UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

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ASSESSING CATCH-UP GROWTH IN EXTREMELY LOW BIRTH WEIGHT INFANTS OVER TWO YEARS IN A TERTIARY HOSPITAL IN SOUTH AFRICA

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Contents

Declaration

- I, Samantha Magdalene Kyei, declare that this research report is my unaided work, except where I have indicated differently. I have used requisite conventions in referencing the thoughts and ideas of others. This report is being submitted for the Master of Medicine Degree in the Department of Paediatrics and Child Health at the University of the Witwatersrand, Johannesburg. It has not been previously submitted for any degree or examination at any other university.

Signature: Kyei Date: 07/08/2024

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Dedication

To God, my creator, I am eternally grateful for your grace, favour and strength you gave me to see this project to completion. I dedicate this research report to my dear husband and best friend, Papa Kyei; your love and support mean the world to me; thank you for being my biggest cheerleader; without you, I would not have been able to see this project to completion. To my son Kwabena J. A Kyei, thank you for the joy you bring us. May you know your dreams are always valid. To my mother, Marilyn, my siblings, family in love, and friends, thank you for your prayers, immense support, and belief in me. To Esther, thank you for caring for our son and home while we pursue our careers; we are eternally grateful to you.

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Abstract

Background: Data on catch-up growth of extremely low birth weight infants (ELBWI) in low- and middle-income countries (LMIC) is lacking. Multiple factors affect growth in ELBWI, and catch-up growth is noted to impact neurodevelopment.

Objectives: The aims of this study were to determine the rate of catch-up growth in surviving ELBWI post-discharge at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)and to determine the relationship between catch-up growth and neurodevelopmental outcome at two years corrected age in ELBWI.

Methods: This was a retrospective, descriptive study of surviving ELBWI infants at CMJAH, a tertiary hospital in Gauteng. Data was obtained from the university database of ELBWI attending the follow-up clinic, born between 1 January 2015 and 31 December 2020.

Results: 97 ELWBI were included in the final sample size. The mean gestational age was 27.5 weeks, and the mean weight was 877g. The primary outcome was catch-up growth. At 18 months,90% of females achieved catch-up growth > -2SD for weight, 79% for length, and 92% of females achieved catch-up growth for HC. Males achieved 76%, 67%, and 88%, respectively. Sepsis was associated with being -2SD for weight at 18 months, trending towards statistical significance OR = 4.64 (95%CI: 1.12, 31.71), p-value = 0.0587. Sepsis was also significantly associated with being -2SD for length at 18 months OR = 5.47 (95%CI: 1.54, 26.34), p-value = 0.0158. When looking at the relationship between Bayley scores and growth parameters, weight and length were associated with abnormal Bayley scores at 9-12 months. Infants with normal Bayley scores at 9-12 months had higher weights and were taller than infants with abnormal Bayley scores at this point of assessment. This association was not shown at 18-24 months.

Conclusion: Most ELBWI catch up to -2SD or above by 18 months corrected age for weight, length, and head circumference for age with good neurodevelopmental outcome. Sepsis is a significant risk factor for poor catch-up growth. These results should be interpreted with caution as there was a significant loss to follow-up.

Abbreviations

AIC	Akaike Information Criteria
AGA	Appropriate for gestational age
BPD	Bronchopulmonary disease
BSD III	Bayley scale of infant development III
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CP	Cerebral Palsy
CSG	Child Support Grant
ELBWI	Extremely low birth weight infants
EOS	Early Onset Sepsis
HC	Head circumference
HICs	High income countries
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
ICU	Intensive care unit
IVH	Intraventricular Haemorrhage
KMC	Kangaroo Mother Care
LMICs	Low- and middle-income countries
LOS	Late Onset Sepsis
NEC	Necrotising Enterocolitis
NHC	Neonatal High Care
NICU	Neonatal Intensive Care Unit
PDA	Patent Ductus Arteriosus
RDS	Respiratory Distress Syndrome
REDCap	Research Electronic Data Capture

SA	South Africa
SD	Standard deviation
SDS	Standard deviation score
SGA	Small for gestational age
VLBWI	Very low birth weight infants
WHO	World Health Organization
Wits University	University of the Witwatersrand

List of figures

List of tables

Introduction

Background

The introduction of surfactant as part of the management for Respiratory Distress Syndrome (RDS) in the late 1980s, as well as advances in care for premature infants, has significantly improved the survival of extremely premature infants (1). The prevalence of preterm birth in low and middle-income countries (LMICs) is not well documented (2). The estimates are about 12.4/ 1000 live births in LMICs are preterm, and even fewer are extremely low birth weight infants (ELBWI, <1000g) (2). It is documented that ELBWI have prolonged hospital stays and are at increased risk for poor growth and neurodevelopment (3). Nevertheless, data on medium and long-term outcomes of premature infants in South Africa (SA) is deficient (2).

Catch-up growth is a complex concept. Many factors affect catch-up growth, such as birth weight, gestational age, intensive care unit(ICU) admission, caregiver's feeding choice and supplementation, amongst others (4). Literature defines catch-up growth as reaching a standard deviation (SD) score of > –2 SD of the reference population or a change of > 0.67 SD between birth and two years (5). According to literature, most preterm infants, including very preterm infants, reach catch-up growth by two years; however, they remain shorter and lighter in adulthood when compared to term infants (5).

The literature on growth patterns in ELBWI is scarce in Africa (2). In SA, poor socio-economic circumstances are prevalent. Family income is essential in assessing and monitoring growth (4). ELBWI are predisposed to conditions such as RDS, necrotising enterocolitis (NEC), and bronchopulmonary dysplasia (BPD), amongst others. Hence, catch-up growth is also described as an increase in growth in response to recovery from illness (6). These risk factors impair neurodevelopmental outcomes (7).

Early catch-up growth before two years of age is considered beneficial for public health in the long term. However, related studies exist primarily in high-income countries (HICs) (6,7). Catch-up growth's benefits include improved neurodevelopmental outcomes, improved immunity and improved childhood survival (8). The long-term health consequences of rapid catch-up growth include metabolic, renal, and cardiovascular disease risk in adulthood. However, it is noted that further studies are needed in (5,6,8). In an SA study looking at growth in very low birth weight infants (VLBWI), these infants initially have poor growth compared to term infants, a finding attributed to the initial loss of body water and inadequate nutritional intake, which is then followed by catch-up growth (9). This finding increases with decreasing gestational age (9). Similarly, a study in a Norwegian hospital looking at first-year growth among VLBWI showed growth during the first year persistently less than full-term peers (10).

Growth charts are key when assessing growth; the Fenton growth chart can be used for premature infants up to 50 weeks of life: after that, World Health Organisation (WHO) growth charts are often used (11,12). The Bayley scale of infant development (BSID III) is a good tool commonly used to assess development during the first three years of life. A child with a score of < 70 is described as having developmental delay, with a score between 70 - 85 interpreted as at risk for developmental delay. Cognitive, motor and language delays are increased in EWLBI (13). Therefore it is imperative to monitor growth and neurodevelopment in ELBWI.

The aims of this study were to determine the rate of catch-up growth in surviving ELBWI post discharge at CMJAH and to determine the relationship between catch-up growth and neurodevelopmental outcome at 2 years corrected age in ELBWI.

Methods

This was a retrospective, descriptive study of surviving ELBWI infants seen at CMJAH neonatal follow-up clinic (14).CMJAH is a tertiary hospital which provides neonatal services to regional hospitals and local clinics. The neonatal unit consists of a Kangaroo Mother Care (KMC) and low care ward as well as a 35-bed neonatal high care (NHC) and 15-bed neonatal intensive care unit (NICU). The study sample included all infants with birth weight <1000g, i.e. ELBWI, who were born in CMJAH or referred from local clinics and referral sites between 1 January 2015 and 31 December 2020. Infants were excluded if they had chromosomal or major congenital abnormalities such as complex congenital cardiac lesions, major gastrointestinal tract abnormalities and central nervous system defects or if there was inadequate data on follow-up visits.
The data used in this study was obtained from the REDcap(Research Electronic Data Capture) neonatal database (15). The database is hosted by the University of Witwatersrand (Wits University) and is used for clinical audits. Data is collected and entered into the REDcap database upon discharge of neonates.

Data obtained from REDcap included: gestational age in weeks, weight, length, and head circumference of ELBWI at birth, discharge and follow-up, Apgar score < 5 minutes, presence of RDS, NEC and patent ductus arteriosus (PDA), culture proven sepsis before and after day 3, invasive ventilation and whether infants were breastfed on discharge. Maternal information obtained from REDcap included antenatal care, antenatal steroids, maternal human immunodeficiency virus (HIV) status, maternal employment status and whether the mother or caregiver received a child support grant(CSG) for the index child. The Bayley scale for infant and toddler development III (Bayley score) was taken from a sub-study for neurodevelopmental assessment. The substudy was a prospective follow-up study where all ELBWI who survived to discharge between 1 July 2013 and 31 December 2017 were invited to the clinic. Bayley Scales of Infant and Toddler Development (version III) were conducted at 9 to 12 months and 18 to 24 month (14).

Statistical Analysis

A Microsoft Excel sheet was created with data taken from the REDcap database, and the data was then imported into the statistical program R version 4.02. Frequencies and percentages were used to describe categorical variables; continuous variables were described using mean and standard deviation. For categorical variables, counts and proportions are reported. Fisher's exact test assessed the association between two categorical variables. A linear mixed-effects regression model was used to model anthropometry over time. To determine the association between weight, head circumference and length and Bayley score at 9-12 months and 18-24 months, a linear mixed effects regression model was used with a linear term for abnormal Bayley score at 9-12 months and 18-24 months, respectively, a linear term for gender, a linear and quadratic term for age, and an interaction between gender and both the linear and quadratic term for age as fixed effects. A logistic regression model assessed the association between categorical variables and catch-up growth. A p-value of < 0.05 is regarded as statistically significant.

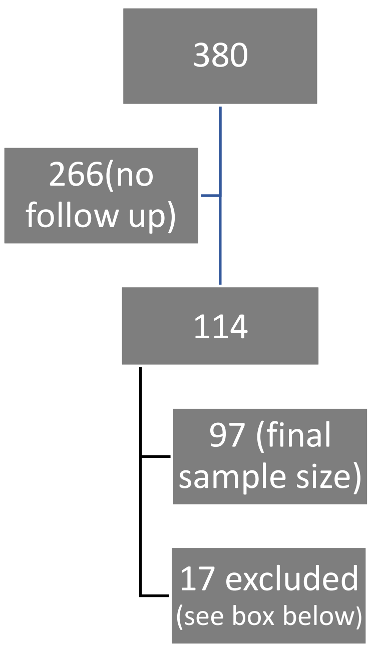
Ethics

Ethics approval for this study was obtained from the Human Research Ethics Committee (HREC) at Wits University. The reference number is M210730. Parents consented to the collection of information for the database.

Results

380 ELBWI born between 1 January 2015 and 31 December 2020 survived hospitalisation; of these, only 114 had follow-up visits. Of the 114 patients, 17 were excluded due to missing data, not meeting weight criteria, and one patient demised during the follow-up period. Hence, the final sample size was 97 patients, as shown in **Figure 1**. The characteristics of ELBWI in sample size are described in **Table 1**. Characteristics for comparison of the 283 patients who did not follow up have also been included.

Figure 1. Final sample size determination



17 excluded
→ 12 missing data
→ 4 not meeting weight criteria
→ 1 demised

Table 1. Maternal and ELBWI characteristics at a tertiary hospital in Johannesburg

	N=97 **Multiple gestation** **5(5.2%)**	**Loss to follow up N=283** **Multiple gestation** **26(9.2%)**
Mean GA in weeks	27.5± 1.8	27.8 ± 1.9
Mean birth weight in grams (g)	877 ± 91	903 ± 95
Mean birth head circumference in centimeters (cm)	26.1 ± 1.7	25.9 ± 1.9
Mean discharge weight in grams (g)	1727 ± 256	1736 ± 309
Females	63(65%)	151(53%)
Mean chronological age at last follow up in months	17.5	
Mean corrected age at last follow up in months	14.4	
Mean weight at last follow up in grams (g)	8593.1	
Antenatal Care	87(89.7%)	217(76.7%)
Antenatal Steroids	60(61.9%)	92(32.5%)
Maternal HIV	23(23.7%)	90(31.8%)
Apgar Score <5 at 5minutes	6 (6.2%)	21(7.4%)
RDS	91(93,8%)	269(95.1%)
Invasive Ventilation	19(19.6%)	59(20.8%)
NCPAP	77(79.4%)	231(81.6%)
Surfactant	48(49.5%)	234(82.7%)
Grade 3 or 4 IVH	2(2.1%)	20(7.1%)
BPD	70(71.2%)	184(65.0%)
NEC	10(10.3%)	21(7.4%)
PDA	12(12.4%)	54(19.1%)
Bacterial Sepsis on or before day 3	3(3.1%)	14(4.9%)
Sepsis after day 3	55(56.7%)	157 (55.5%)
Meningitis	2(2.1%)	3(1.1%)
Breast milk only on discharge	41(42.3%)	115(40.6%)
Mother employed	27(27.8%)	
Child Support Grant for index patient	36(37.1%)	

The **figures (1-3)** below depict the patterns of growth for the sample of ELBWI. Corrected age in months is on the X-axis, and anthropometry (weight in grams, length in cm and head circumference in cm) is on the Y-axis. As per WHO reference charts, males (35%) and females (65%) were separated. For each participant, growth was plotted using the available data (grey). The WHO medians were then overlaid onto the graph; two standard deviations were used.

Figure 2: Weight for corrected age for males and females compared to WHO mean and 2SD above and below the mean

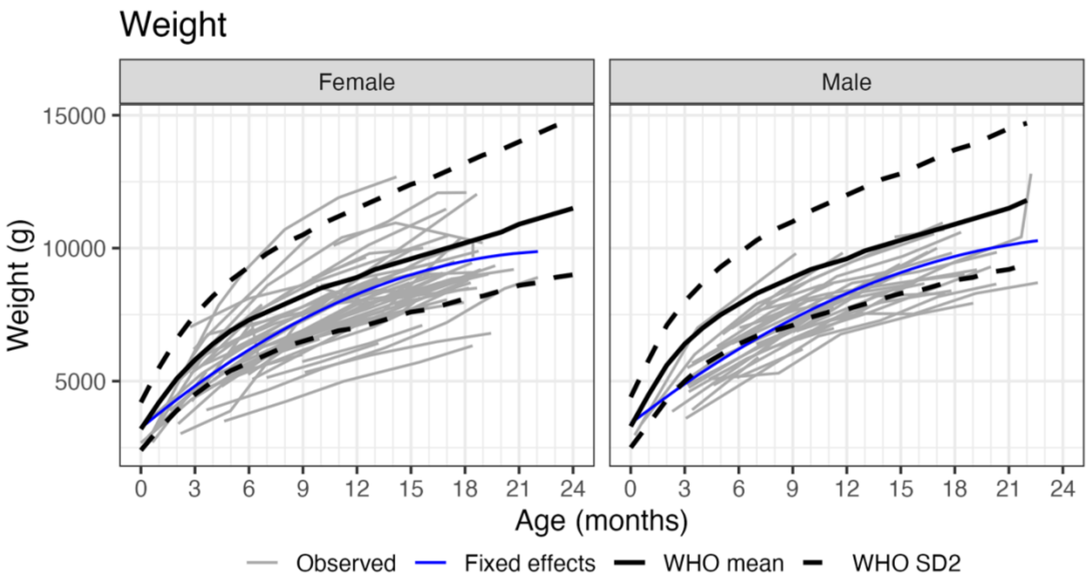


Figure 3: Length for corrected age for males and females compared to WHO mean and 2SD above and below the mean

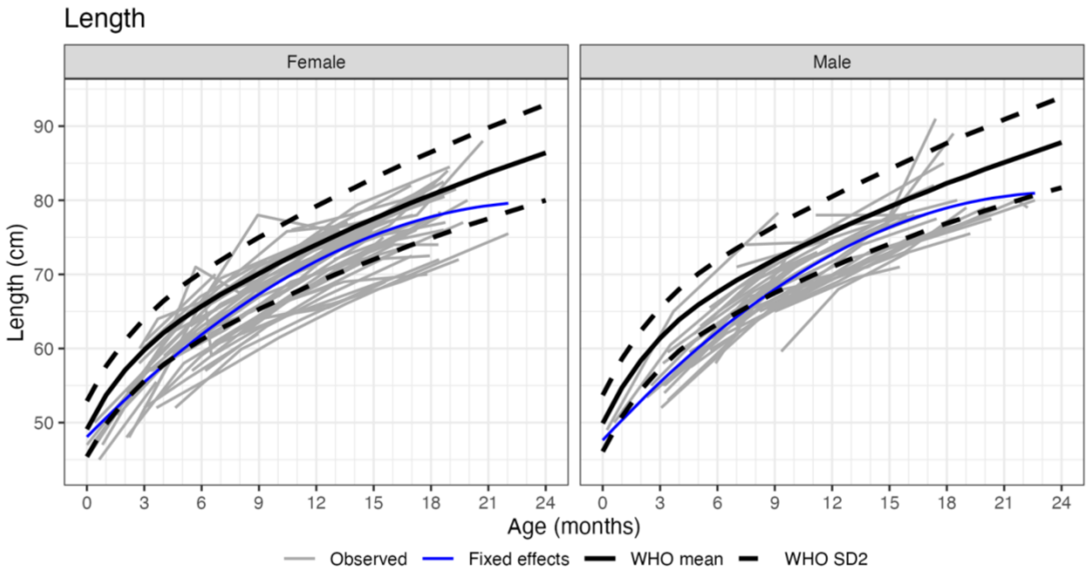
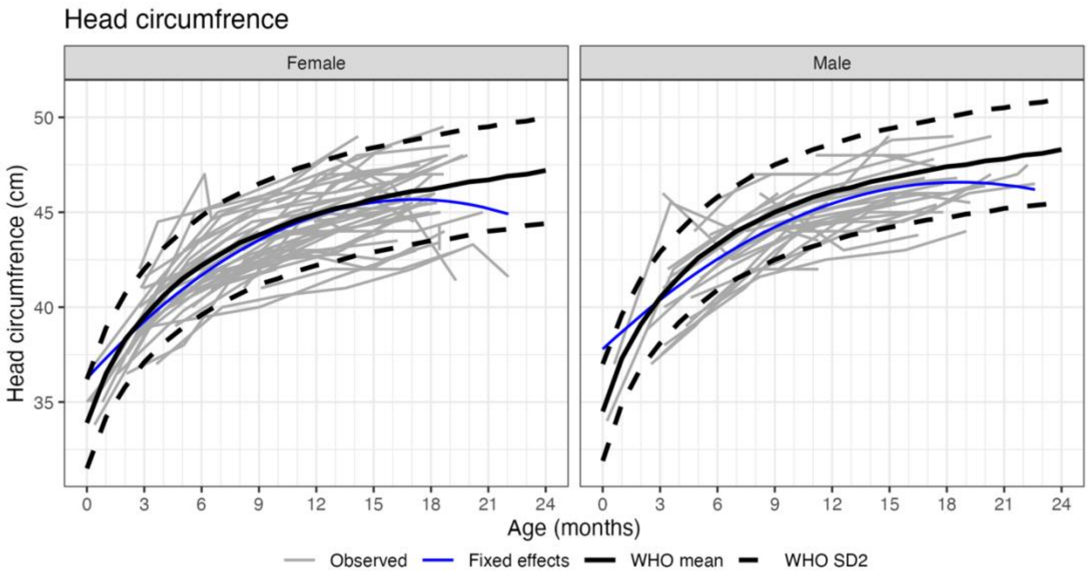


Figure 4: Head circumference for corrected age for males and females compared to WHO mean and 2SD above and below the mean



Bayley scores in relation to growth

When looking at cognitive, language and motor domains, patients with abnormal Bayleys included those with a mean composite score of 70-85, i.e. at risk and those with developmental delay, i.e. a score below 70. At 12 months of corrected age, 46 patients (males and females) out of the final sample size of 97 had Bayley scores; of these, 14 had abnormal Bayley scores. Of those patients with abnormal Bayley scores, 6 out of 14 had weight for age < -2 SD, 9 out of 14 had a length for age < -2SD and 1 out of 14 had a head circumference < -2SD.

At 18 months of corrected age, 26 patients (males and females) had Bayley scores, and 9 had abnormal scores. Of those with abnormal Bayley scores at 18 months, 1 had weight < -2SD, 3 had length below < -2SD and 1 had HC be < -2SD. Two patients were noted to have cerebral palsy. Graphs comparing Bayley scores to growth are below. When assessing the association of weight, length and head circumference with abnormal Bayley scores at 9-12 months, weight and length were associated with abnormal Bayley scores at 9-12 months, with children with abnormal Bayley scores weighing on average 919g (95%CI: 297, 1541) less than babies with normal Bayley score and children with normal Bayley score were on average 2.3cm taller (95%CI: 0.4, 4.3) than children with abnormal Bayley score. There was no association between weight, length and head circumference with abnormal Bayley score at 18-24 months, but this could be attributed mainly to the small sample size. Thus, one would interpret these results with caution.

Figure 5:Weight versus normal and abnormal Bayley at 9-12 months

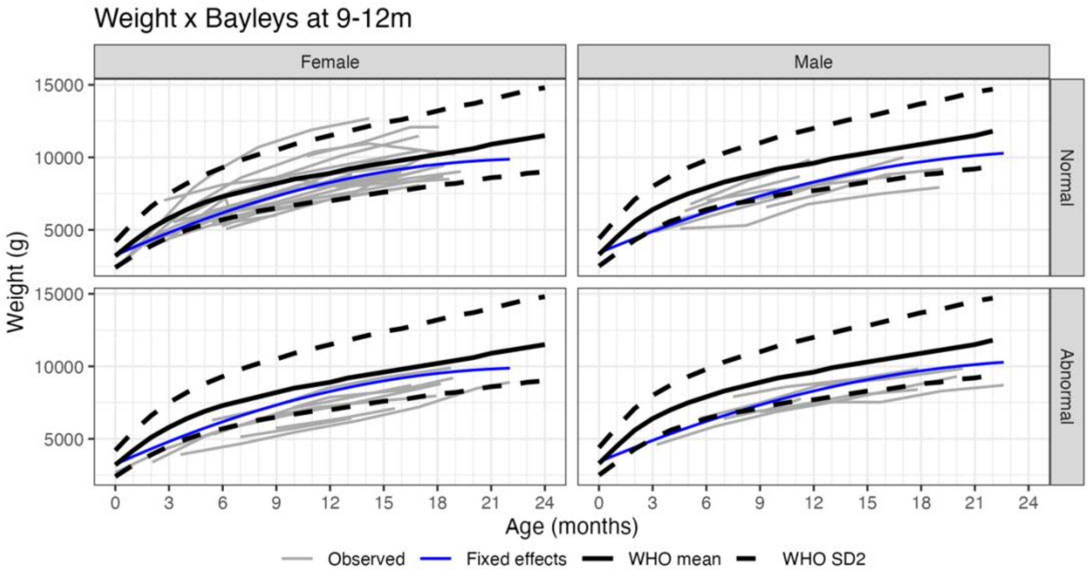


Figure 6: Length versus normal and abnormal Bayley at 9-12 months

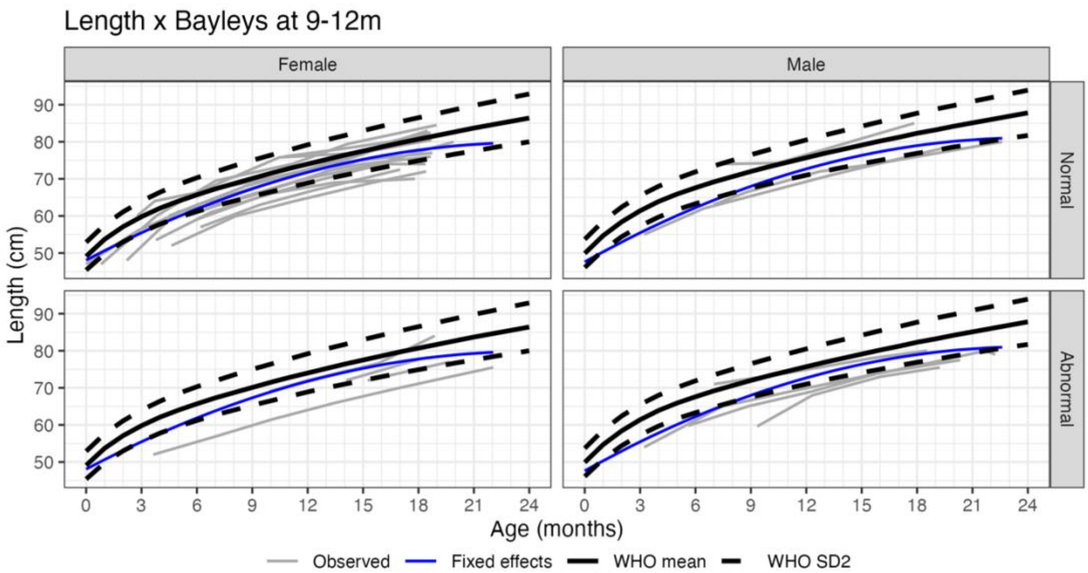


Figure 7: Head circumference versus normal and abnormal Bayley at 9-12 months

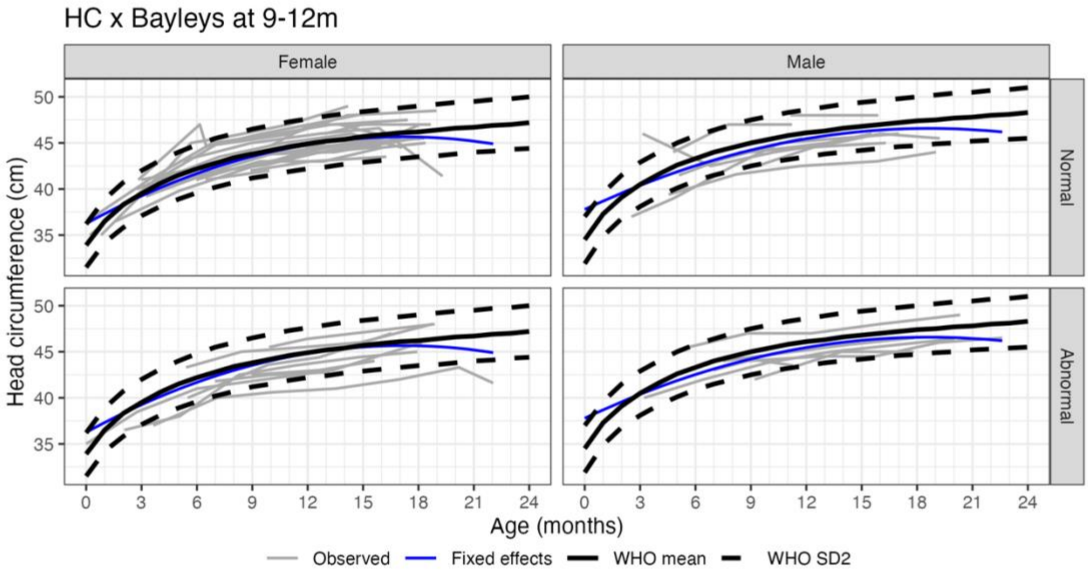


Figure 8: Weight versus normal and abnormal Bayley at 18-24 months

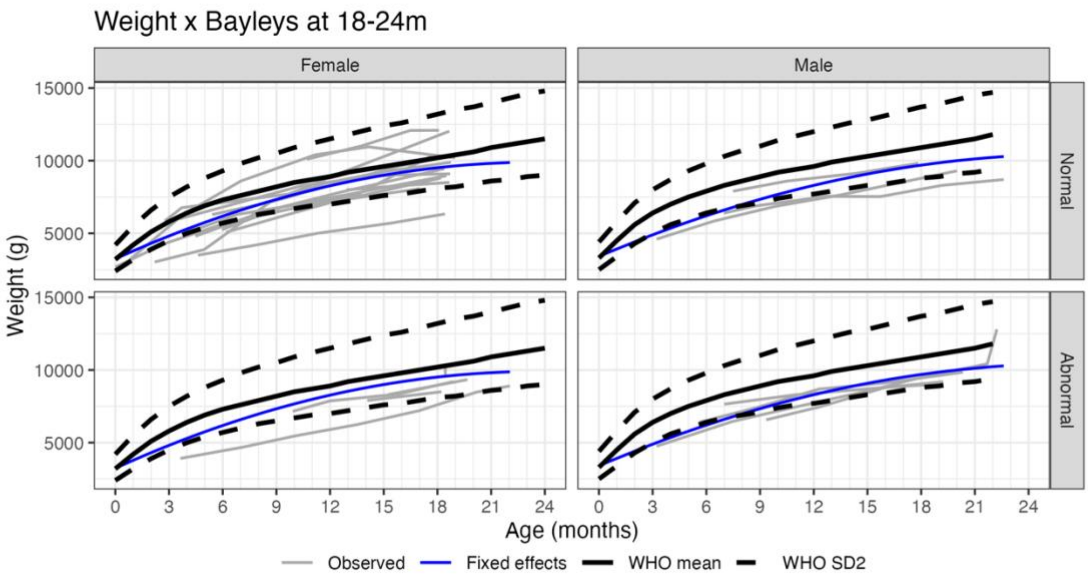


Figure 9: Length versus normal and abnormal Bayley at 18-24 months

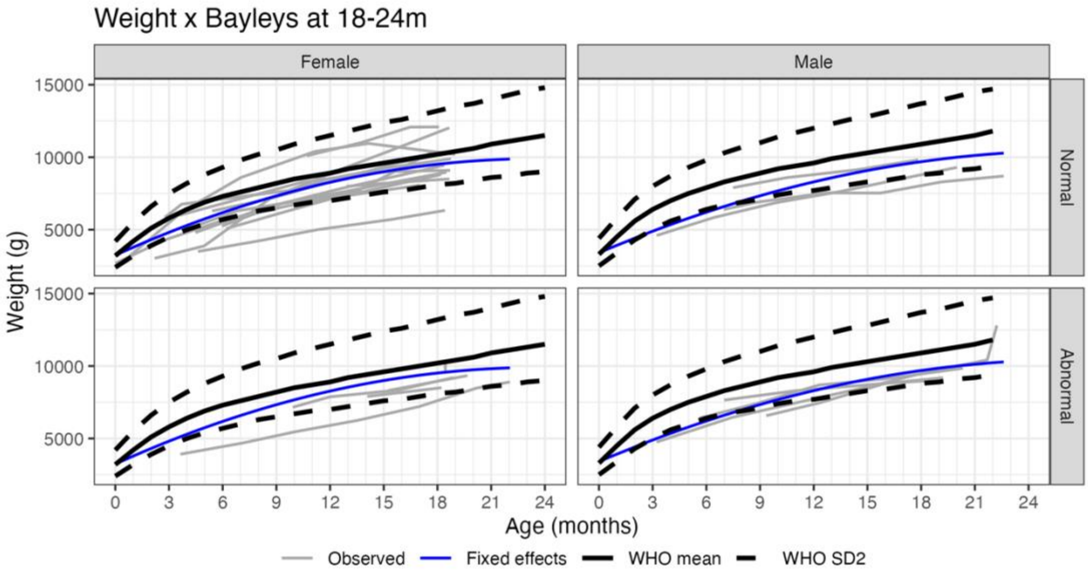
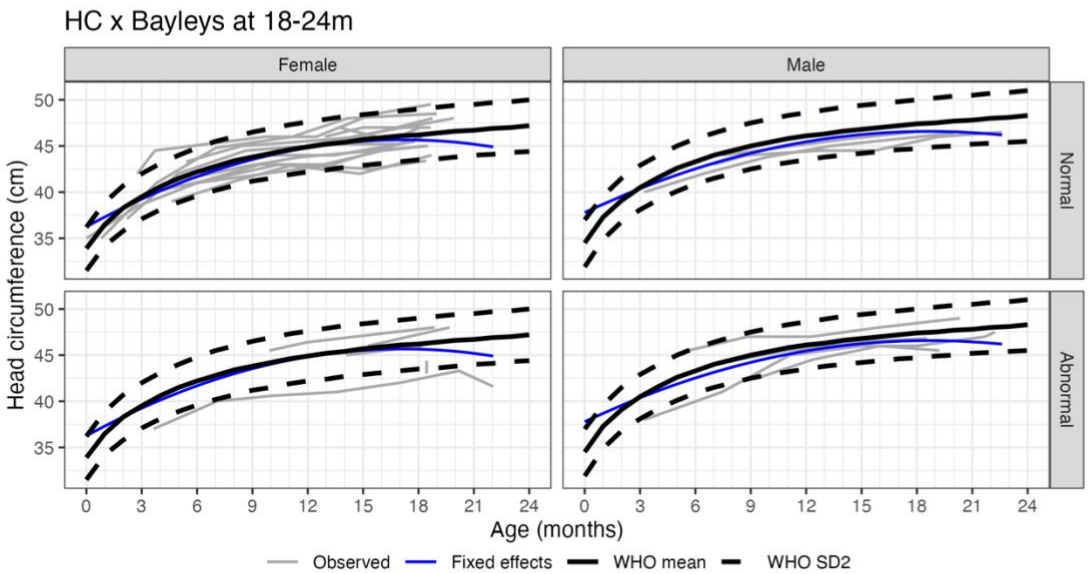


Figure 10: Head circumference versus normal and abnormal Bayley at 18-24 months



Risk factors associated with catch-up growth

To determine risk factors associated with catch-up growth for weight, length and head circumference, risk factors associated with the fitted value being < - 2SD of the WHO score at 18 months were analysed.

Weight

When assessing catch-up weight, sepsis was the only risk factor included in the final comparison. Sepsis was associated with being -2SD for weight at 18 months, trending towards statistical significance.

OR = 4.64 (95%CI: 1.12, 31.71), p-value = 0.0587

Length

Using a stepwise approach, the final comparison included sepsis, face mask ventilation and antenatal care. Only sepsis was significantly associated with the length being < -2SD at 18 months.

OR = 5.47 (95%CI: 1.54, 26.34) , p-value = 0.0158

Head circumference

When assessing head circumference, sepsis and face mask ventilation were included in the final comparison. Neither was significantly associated with HC being < -2SD at 18 months.

Discussion

Advances in antenatal and postnatal care have led to improved outcomes in ELBWI; hence, there is a need to understand their growth and development better.

The mean gestational age of this study population was 27.5 weeks, and the mean birthweight was 877g. Few studies look at growth patterns in ELBWI in relation to neurodevelopment in a LMIC setting. Some studies focus on extreme prematurity as opposed to ELBWI. However, in our setting, gestational age is frequently assessed by Ballard score, as early ultrasounds (which are ideal) are often not done. Ballard scores can vary greatly and often overestimate gestation (9).

Catch- up Growth

This study, based in a tertiary academic hospital in SA, depicts that at 18 months of corrected age, most males and females achieve catch-up growth in all three i.e. weight, length and head circumference. This finding is similar to other studies; however, of note, some studies focus on weight only to define catch-up growth (4,5). When using Euser et al. definition of catch-up growth, this study population achieves catch-up before two years of age (5). An unexpected finding, as one anticipates the growth of ELBWI, would be negatively influenced by their prolonged and often complicated hospital stays, even in later years. Studies also describe the postnatal growth restriction in these prolonged stays leading to initial poor growth (5,9,16). A study done in the same setting on VLBWI , comprising 15% ELBWI, described gradual catch-up growth but incomplete up for length by 20 months of age (9). The persistent deficit in length is also described in the first world countries (1).

The index study had a high antenatal care attendance rate, a low maternal HIV rate and most patients received antenatal steroids. The preceding factors might be favourable as the sample size was chosen based on those who survived to follow-up. These factors could also be the reason for the catch-up growth obtained by 18 months of corrected age. Other reasons could be that the results were skewed because merely a third of ELBWI in this period could be assessed as most did not follow up. A different outcome could thus have been possible.

Associated Risk factors

When assessing risk factors and their relationship to growth, sepsis was significantly related to poor catch-up growth for weight and length. Still, no association was noted with catch-up growth for head circumference in this study. Poor growth and neurodevelopmental impairment are known complications of sepsis (17). Sepsis prevention in neonatal units is of utmost importance, and its association with being underweight and stunted in this study is not surprising. Velaphi et al. when looking at VLBWI, described sepsis as the second most common cause of death, prematurity being the first (18).

A multicentre study looking at factors influencing catch-up growth in premature infants noted monthly family average income, regular health care, and breast milk supplementation as some of the risk factors that affected catch-up growth (4).There are various possible reasons for the added risk factors, mainly that the multicentre study had a larger sample size compared to our study and was also undertaken in a first-world country.

It is also important to note that some studies describe rapid catch-up growth and increased risk for future metabolic disease (1,19). No studies to this effect were found in our setting (2). This could be due to the lack of long-term follow-up of these surviving ELBWI into adulthood.

Growth and Neurodevelopmental Outcome

When looking at the relationship between Bayley scores and growth parameters, weight and length were associated with abnormal Bayley score at 9-12 months .Infants with normal Bayley scores at 9-12 months had higher weights and were taller than infants with abnormal Bayley scores at this point of assessment. This association was not shown at 18-24 months and this is likely attributed to the small sample size and even smaller number of initial sample having Bayley scores at 18 months corrected age.

The population of ELBWI are particularly at high risk for developing neurodevelopmental delay and Cerebral Palsy(CP). There were two reported cases of CP in this study population. Our study included at risk infants in the abnormal Bayley scale category. A study done on VLBWI and a recent study on ELBWI in this setting show that both groups have good neurodevelopment outcomes but also highlight that these results should take into consideration the high mortality rate in these group of infants (14,19).

Stein et al. define growth failure as stunting. They describe premature SGA infants' association with reduced schooling performance and adult height and how increased postnatal growth improves these outcomes in later life (7). Our study did not delineate between ELBWI who were SGA or AGA; hence, we could not identify if SGA ELBWI are more prone to stunting as literature suggests. This could provide for interesting future research in this setting as many studies mention that SGA premature babies, especially ELBWI who are SGA, have poorer neurodevelopmental outcomes.

Strengths and Limitations

Trained paediatricians and neonatologists performed the Bayley assessments, and the results were verified; however, some interobserver bias may be present with different examiners assessing patients at different visits. This was a retrospective study; hence, when reviewing data, some participants had missing data and, therefore, had to be excluded. Although this study was performed in one centre with a small sample size, the data was collected and analysed meticulously.

Determining gestational age in ELBWI is challenging due to the lack of early sonars; hence, gestational age is often inaccurate.

A total of 266 patients were excluded due to no follow-up. This is alarming as only a third of the initial sample could be assessed. Selection bias could thus result in skewed results. However, most of these characteristics are similar when comparing the characteristics of the 283 infants who did not follow up or were excluded. The main difference was only 32.5% received antenatal steroids compared to 61.9% of those who followed up. It would have been ideal to have information on patients who attended the follow-up clinic every three months until 24 months of age. Still, many participants did not follow up at these intervals or until two years of corrected age. There are many challenges involved in following up this special population of neonates. In the South African context, follow-up with patients is becoming increasingly difficult. Reasons for no follow-up are multifactorial: relocation, moving locally and to other countries, difficulty accessing health services at CMJAH for foreign patients, poor socio-economic status, and inability to miss work for fear of loss of income. Those who did follow up also did not follow up regularly, likely due to the above factors. We are also uncertain of the number of patients who might have demised after discharge. Ballot et al. (20), when looking at neurodevelopment outcomes in VLBWI in the same setting almost 15 years ago, cited relocation and parents' inability to miss work days as a common basis for loss to follow-up. These are recurring reasons in the current setting. The aim of the study was to follow up patients until two years corrected age. However, due to poor follow-up, the majority of patients were assessed up to the corrected age of 18 months, and analysis was done until then. One is also uncertain if trends would have continued above -2SD if participants followed up to 2 years corrected age .

Conclusions

The survival of ELBWI is increasing due to advances in health care and the availability of resources. Growth is crucial for the healthy development of premature infants; however, it is not well studied, especially in LMIC. ELBWI experience many complications from birth to discharge; a major complication is sepsis. Our study shows that sepsis increases an ELBWI’s chance of not achieving catch-up growth for weight and length for age by 18 months. This highlights the importance of implementing strict infection control policies in the neonatal unit.

Only 30% of ELBWI infants discharged returned for follow up. These reasons are multifactorial, as highlighted above, but the main reasons include likely complications of prematurity after discharge, relocation to provinces outside of Gauteng or emigration back to other African countries. Even though this study highlights that most ELBWI catch up to -2SD or above by 18 months, corrected age for weight, length, and head circumference for age with good neurodevelopmental outcome. This might be mainly due to significant selection bias. Interestingly, as noted, the characteristics of the study sample and those lost to follow-up are similar. These results should thus be taken with caution. Only 32.5% of those lost to follow-up received antenatal steroids,50% less than those who did follow-up. The rest of the variables were similar when compared between the study sample and those lost to follow-up.Further multicentre studies in limited resource settings are needed to enhance insight into the growth and neurodevelopment outcomes of ELBWI.

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Annexures

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

R49 Dr S Kyei

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M210730

NAME: (Principal Investigator)	Dr S Kyei
DEPARTMENT:	School of Clinical Medicine Department of Paediatrics and Child Health Medical School University
PROJECT TITLE:	*Assessing catch-up growth in extremely low birth weight infants (ELBWI) over two years in a tertiary hospital in South Africa* **Change of study title noted on 2021/11/29**
DATE CONSIDERED:	2021/07/30
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Dr T Ramdin
APPROVED BY:	CB Penny Dr CB Penny, ~~Chairperson~~, HREC (Medical)
DATE OF APPROVAL:	2021/11/11

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in July and therefore reports and re-certification will be due in the month of **July** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator ____________ Date ____________

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

2022/02/03

Dr S Kyei
School of Clinical Medicine
Department of Paediatrics and Child Health
Medical School
University

Sent by e-mail to: dyantyisamantha@gmail.com

Dear Dr Kyei

Re: **Protocol Ref No:** M210730
Protocol Title: *Assessing catch-up growth in extremely low birth weight infants (ELBWI) over two years in a tertiary hospital in South Africa Change of study title noted on 2021/11/29*
Principal Investigators: Dr S Kyei

I refer to your letter of 2022/01/27.

I confirm that we have noted and approve of your proposal to:

1. halve your sample size to about 100 participants
2. take the start date for data collection back to 1 January 2015

Thank you for keeping us informed.

Yours Sincerely

I. Burns
....
Mr I Burns
For the Human Research Ethics Committee (Medical)

CB Penny
....
Dr CB Penny, Chairperson, Human Research Ethics Committee (Medical)