphyxia and acquired central nervous system infections such as meningitis or encephalitis in this population [136,138,152]. This situation calls for a more focused concerted effort to support maternal and child health systems in these underserved populations.

We noted that multiple comorbidities were a common feature in children with CP especially those with the dyskinetic type and with the majority having more than two varieties. This finding is not surprising considering that many of the children were severely impaired. While the variety of the most common comorbidities seen in this clinic has remained unchanged over the years with learning disability (mental retardation) followed by epilepsy being among

the top two comorbidities observed [138], the percentage of children affected has increased. We noted 75% of the children had a learning disability and 45% had epilepsy, while in the earlier study the figures were 50% and 41% respectively [138]. This may reflect improved care seeking of the caregivers following increased awareness, a bias by the health workers to refer such children to this clinic, differences in diagnostic criteria and/or assessment methods used, or may also suggest a true increase. This increase may also be attributed to inequalities related to geography and socio-economic status of the patients. MNRH is within the vicinity of a number of slum areas in the urban Kampala city. In our cases, 70% of the caregivers were from the urban areas, with only 15% having an education beyond secondary school and half dealing in daily petty business. While we did not stratify to identify those that came from the upscale or low scale areas, we presume a considerable number were from the settings where there is often overcrowding in the slum (low scale) areas, with high rates of poverty and malnutrition. Such a situation could confer a much higher risk of acquired central nervous system infections like meningitis with the attendant complications.

Learning disability, the most frequent comorbidity seen in studies of children with CP in LMIC, has been reported in several other studies [40,139,160], with almost similar rates [72.5%] being reported [162]. On the contrary, studies performed in Nigeria [139,154] and Tanzania [136] have reported epilepsy with a frequency in the range of 35-37%, as the most frequent comorbidities, and more recent studies done in India [39] have reported speech and language problems at 83.7% as the most common. The differences may reflect differences in the pattern of the brain injury in these children, or may be as a result of different speciality bias in these different clinical settings. Our numbers with learning disability were rather high and may suggest a higher frequency of severe brain injury.

This thesis highlights the rate of malnutrition in this study population which was remarkably high. The figure of 53.3% was six times the level reported in an earlier Ugandan study in children attending this clinic [138], though much lower than the 86% found in a study performed in India [163]. This difference may partly be as result of using different growth reference standards of reporting that has changed over the years, or indicate the true deplorable state of poor nutrition in this vulnerable group of children. Regarding the specific types of malnutrition, underweight is measured by weight for age and is caused by both acute and chronic malnutrition. The finding of higher rates of underweight, in comparison with the other malnutrition types has also been reported in studies performed in other developing countries in Turkey [164], Nigeria [165] and Brazil [166]. The underweight rates were lower in Turkey and Nigeria at 35% and 36% respectively, higher in Brazil at 51%. Our underweight rates were three times higher when compared to the normal Ugandan population [167], but comparable to a study carried-out in a CP population in a high income country (Greece) [88] using similar measurement parameters. Stunting measured by low height for age is a sign of chronic malnutrition and has a multifactorial etiology. Stunting was noted in 38% of the children with CP which was slightly increased from that seen in the normal Ugandan population (35%) [167] and a study performed in Turkey (30%) [164], but comparable with a study done in Brazil (39%) [166]. Wasting on the other hand is measured by weight for height and denotes rapid weight loss as a result of a recent illness. Our finding of 18% with wasting was similar to the 16.3 % recorded in a study done in Nigeria [165], but almost four times when compared to the normal Ugandan population [167].

Among the factors associated with malnutrition were perinatal issues, thus stressing the importance of providing comprehensive emergency obstetric and neonatal care in these children. Despite a low frequency of feeding among the children with CP, this was not associated with any poor nutritional indicator. This may be because almost all children were infrequently fed. Cognitive impairment (learning disability) was an associated factor for malnutrition and underweight, which emphasizes how comorbidities can further complicate the challenge of coping with motor dysfunction in patients with CP. Although it is methodologically difficult to differentiate the effects of malnutrition on the child's learning ability, it is possible that the presence of malnutrition coupled with a deprived environment may have also contributed to the cognitive impairment seen in these children. Malnutrition may exert its effect either by direct injury to the brain, particularly the cortex, hippocampus and cerebellum [168], or as a result of altered mental development resulting from poor environmental stimulation [169]. Malnourished children generally lack energy and are hence less inquisitive and playful, leading to reduced communication with the people in their environment, which impairs their physical, mental and cognitive development.

9.2 PROBABLE ETIOLOGIES OF CP IN UGANDA

The outcome of Study III in this thesis shows that most of the children in our sub sample with CP were term babies, with very few born preterm. Grey matter brain injuries featured prominently with more than half of the children with this pattern having the bilateral spastic type of CP and severe gross and fine motor impairment. This pattern indicates injury to the brain occurring as a result of events happening around the time of birth, such as birth asphyxia, and has been reported in other neuroimaging studies [64,151], denoting a perinatal etiology. The context in which the brain injury occurs involves conditions in which the blood circulation, oxygenation or metabolism of the child's brain is compromised leading to brain damage. Similarly, such a situation may have an impact on the child's general health condition necessitating admission to hospital, and may explain the higher likelihood of children with PGMI that we noted having been admitted to hospital. Whereas the literature states that birth asphyxia plays a relatively minor role in the etiology of CP (contributing 10-20% of CP cases) [170], the reverse may still be true in many low resource settings [39,169] including ours. There is a need to exercise caution in this aspect though since our definition of asphyxia was not based on the presence of encephalopathy as has been recommended [171]. The higher figures of PGMI in our sub sample is in marked contrast to the common pattern seen in cohorts in patients from high income countries [64,151], where primary white matter injuries (PWMI) predominate.

Surprisingly normal CT scans were the next frequently reported brain pattern in our sub sample. This figure was much higher than that reported in larger neuroimaging studies [64,151] that used the MRI modality, but comparable to one study that utilized CT scans performed in a high income country which noted 27% of their CT scans as normal [172]. MRI is known to have improved sensitivity and spatial resolution compared to CT scans [173], so it is possible that unidentified lesions in our sample that may have been detected using the MRI modality were missed. It is also probable that the high number of normal CT scans may point to possible genetic or metabolic causes that could not be detected by any structural brain

imaging method, implying a prenatal etiology. The reasons behind this argument stem from the finding that half of the children with normal CT scans had severe forms of CP and severe gross and fine motor impairments indicating that there was a pathological process that had taken place. This postulation may lend support to the debate ensuing from the current advances in sequencing the entire human genome which suggest 14-31% of CP cases have a genetic basis [48,49].

There were few (17%) cases with a heterogeneous brain injury pattern identified, however this figure was more than twice that reported in other studies which reported 7% in this category [64]. This pattern comprises a combination of both primary white and grey matter damage which is seen in postnatally acquired disorders such as postneonatal meningitis, cerebral malaria, encephalitis, infarcts or brain trauma. Infections are the leading cause of neonatal deaths in Uganda [174] and 30% of these deaths occur during the first week of life [175]. Our findings may thus suggest that more children with this pattern of injury which comprises postnatally acquired CP may be dying within the first weeks of life from fatal neonatal infections and the estimates we obtained regarding this pattern may be an underestimate.

We noted very few primary white matter injuries in our sub sample which is the largest difference when compared to results of brain imaging done in high income countries. The PWMI are more common in children with CP born preterm and are reported to happen around the time of foetal brain development -gestational weeks 24–34 [176], unlike PGMI which happen in the later stages of gestation close to term and often in relation to the birth process [64]. The fewer PWMI (4%) may imply that there are fewer Ugandan children with CP who are born preterm that are surviving the neonatal period. This may be as a result of the limited capacity of the Ugandan health systems to handle the care of the new born [34,177]. The findings of fewer numbers of children with PWMI and heterogeneous brain injury pattern is further supported by the high neonatal mortality of 29 per 1000 live births in Uganda which is dominated by infections (31%), birth asphyxia (27%) and preterm delivery complications (25%) and all these conditions are amenable to prevention [174].

9.3 CROSS CULTURAL ADAPTATION OF THE PEDI AND EVALUATION OF ITS PSYCHOMETRIC PROPERTIES

In this thesis the outcome of study IV looked at cultural adaptation of the PEDI to the Ugandan context in order to create the PEDI-UG instrument, while study V examined the PEDI-UG validity as a unidimensional measure. The information from our results indicate that the PEDI can be culturally adapted for Ugandan children after modifying its format and a few terms and items. The PEDI-UG that we created is a unidimensional measure because it consistently measures the same underlying skill or construct.

There is high priority conferred on the early identification of children with disabilities in view of the benefits that commencing early rehabilitation has on the reduction of impairments [178,179]. The early identification and characterization of disability in LMICs is however hampered by the lack of culturally appropriate and language-specific tools for assessment [180]. Whilst the validated assessment tools from the developed world perform very well in the settings for which they were created, often times they are not representative of the different

cultural settings in the LMICs. Some of these assessment tools have inappropriate or unfamiliar terms, irrelevant items or invalid reference values for the varied LMIC contexts, consequently leading to misleading results. The indiscriminate use of such tools without prior adaptation to the culture in question may explain in part the variation in prevalence figures in many LMICs. Additionally it may be responsible for the missed detection of some children with disabilities, and as such deny them from receiving the required services.

With hardly any appropriate assessment tool to measure the functional performance of children in Uganda, and as part of the preparatory plans to carry out a rehabilitative intervention program for children with cerebral palsy, we opted for the adaptation of an existing Western tool as the best possible alternative rather than create a new tool. Reasons for this were based on the time constraints and cost implications. This procedure of adaptation is not unfamiliar in the Ugandan [181,182] and other African contexts [183,184] as other researchers have also adapted other Western assessment tools to conform to their respective settings.

The choice for selecting to adapt the Pediatric Evaluation of Disability Inventory (PEDI) was based on the fact that it is an important, commonly used and researched functional assessment tool in pediatric clinical practice that captures important aspects of function in the day to day life of children. Furthermore the PEDI has been adapted in diverse cultures in countries in Europe and Asia [108-111,185] but never in Africa, hence its adaptation would allow for cross-cultural comparability both nationally and internationally.

The cross cultural adaptation process was systematically carried in eight steps which were satisfactory and resulted in an adapted PEDI-UG following a procedure adapted from the Beaton guidelines [186] and recommendation by the WHO [187]. The step by step process of cross-cultural adaptation is very important, especially when the instrument to be adapted is used in a different language, setting, and time, as this minimizes the risk of bringing bias into a study [188]. In the process of the adaptation and translation of tools, it is fundamental that field tests are initially conducted using the adapted tool in order to determine how applicable the alterations made are in the particular cultural environment to which they are to be applied [189]. In the cross-cultural adaptation of the PEDI-UG, we performed two field tests on the target population to explore the PEDI-UG's applicability.

The Technical Advisory Group (TAG) evaluated the instrument according to the semantic, conceptual and experiential equivalences. With respect to the semantic equivalence, certain words that were non-illustrative of local conditions were replaced with more appropriate ones, for example "carton or pitcher" with "Coca Cola bottle". Experiential equivalence was attained using locally known examples, such as popular local games, that clearly depicted the local Ugandan context. Furthermore, certain words that differed in conceptual meaning between the cultures were deleted.

Among some of the revisions during the adaptation was the introduction of alternative items to accommodate for the variations in existing facilities and socioeconomic background for children living in the urban or rural areas. The alternative items were created with regards to the type of toilet and the type of bed. The addition of created items to the original PEDI has also been done in the translation and adaptation of the PEDI-G for use in Austria, Germany and Switzerland [111]. The expert committee proposed the creation and addition of two

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subscales in the mobility domain ("Transfer bike trailer" and "Transfer stroller") with four items in each subscale so as to cater for a pertinent activity common across the three countries. These examples illustrate the importance of considering the local context in which the tool is to be applied when you translate and adapt instruments. The addition of new items in an originally created Western assessment tool has also been performed in the adaptation of other Western tools to the Ugandan context [190].

Through the field tests, in depth interviews and validation, we have demonstrated that in some domains of Western tests (such as the PEDI), there are some items which are culturally inappropriate for the Ugandan and probably similar African contexts. For example, questions such as "child initiates hanging up coat when coming indoors", is irrelevant since Uganda has a warm tropical climate with no winter season. Other cultural influences such as over protectiveness of children shown by some caregivers who expressed fears of their children being kidnapped or harming themselves when using a knife to eat or the specified gender roles that indicated activities for boys and girls may have affected how some of the children performed on the PEDI-UG in the social function domain, resulting in different ages of attainment for certain tasks compared with their age/sex-matched peers. These examples highlight the role that culture plays during the adaptation and translation of instruments, and the necessity of not overlooking its importance in this process since child development has been shown to be influenced by culture in the areas of social development, cognition, and gross motor development [191,192]. In this cross cultural adaptation process of the PEDI–UG which involved the creation of alternative items, deletion of irrelevant items, insertion of new items, modification of the wording, and incorporation of local examples, we have demonstrated that 90% of the items from the original PEDI can work well when modified and translated for the Ugandan settings.

In the psychometric analysis of the adapted PEDI-UG, none of our created alternative items was a misfit. For an item to qualify as a misfit the analysis using the Rasch model had to show that the responses to that item had been answered in an unexpected way so that, some children obtained either an unexpectedly high or low score on the items given their ability level. The initial question for the item on Flushing toilet "Does child sit on potty or on a toilet supported by equipment or the caregiver?" was noted as a misfit. The reasons for this are not clear, however in spite of this item being considered a misfit we have kept it in the final PEDI-UG because it had a positive Positive Point Measure Analysis correlation (PTMA) [101,193]. PTMA implies that it contributes positively to the total raw score in the mobility domain of the PEDI-UG. We hope that in the future following further analysis of the responses from the disabled children towards this item we will determine whether it still misfits and needs to be adapted.

In the final PEDI-UG, all domains in the Functional skills part fulfilled the criteria for person and item reliability. The excellent item reliability signifies that we can trust that the hierarchy of items in the PEDI-UG is based on the level of difficulty along the latent variable. With five of the six domains demonstrating acceptable person reliability, this signifies that the PEDI-UG can separate children of different levels of mobility, self-care, and social function. Person reliability is an especially important parameter for an assessment tool to possess since

it determines whether any small differences can be detected following an intervention in clinical practice and/or research.

We noted a fairly weak person reliability of the PEDI-UG in the Mobility domain under the Caregiver assistance section. This may have resulted from the low number of items (6 items) and high number of children who received the top total score in this domain making it more difficult to separate children of different functional abilities. We hope this situation may be corrected when the PEDI-UG is used for its target population, that is, children with disability [101].

The one item "Tub transfers" in the Mobility domain in the Caregiver assistance part was answered by only one respondent and had a non-positive PTMA, hence was deleted because it was deemed irrelevant for the target population in Uganda. The unsuitability of this item has also been noted with PEDI research teams in Sweden, Norway, and the Netherlands, who reported that bath tubs are rarely used in their countries [194]. The deletion of culturally inappropriate test items during the adaptation of other Western developed tools to the Ugandan context, is typical of this process and has been carried out in other studies [181].

Based on the results obtained from the Rasch analysis it is apparent that the respondents might have found it hard to discriminate between some of the adjacent categories in the original 6-category scale. We hope that by combining the categories into a new 4-category scale, we have created a more meaningful scale for the target population.

10 METHODOLOGICAL CONSIDERATIONS

10.1 SAMPLING

It must be recognized that this group of CP patients, as with any institutionally recruited patient series, may be seriously biased and not representative of the whole country. This study was performed only at one site, a health facility, and not in the community where the picture of CP may be different. Despite MNRH's catchment area being nationwide, this may bias our findings towards information for a clinical setting and this should be considered when interpreting the data.

10.2 SELECTION BIAS

The CP patients that attend this specialized clinic probably represent the severe sub types of CP whose caregivers can afford to travel to Mulago Hospital to seek specialist care. Secondly, the socio demographic data shows there were more cases from the urban than the rural areas, and thirdly, sixteen eligible cases were not included due to caregiver issues. These factors may have affected our results by giving us higher numbers of more severe CP cases of a specific socio-economic class hence limiting the generalizability of our findings. In the cross cultural adaptation of the PEDI, the convenience sample of 75 typically developing children was not completely random. However, we have no reason to think that our sample is not representative of typically developing Ugandan children.

10.3 STUDY DESIGNS

All of the five studies in this thesis are cross sectional in design, measuring specific outcomes at a point in time. We calculated the sample sizes for all our studies and are confident that they were adequately powered; however, while cross sectional studies are faster and cheaper than longitudinal ones, any causal or directional conclusions cannot be drawn, only causal associations.

10.4 AGE AT CONFIRMING DIAGNOSIS OF CP

We used the age of 2 years onwards to diagnose a child as having CP. The SCPE (62) recommends that this should be done from the age of 4 years onwards since the subtype may change with time. We are confident that despite the difference in age, the children we classified as having CP fulfilled the accepted definition [140]; however, it is likely that some of the subtypes we diagnosed may change with time.

10.5 DETERMINING THE LEVEL OF GROSS AND FINE MOTOR FUNCTION

We developed scales to classify the level of gross and fine motor impairment in these children, because at the time of conducting the study we had no one trained in administering the standardized GMFCS or MACS. We did not carry out psychometric testing of these scales we developed, therefore we cannot ascertain their validity or reliability.

10.6 DIAGNOSIS OF THE COMORBIDITIES

There were no confirmatory tests conducted to ascertain which diagnostic category the children had. We utilized the standard general and neurological examination and based the diagnosis on the clinical signs and symptoms, examination findings and testing. It is likely that some children qualified for many more comorbidity diagnoses. For example, certain conditions could be classified into multiple diagnostic categories, such as children with severe learning disability by definition are non-verbal, but may be included in the definition of speech and language impairments, or children with autistic traits, but do not fulfil an autism spectrum diagnosis.

10.7 RECALL BIAS

We obtained a significant amount of information from the questionnaires we designed and administered to the mothers/caregivers. The questions required them to recall events that had taken place at the time of birth of the child. Some of the caregivers of the older children may have forgotten some events, some minor incidences may have been missed, the severe events may have been much easier to recall than the less severe, or alternatively, because these children already had a motor disability, the caregivers may have assigned some event to provide a response to the questions asked. Information obtained through questionnaire interviews that depend on the recipient's memory of past events pose both reliability and validity issues [195]. Other issues to be considered include the interviewing technique we employed, the flow of questions in our design of the questionnaires, and the motivation of caregivers to put an effort into remembering and responding to the questions we asked them.

10.8 NUTRITIONAL ASSESSMENTS

We measured the anthropometric indices at one point in time and were not able to do serial measurements which would have provided a more informative picture of the nutritional status. The segmental length measurements we employed to measure the length of the children were prone to measurement errors especially for children with contractures.

10.9 DETERMINING PRESENCE OF BIRTH ASPHYXIA

With the limitation of a lack of metabolic and neuroimaging tests performed routinely in our setting we were not able to confirm whether these children had suffered encephalopathy, the criteria recommended to diagnose birth asphyxia [42]. We used a proxy of the history of the

child having been admitted to hospital after birth in this regard, which has also been noted in other studies to be highly associated with birth asphyxia [196], but is not specific.

10.10 INCONSISTENCIES IN THE INTERPRETATION OF THE PEDI-UG ITEMS BY THE CAREGIVERS

We had a team of 12 different research assistants administering the PEDI-UG to the caregivers through interviews. It is possible that this could have created inconsistencies in the interpretation of the questions. We however minimized this happening by conducting a pre-training course on administering the PEDI with the research assistants, and with pretesting of the questionnaire prior to the data collection exercise. Test-retest reliability data was undertaken, but results are yet to be analyzed.

11 CONCLUSIONS AND CLINICAL IMPLICATIONS

While the studies in this thesis are not population based and cannot inform us about the exact prevalence of CP in Uganda, they do provide important insights regarding the clinical panorama and possible causes of CP in Ugandan children by providing current information regarding CP in children from a low and middle income country in sub-Saharan Africa. Furthermore, they provide lessons learned in the experience of adapting an assessment tool developed in the West to measure functional performance of Ugandan children. In conclusion:

• Bilateral spastic CP was the most frequent clinical subtype in children with CP in Uganda and has remained the same over the years. Children with bilateral spastic and dyskinetic CP had more severe gross and fine motor function. There was underrepresentation of the children above the age of five with CP (**Study I**).

• There is variability in the patterns of comorbidity in Ugandan children with CP, with learning disability and epilepsy predominating. Children with the dyskinetic type of CP, and those with severe levels of gross and fine motor function, have more comorbidities (**Study I**).

• Children with cerebral palsy in Uganda are burdened with malnutrition and feeding challenges. In comparison with the normal Ugandan population, the malnutrition states of underweight and wasting are fairly common with the children above the age of five and those with intellectual disability being at greater risk (**Study II**).

• Primary grey matter brain injuries predominate in children with CP in Uganda with very few white matter brain injuries and also preterm born infants as compared to that seen in high income countries. Our findings suggest that the probable etiology of CP in children in the Uganda setting is often perinatal, followed by prenatal and postnatal origins (**Study III**).

• The adapted Pediatric Evaluation Disability Inventory-Uganda (PEDI-UG) tool provides a culturally appropriate instrument for measuring the functional performance of children in a Ugandan context having good to excellent psychometric properties. The PEDI-UG is thus an acceptable and valid instrument to assess the abilities of typically developing children in Uganda (**Study IV &V**).

The clinical implications from the studies in this thesis, with bilateral spastic CP being the more frequent sub type in our environment, may reflect persistence over the years in the role of obstetric problems happening around the time of birth, such as severe birth asphyxia. The presumed role of obstetric casualties in the etiology of CP in Uganda, which is also supported by our neuroimaging findings, calls for a change in focus of the Ugandan Ministry of Health and development partners, so as to devise more strategic ways to curb the mortality and morbidity in the mother-baby pair around the time of birth. Our findings infer that if the conditions leading up to birth asphyxia could be prevented through a concerted effort to establish a comprehensive program of supervision that can significantly improve emergency obstetric and neonatal care and also promote fetal survival, the number of children with CP

in our setting could probably be reduced. A possible solution to this could be through the development of integrated intervention programs in the health systems rather than continuing with the fragmented ones. To achieve this will require sustained, coordinated and collaborative efforts from the Ministry of Health with greater participation of all partners and stakeholders at the community and individual level. Such programs will hopefully provide the continuum of care necessary to ensure efficient and effective use of the often, limited resources, and make an impact in preventing unnecessary morbidity around the time of birth and hence contribute to a decline in CP incidence in Uganda.

Screening for comorbidities should be part of the mandatory work up in the clinical evaluation and management of children with CP. The efficient management of these children will require a multidisciplinary care team in order to obtain the best optimal care of their medical and psychosocial needs. The effective management of these comorbidities may also aid to make the most of the developmental and educational potential of these children depending on the extent of the brain pathology they have. Currently, the health care delivery provided in Uganda with respect to CP is heavily physician-centric and poorly coordinated. The delivery health system with regard to care of CP children needs to be redesigned to form well organized, coordinated and comprehensive health care teams and involve many more professionals equipped to manage these children and improve their quality of life. This requires support from government and development partners to invest in human resource training and capacity building as well as provision of the drugs and other facilities necessary for their care.

The findings from the nutritional study underscores the poor nutritional state found in these children with CP. There is a need to advocate for early diagnosis of malnutrition so as to institute measures for the satisfactory nutritional and social rehabilitation of these children. The developed nutritional rehabilitation programs need to be tailored to the children with CP living in Uganda and appraised following implementation. It is therefore recommended that close monitoring of the nutritional state of children with CP should be routinely done to ensure that these children do not tip into any of these severe forms, especially for those with the designated associated factors we identified.

Findings from the brain neuroimaging study highlight the importance of how advanced neuroimaging technology can help to explain the cause, the nature, and possible timing of brain injury in children with CP, as well as help us better understand the clinical differences in etiology. Our findings suggest that children with CP often incur brain injury around the perinatal period following severe birth asphyxia which necessitates respiratory support and observation for some time in a hospital environment. Clarification of the underlying causes of the birth asphyxia need to be expounded; however, this issue has medico-legal implications and needs to be handled with caution. While we used CT scan imaging in our study, MRI studies would have been preferable if the investigation were available in Mulago Hospital. Depending on the logistics of acquiring MRI in the future Ugandan general clinical setting, related information obtained from MRI diffusion-weighted imaging, conventional imaging, and magnetic resonance spectroscopy studies should be explored. These studies should preferably be done within the first 24–96 hours of life with further follow-up imaging to

define the full nature of the abnormalities between 7 days and 21 days of life as is recommended [42].

The rehabilitative care for the children with CP also needs to be given priority at the earliest opportunity in order to maximize the optimal chance of therapeutic intervention. Most importantly, rehabilitation gives the child the best opportunity to learn to live with his impairment and thereby minimize his handicap. From the experience we had in the adaptation of the PEDI-UG, we illustrate the importance of systematically following the procedure recommended for tool adaptation. We demonstrate that it is not advisable to wholeheartedly embrace Western developmental assessment tools for use in low income countries, since these tools need to be comprehensible and acceptable in the cultural context in which they are to be applied. The PEDI-UG has the potential to be used in both clinical practice and research to assess and evaluate rehabilitative procedures in children with developmental disabilities and may benefit other researchers in similar African contexts.

12 FUTURE PERSPECTIVES

There is a need to determine the epidemiology of CP in LMICs through the use of large prospective population based studies. The methodological limitations we have noted need to be addressed during the designs of such studies.

Neuroimaging studies using the modality of MRI need to be developed in LMIC studies on children with CP to ascertain whether we still observe the same neuroimaging pattern, and also to help us to determine the exact timing of the brain injury which is an important predictor of neurodevelopmental outcome.

In view of the limitations in metabolic and neuroimaging studies in many health facilities in Uganda, standardized definitions of community-based birth asphyxia need to be developed, taking into considerations that most births in Uganda take place at home. In addition, strategies to evaluate its identification, causes and management in the home, community, and peripheral health units should be established.

Given the fact that we noted fewer preterm born infants in our sample, probably as a result of reduced survival following multiple perinatal complications, there is a great need to support their survival. Efforts to develop cost effective neuroprotective strategies and postnatal interventions that support neurodevelopment are urgently needed.

Furthermore, there is a need to evaluate the validity evidence for using PEDI-UG with the disabled population and to evaluate the instrument's test-retest reliability and better responsiveness to change. This would provide valuable information for the future development and appraisal of interventions to improve the situation for Ugandan and other African children with disability.

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