Growth velocity of young children in two low-resource settings

Patterns and abilities to predict negative health outcomes

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Abstract

Introduction

Measuring child growth repeatedly over time has theoretical advantages over measuring growth at a single time point, such as the early detection of deviations in growth. A timely identification of children at risk could guide effective preventive or therapeutic action. Although the WHO growth velocity standards offers the opportunity to score weight and length velocity according to the rate at which children ought to grow, it is rarely used. This thesis aims to describe growth velocity in children under the age of two years in two low-resource settings, using the WHO Child Growth Standards, and to examine the ability of growth velocity Z-scores to predict short-term mortality and future nutritional status.

Methods

We used data from children under the age of five years enrolled in two large community-based cohort studies in the Democratic Republic of the Congo (DRC) and Nepal. Both settings represent areas with a high prevalence of malnutrition. The study in the DRC was conducted in Bwamanda, a rural area with the main livelihood of subsistence farming. In total, 5,657 children were enrolled over the study period. Weight, length/height and mid-upper-arm-circumference (MUAC) were measured up to six times on average every three months. The study in Nepal was conducted in the municipality of Bhaktapur, a peri-urban area, where food items are available all-year round, but food prices vary according to the season. All 240 children were enrolled within 17 days after birth, and weight and length were measured every month up to two years of age.

All anthropometrical measures were scored according to the WHO Child Growth Standards, and children defined as being malnourished if the Z-score was $\leq$-2. Attained growth indices considered in this thesis were length-for-age (LAZ), weight-

for-length (WLZ), weight-for-age (WAZ), and MUAC-for-age, and longitudinal indices were weight velocity and length velocity. Changes in MUAC were calculated as the difference in cm or Z-score and standardized to an exact 3-month period.

Multiple mixed effect models were used to describe if weight or length velocity Z-scores changed according to season and distance to sources of food and health care. We built generalized estimating equation (GEE) models to assess the risk of mortality within three months, separately for indicators of attained and longitudinal growth. To assess the risk of malnutrition at the age of two years, we used simple linear and logistic regression models with growth indicators during infancy as the independent variables. Areas under the ROC curves (AUROC) were the basis for evaluating and comparing the predictive abilities of growth velocity and attained growth to predict death within three months or malnutrition at the age of two years, respectively.

Ethical approval was obtained from appropriate institutions and ethical principles were respected.

Results

Growth velocity Z-scores were low just after birth in the Bwamanda cohort and improved slightly with increasing age. In the Bhaktapur cohort, weight and length velocity Z-scores were above the median of the WHO standards in the first three months of life. After a decrease until the age of 5 and 13 months respectively, Z-scores improved marginally until 24 months.

Weight and length velocity Z-scores showed a marked seasonal pattern in the Bwamanda cohort, whereas indices of attained growth decreased continuously over time. Age and season were independently associated with weight and length velocity.

Weight and length velocity were better in predicting death within the next three months compared to their attained growth counterparts in the Bwamanda cohort. In contrast, there was no advantage to assess MUAC longitudinally. In the Bhaktapur cohort, attained growth indices at the age of 12 months had better abilities to predict undernutrition at the age of two years than weight and length velocity during periods in infancy.

Conclusions

Our results show that measures of attained and longitudinal growth used for this thesis capture partly different aspects of child growth. Therefore both approaches are useful to understand and study malnutrition. Currently, the practical use of growth velocity Z-scores has some limitations, but their value for research and for short-term prediction of unfortunate health outcomes should be considered.

List of publications

Schwinger C, Lunde TM, Andersen P, Kismul H, Van den Broeck J. **Seasonal and spatial factors related to longitudinal patterns of child growth in Bwamanda, DR Congo.** Earth Perspectives 2014;1.
http://www.earth-perspectives.com/content/1/1/26

Schwinger C, Fadnes LT, Van den Broeck J. **Using growth velocity to predict child mortality.** Am J Clin Nutr. 2016 Mar;103(3):801-807.
http://ajcn.nutrition.org/content/103/3/801.abstract

Schwinger C, Fadnes LT, Shrestha SK, Shrestha PS, Chandyo RK, Shrestha B, Manjeswori U, Bodhidatta L, Mason C, Strand TA. **Predicting Undernutrition at Age 2 Years with Early Attained Weight and Length Compared with Weight and Length Velocity**. J Pediatr. 2017 Mar;182:127-132.
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Contents

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Important abbreviations

AUROC	Area under the receiver operating characteristic curve
CI	Confidence interval
DRC	Democratic Republic of the Congo
DHS	Demographic Health Survey
GEE	Generalized estimating equations
HAZ	Height-for-age Z-score
LAZ	Length-for-age Z-score
LFU	Lost to follow-up
LVZ	Length velocity Z-score
MGRS	Multicentre growth reference study
MUAC	Mid-upper-arm-circumference
NGO	Non-governmental organization
RCA	Random coefficient analysis
ROC	Receiver operating characteristic
SD	Standard deviation
SGA	Small for gestational age
UNDP	United Nations Development Programme
WAZ	Weight-for-age Z-score
WHO	World Health Organization
WHZ	Weight-for-height Z-score
WLZ	Weight-for-length Z-score
WVZ	Weight velocity Z-score

1 Introduction

Child growth has long been recognized as a mirror of an individual's well-being. More recently it has also been acknowledged as an indicator of the functioning of health services, inequality in health, wealth and nutrition within and among populations [1]. The periods during pregnancy and early childhood are suggested to be critical for child growth with inadequate growth potentially leading to permanent impairments in health, school attainment and economic productivity [2-4]. Globally, malnutrition in all its forms affects one in three people of all ages and together with poor diet contributes by far the most to the burden of disease [5, 6].

Monitoring of child growth is nearly practiced universally in pediatric care worldwide with the aim to detect children at risk of malnutrition or any other negative health outcome as soon as possible [7]. Ideally, it can be used to detect a deviation before a disease has manifested itself and to timely start further investigations and adequate treatment. A longitudinal approach can evaluate the development over time and thus distinguish those children who continously have been small from those who are faltering. The WHO published growth velocity standards which allow the scoring of the growth rate in relation to that of an international healthy reference population. However, these standards have not been used extensively yet.

This introduction provides a definition of malnutrition. Approaches to the assessment of malnutrition, with indicators of both attained growth and longitudinal growth, are described with an emphasis on growth velocity as one measure of longitudinal growth. To complete this chapter, the multifactorial etiology of malnutrition is indicated and selected determinants are outlined.

1.1 Definition of malnutrition

In this thesis I will refer to growth on the organismic level, i.e. the child as a whole, as the increase in linear dimension (measured as height or length) as well as the change in body composition (measured as weight, arm circumference etc.). There are many conditions and reasons for a slower or faster growth than that expected. The European Society for Pediatric Endocrinology distinguishes primary, secondary (and idiopathic) growth disorders [8]. Causes of primary short stature include clinically well-defined syndromes (e.g. Turner syndrome), being small for gestational age with no catch-up, and skeletal dysplasias. Secondary growth disorders can be due to amongst others metabolic and endocrine disorders, psychosocial factors, medical treatment and malnutrition.

Malnutrition can be defined as an abnormal physiological condition in which the body does not receive an appropriate amount of nutrients for proper functioning (adapted from [9]). Although the definition covers both over- and undernutrition, in this thesis I use the expressions malnutrition and undernutrition interchangeably and do not consider over-nutrition.

1.2 Assessment of malnutrition

Undernutrition presents in different forms such as intrauterine growth restrictions (IUGR), low birthweight, stunting, wasting, underweight, marasmus, kwashiorkor, and micronutrient deficiencies. Hence, the various facets necessitate different assessment tools, such as anthropometric measurements, biochemical analyses, assessment of dietary intake or clinical evaluation [10]. Anthropometry is regarded as the most feasible, because it is non-invasive, relatively cheap and easy to obtain, and more sensitive to moderate forms of malnutrition. However, it has limited diagnostic relevance [10]. Anthropometry is not only an indicator of the growth of an individual. It can be used to identify an individual or a population at risk, to select an indivdual or a population for inclusion or exclusion of an intervention (predict benefit or reflect lack of risk), to evaluate or monitor an intervention or other changes, and for research (to analyse risk factors) [1]. The most common anthropometrical measurements are length or height, weight, circumferences (head and arm) and skinfold-thickness (triceps, sub-scapular, supra-iliac). Detailed descriptions of measurement techniques are available for example from WHO [11].

In general, malnutrition can be assessed cross-sectionally, i.e. at a single time point, or longitudinally, i.e. repeatedly at two or more time points. A measure of growth at a single time point reflects what dimension the child has attained up to that time point and is therefore a cumulative measure of all the events in the past. It is referred to as “attained growth” in this thesis. In contrast, longitudinal growth is an instantaneous measure describing the events that have happened in the time between two measurements. Both approaches are described in more detail below.

1.2.1 Attained growth

The most common indices of attained growth are length/height-for-age (indicating stunting), weight-for-length/height (indicating wasting) and weight-for-age (indicating underweight). The condition is commonly classified as moderate when the Z-score is ≤-2 and as severe when the Z-score is ≤-3. These cut-offs are based on statistical grounds, but ideally, they should be determined by their level of association with negative risks [1]. Levels of deficits in attained Z-scores have been shown to correspond to negative health outcomes such as death [12]. Still, the cut-offs remain somewhat arbitrary.

Plenty of attained growth references exist, which describe how a population in a defined geographical region grew at a specific time. In contrast, a standard is the attempt to describe how a child ought to grow and is of prescriptive nature. The underlying reference population for a standard is thus a sample of healthy children which grew up under optimal conditions, i.e. with minimal exposure to factors known to influence their growth negatively. The WHO Child Growth Standards [13-15] for which children in six countries across continents were sampled (Brazil, Ghana, India, Norway, Oman and USA), applied very strict inclusion criteria to define a healthy reference population. These growth standards are widely used with 125 out of 180 governments indicating the implementation in their country in 2012 [16].

1.2.2 Longitudinal growth

Longitudinal growth can be assessed in different ways. Various approaches to define and score longitudinal growth evolved over the past, which will be briefly described here.

The first velocity growth chart was published in 1959 by Bayer and Bayley [17]. Their main intention was to understand linear growth rates during puberty and to assess possibilities to monitor it. James Tanner advanced this field of research with his foundational work on growth and growth velocity [18]. Their main interest was different developmental tempi in adolescence. They emphasized the importance of assessing individual growth longitudinally, arguing that measures of attained growth can be misleading, because they are affected by the timing of the pubertal growth spurt [19]. In 1966, they published growth charts for velocity with 18 tables for each sex from birth to adulthood (18 years) [20]. They used them to plot weight and height curves according to developmental age instead of chronological age. Although the Whitehouse-Tanner charts were quite popular, a common problem with these and other growth velocity charts are that they are rather complicated to use [21]. Other approaches were explored, as for example centile crossing, which does not express velocity in units of change in the raw measurement per time period (e.g. cm/year), but in units of change in percentiles per time unit. Cole [22] presented a combined chart with attained growth and conditional growth velocity in one. These conditional velocities (also called thrive lines) could alternatively be superimposed on growth charts with a set of transparent overlays or by an electronic version which can be added to the screen. The aim of the thrive lines was to quantify centile crossing while taking into account the age and the starting centile. Further methodologies to describe longitudinal growth are reviewed by Argyle [23].

Today, proponents of the longitudinal assessment of growth still agree that attained growth is convenient for screening and cross-sectional population-based studies, but it misses information on temporary changes, especially concerning disease progress or success of intervention. In these cases, growth velocity is considered a more sensitive measure of individual growth, which can detect more subtle changes [24-26]. Far fewer references for velocity exist compared to attained growth. Disadvantages in practical application and a lack of good quality longitudinal growth studies might be reasons for this scarcity. Some examples of current published velocity references are: Falkner [27], Tanner *et al.* [28], Tanner *et al.* [29], Roche *et al.* [30], Sorva *et al.* [31], Sorva *et al.* [32], Zumrawi *et al.* [33], Berkey *et al.* [34], van't Hof *et al.* [35]. All these velocity references differ considerable in their underlying population (e.g. the feeding mode, the age of gestation), as well as growth increments used (between three month and one year), in age span reported (from 0–12 months to 0–18 years), and in the graphical display.

In 2009, WHO published the first international standards for growth velocity for the measures weight, length and head circumference [15]. These standards are used throughout the analyses within this thesis to score weight and length velocity. Details on the calculation are discussed in chapter 4.4 and other implications in chapter 6. The same cut-offs as for attained growth can be used with the same statistical reasoning. However, no consent on cut-offs for defining malnutrition with longitudinal indices exists, and associations with levels of risk have not been established.

1.3 Determinants of malnutrition

A common framework to summarize the main determinants of malnutrition was published by UNICEF in 1990 [36]. It describes determinants on three different levels that build upon and interact with each other. The framework was adapted in the Lancet series 2013 in the light of a lifecycle approach and adds possible interventions at the different levels (Figure 1). This framework will be used to briefly mention some of the main determinants of malnutrition. Stunting and wasting, also referred to as chronic and acute malnutrition respectively, are often presented as two different forms of malnutrition, for example in the Lancet series 2013 [37-40]. Nevertheless, some authors claim that they are undoubtedly linked and suggest that they might share many causal pathways [41, 42]. An overview of determinants for malnutrition independent of the anthropometrical assessment method is given in this chapter.

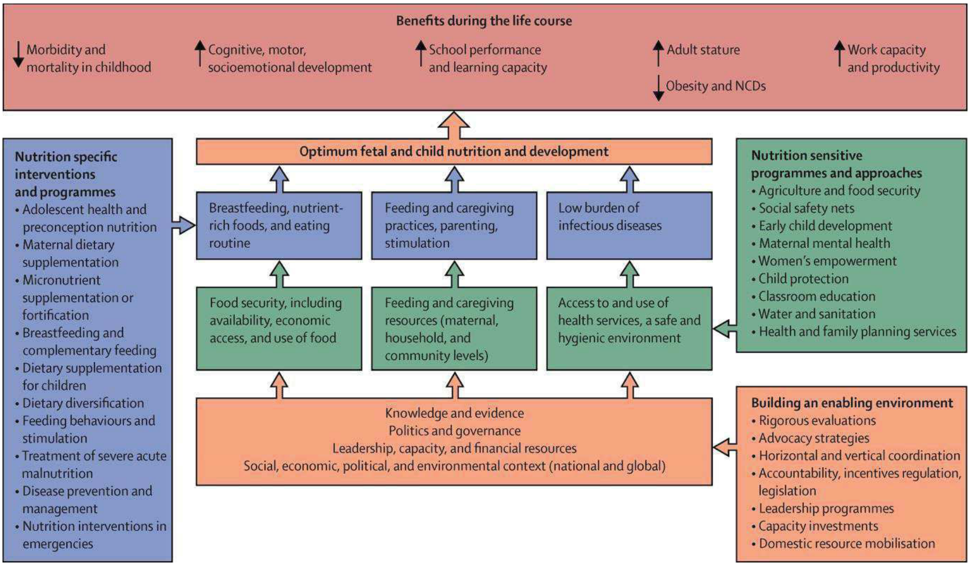

Figure 1: Conceptual framework for causes of child malnutrition, reproduced from Black *et al.* [37, p.2] with permission from Elsevier

1.3.1 Immediate causes

On the immediate level, an inadequate diet and the disease burden are the main determinants of malnutrition.

An inadequate diet can be the result of a decreased nutrient intake, an impaired absorption or metabolism of nutrients or a higher demand for nutrients [43]. Feeding recommendations for children by the WHO include the initiation of breastfeeding within 24 hours after delivery, exclusive breastfeeding up to six months of age and continued breastfeeding up to two years of age combined with complementary feeding of adequate quality and quantity [44]. Studies included in a recent review on breastfeeding counseling interventions (not breastfeeding *per se*) on growth was not conclusive, and their meta-analysis did not show any difference in attained weight or length at 6 months of age [45]. Nevertheless, a protective effect of exclusive and partial breastfeeding was seen for mortality and morbidity (diarrhea and respiratory infection) [46].

Although there is no doubt that an adequate diet is central to child growth, simple indicators to measure infant feeding are more difficult to define. WHO suggested indicators for infant and young child feeding (IYCF) practices in 2008 to assess, target and monitor adequate feeding among children 6–24 months. The eight core indicators include five for complementary feeding practices, namely introduction of solid, semi-solid or soft foods, minimum dietary diversity, minimum meal frequency, minimum acceptable diet, and consumption of iron-rich or iron-fortified foods [47]. Associations of those indicators with child anthropometry were shown at different levels [48, 49].

A diverse diet is important to meet requirements for all necessary nutrients, especially for vulnerable individuals such as growing children. Research has been carried out to explore the role of single micronutrients in child growth. Up to date, the only micronutrient that has a documented effect on growth is zinc [50]. Nevertheless, effect sizes in children younger than five years were small, although more prominent in those children who initially were zinc deficient or stunted [51, 52]. The effect of zinc has been questioned by others who found no improved lengths and weights in children after zinc supplementation [53-55]. Results of studies on iron and growth are inconclusive, as much of the evidence comes from observational studies, not being able to adjust for relevant confounders, such as other micronutrient deficiencies and coexisting morbidities [51]. A meta-analysis of intervention studies found no overall effect of iron supplementation on changes in length, weight, or WHZ [53]. Vitamin D is important for calcium homeostasis which in turn is needed for normal growth. A randomized controlled trial found small but significant effects on weight and length in Indian term but low birthweight infants [56]. Nevertheless, a vitamin D deficiency leads to rickets rather than short stature [51]. The mechanisms of vitamin A on growth are unclear. Observational studies and supplementation studies on the effect of vitamin A on growth are inconsistent [51], and there was no overall effect on either weight or length in a meta-analysis [53]. The impact of multi-micronutrient supplements on growth does not allow any conclusions due to inconsistent results [57, 58]. Pooling the data of 27 datasets, Ramakrishnan *et al.* [53] found a small effect of multiple micronutrient supplements on length but not on weight or WHZ.

Although most micronutrients have no documented direct effect on growth, they have an impact on morbidity- the other immediate determinant of malnutrition. For example, there is some evidence that zinc and vitamin A are linked to the burden of diarrhea [59, 60]. Also, exclusive breastfeeding has an additional indirect effect on nutritional status via a reduction of infections [61, 62]. Main morbidities that were shown to affect growth are diarrhea [63-65], malaria [63, 66], unspecified fever or non-malaria associated fever [63, 65], and parasitic infection [67, 68]. Environmental enteric dysfunctions (EED) have been linked to childhood growth failure as well [69-71], probably through the pathway of malabsorption and chronic intestinal inflammation [72].

The interaction between disease burden and nutritional status is complex and reciprocal. Malnutrition compromises the immune system, leaving the children more susceptible to infections, which in turn causes or worsens low dietary intake by reducing the appetite, affecting the absorption of nutrients and/or increasing the nutrient demand [43, 73].

1.3.2 Underlying and basic causes

Underlying causes define the setting on a household level in which the immediate determinants operate. In the Lancet framework, they are summarized as access to food (food security), feeding and caregiving resources, and access to health care and a healthy environment.

Food security is a broad term, and a clear definition and a comprehensive measure of food security are therefore challenging [74, 75]. One definition was suggested at the World Summit of Food Security in 2009 [76]:

"A situation that exists when all people, at all times, have physical, social and economic access to sufficient, safe and nutritious food that meets their dietary needs and food preferences for an active and healthy life. The four pillars of food security are availability, access, utilization and stability."

Food insecurity was consistently associated with stunting [77, 78] and wasting [78] across different countries. Especially in households that were chronically food insecure, children had lower HAZ [78]. Only a few studies did not find any association between food security and child anthropometry, potentially due to differences in methodologies [78].

The caring component of the underlying factors includes amongst others health seeking behavior, cognitive stimulation of the child, and antenatal care for the mother. Time and attention given to the physical and mental care are in turn influenced by the economic status, the mental and physical health status, and the autonomy and the knowledge of the caretaker [79]. Especially the mother's education has been given attention, showing a positive influence on how mothers care for themselves and their children [39, 80, 81].

The third category of underlying determinants of malnutrition includes factors such as access to safe drinking water and hygiene [82, 83] and preventive and therapeutic health care [79]. Improved sanitation facilities and hygienic behavior such as handwashing have been shown to reduce the disease burden [84-86] and affect nutritional status [86-91]. Measuring fecal exposure and not merely the existence of latrines are preferred because even defecations from closed toilets can be returned into soils, and if the water is completely untreated it poses an environmental risk for people without proper sanitation [92, 93] and poor hygienic behavior [86].

Poverty is a factor with the potential to affect all three determinants on the underlying level. In an analysis of surveys from 79 countries, stunting was 2.5 times more prevalent in the poorest 20 % compared to the richest 20 % [37]. The association of household poverty with different anthropometric indicators was also observed across different settings [42, 94].

Similarly, the season can unfold its effect on child malnutrition through different pathways at this level of determinants. The main body of evidence is from low-income countries, where seasonal changes in nutritional status in children are affected by varying levels of disease vectors and infections, a difference in quality and quantity of foods and child caring practices [95-113]. The impact of seasonal factors is especially pronounced in settings heavily relying on rain-fed subsistence farming, affecting energy intake, dietary composition and workload. Seasonality is a temporary factor that is repeating more or less regularly and therefore falls in between the often used categories of permanent and transitory food security [74, 75]. Also in urban areas, seasonality of child growth has been described [101, 102, 107, 112]. In high-income countries, differences in growth rates have been linked to temperature [97, 114, 115] and sunlight exposure [114, 116], although the mechanisms remain less clear. The relation of height-for-age or stunting and season is not as obvious [97, 109, 117, 118], probably because attained height is a cumulative indicator that is not sensitive to short-term risk factors such as season [101, 110].

Geographical location is a proxy for several underlying determinants too, but spatial parameters are not extensively studied in the field of public health nutrition. While they have been found to explain differences in the prevalence of malnutrition at different scales in some studies [119, 120], other authors argue that differences exist only at the household level, making targeted interventions at higher levels ineffective [121]. Comparison of urban and rural settings show significant differences with generally higher stunting rates in rural areas [37]. Nevertheless, rapid urbanization combined with poor infrastructure in the often informal urban settlements diminishes this difference [122]. The reasons for spatial differences are vast and include differential access to food, water, health care and education, differences in the quality of health care, cultural values, livelihood activities, quality of soil, housing, and conflict [123-125].

Basic causes can be summarized as wider political, social, economic and cultural determinants. These structural factors on regional or national level define the context in which underlying factors are rooted. Key determinants are national income and good governance [83]. Although some report an association between national gross domestic product and growth and stunting [39], others find no or only a negligible effect with childhood stunting, wasting and underweight [126]. A lack of translation of macro-economic wealth into household poverty alleviation and therefore reduction in childhood undernutrition could be due to unequal impacts across socioeconomic groups and a lack of improvements in “supply-side” infrastructure and services [92, 126], reflecting good governance and political will. This is also pointed out by Sen and colleagues in a comparative analysis of low-income countries. They assign the relative success of some countries to the positive role of government with active public action affecting the whole population, including the poor [127].

1.3.3 Intergenerational effects

In the Lancet series 2013, the importance of intergenerational factors on child malnutrition as an extension of the former UNICEF model are emphasized [37].

Birthweight of the offspring has been associated with maternal intake or status for micronutrients such as zinc, iron, vitamin A, calcium and vitamin B12 [128-132]. However, single nutrient supplementation trials during pregnancy have in general not demonstrated any effect on child growth, such as for example vitamin A and zinc [133, 134]. Maternal stunting and low BMI puts the offspring at higher risk of being born small for gestational age or with low birthweight, as well as being stunted and wasted in childhood [42, 135, 136]. There is some evidence linking the mother’s birthweight to the offspring’s birthweight independent of the mother’s postnatal growth [137], although the latter was also found to influence the offspring’s birthweight [138, 139]. Further, young maternal age at birth (<19 years) [140], birth rank [141] and time between births [142, 143] was associated with low birthweight, preterm birth or low nutritional status in childhood. Low birthweight and being small for gestational age was associated with higher risks of stunting, wasting and underweight in a pooled analysis using data of 19 birth cohorts [144]. Being born term but small for gestational age was found to be the leading risk factor for childhood stunting in 137 countries [88], underlining the importance of maternal health. Mechanisms of inter-generational effects through maternal factors can be explained at a biological level, such as intra-uterine space restriction and epigenetics, but also at a socio-cultural level seen in practices such as eating down and the "heritability of poverty" [145]. Both, total food restriction as well as deficiencies in single micronutrients (folate, vitamin B6 and B12, zinc and selenium), were found to result in epigenetic modifications (changes in DNA methylation) [146].

The former assumption that poor growth of children in low-income countries is mainly attributable to genetic factors has been questioned [112]. Under optimal conditions for growth, variation in adult height is vastly genetically determined; tall parents have tall children and short parents have short children [147]. Also weight at birth and in early childhood was shown to have a high heritability in a healthy population [148]. Nevertheless, several pieces of evidence point to the attenuation of heritability by environmental insults. A study in Finland found that the heritability of adult height increased with better living standards [149]. Other arguments can be drawn from studies showing that growth rates of healthy children growing up in settings with minimal exposure to growth constraining factors are similar, even though setting and anthropometry of the parents were vastly different [150-152]. Also secular trend studies add to the understanding, showing that mean height of populations increased with improved living conditions [153, 154]. Further evidence comes from adoption and migration studies, showing that malnourished children adopted or migrating to better environments show improvements in their nutritional status to a certain extent [145]. These studies in addition to animal studies and quasi-experiments during famines show that the ability of catch-up growth is dependent on the timing and the duration of the insult. Environmental factors seem to have larger effect during childhood than during adolescence [145, 155] and also if they have spanned several generations [145].

2 Rationale

Malnutrition as an aggregate of the different manifestation and its reciprocal relationship with infections has been described as the main cause of immunodeficiency in the world [59] and contributes 21 % to the total disability-adjusted life years lost [156]. The prevalence of each of these manifestations for itself reveals that malnutrition is still an immense problem, primarily in low- and middle-income countries. Globally, 23 % of the children under the age of five were estimated to be stunted in 2016, i.e. they were too short for their age, and 6 % were wasted, i.e. they were too thin for their height [157]. This amounts to 155 million and 52 million, respectively. Not only is the distribution of malnutrition uneven from a global perspective, but also changes in the prevalence advance at different rates. In general, there are decreasing trends in numbers of children malnourished, but in some regions this happens very slowly. In parts of Sub-Saharan Africa, the total number of stunted children is even increasing due to population growth [158]. Also at smaller scales (at national or regional level), this inequality in distribution is seen. A large proportion of undernutrition is suggested to be driven by seasonal cycles [159] with possible mechanisms described in chapter 1.3.2. However, empirical evidence is inconsistent. The importance to reassess seasonal influences on child malnutrition in vulnerable populations using adequate indicators is underlined by findings of the Intergovernmental Panel of Climate Change (IPCC) report, which suggests that already existing health problems will be exacerbated by the occurring climate change [160].

Malnourished children bear a higher risk of short and long-term health consequences, but also neurodevelopmental and economic potentials are compromised, generating a substantial loss in human capital [3, 161, 162]. These consequences can extend into next generations (see chapter 1.3.3). In addition, 45 % of all the deaths of children younger than five years globally are associated with undernutrition [37], with a dose-response relationship also linking mild to moderate levels of wasting, stunting and underweight to higher risks of dying [12, 163].

There is a current focus on the first 1000 days of life for prevention and treatment of malnutrition. It remains unclear to which degree growth faltering beyond these 1000 days is irreversible and if it is reversible, whether catch-up growth also results in resolving of the functional consequences [164]. Nevertheless, an emphasis should be put on preventing malnutrition instead of treating it [92, 165], or at least on detecting children at risk of malnutrition as soon as possible, independent of age.

Questions remain on how to most effectively detect children at risk and which indicator to use for different purposes. Growth velocity has the theoretical advantage over the commonly used attained growth that it is more sensitive to capture alterations. It is thus hypothesized to earlier detect children at risk of adverse health outcomes and to be an important tool for risk factor assessment [15, 23, 166]. Nevertheless, these advantages need to be tested empirically, which has rarely been done up to date. This thesis aims to contribute to filling this gap, taking advantage of the availability of the prescriptive growth velocity standards published by WHO in 2009 [15].

3 Aims and objectives

The aim of this thesis is to describe growth velocity in children under the age of 2, using the WHO growth velocity standards, and to examine the ability of growth velocity Z-scores to early identify children at risk of wasting, stunting and underweight and the ability to predict short-term mortality.

The specific objectives of this thesis are:

1. to describe age- and sex-dependent weight and length velocity of children younger than two years living in Bwamanda, DRC, using the 2009 WHO Child Growth Standards
2. to relate weight and length velocity Z-scores of children living in Bwamanda, DRC, to selected climatic and spatial determinants, with the focus on season and distances to sources of food and health care
3. to determine the ability of weight and length velocity Z-scores as well as changes in MUAC to predict child mortality within three months in a cohort of children under the age of two in Bwamanda, DRC
4. to estimate the ability of weight and length velocity Z-scores in infancy to predict stunting, wasting and underweight in children aged two years living in the Bhaktapur Municipality, Nepal, and
5. to compare the mortality and morbidity predicting ability of velocity Z-scores to that of attained growth measures

4 Methods

Data from two community-based cohort studies constitute the basis for this thesis: one study in the Democratic Republic of the Congo (DRC) and one in Nepal. Both settings and study designs are described below.

4.1 Study setting

Site 1: The Democratic Republic of the Congo

The study was conducted in the health zone of Bwamanda, Democratic Republic of the Congo (DRC). This zone is an administrational unit which is situated in Équateur province, in the northwest of the DRC (Figure 2). It covers about 10,000 km^2 with the most frequent land covers of savannah and equatorial forests along the rivers. The climate is tropical with a dry season from December to February and a wet season from April to November. The average annual temperature in the province Équateur varies between 21°C and 31°C [167]. A total population of 130,000 lived in this rural area in 1991, of which 98 % were from the ethnic group Ngbaka. Ninety percent of the households were traditional subsistence farmers, growing mainly cassava and maize as staple foods. The main harvest was in July, although for some food items harvest was possible several times a year. Diets were monotonous, mostly consisting of a maize-cassava gruel which was only supplemented with smaller amounts of more nutrient-dense but very seldom with animal source foods. Breastfeeding was practiced almost universally after birth. From around four months, it was usually complemented with solid foods, which traditionally was a gruel of maize and cassava. Children were on average completely weaned at age 21 months. Bwamanda village with about 2,000 inhabitants was the main village in this health zone. It had a referral hospital with four medical doctors, which was run by a local NGO called CDI-Bwamanda (Centre de Développement Intégral-Bwamanda). Ten peripheral health centers were located in the surrounding villages. The longest distance from village to hospital was 65 km, with almost no motorized transportation available. In the population of the Bwamanda health zone there was a limited socioeconomic variation. The literacy rate among women was 14%, and only 1% attended primary school for more than two years [168]. Infant and child mortality rate were estimated to be 39 and 98 per 1,000 between 1980 and 1984 with malaria and anemia being the main causes of death. This compared well to the rest of DRC at that time [168].

Figure 2: Map of the Democratic Republic of the Congo (DRC) with the Bwamanda study site

Today, DRC is among the countries performing worst according to the criteria of the UNDP Human Development Index. In 2015, the DRC ranked 176 out of 188 countries [169]. The demographic health survey (DHS) 2014 describes Équateur province as the poorest province within DRC with 94% of the population living below the poverty line of 1.25 dollar a day. The predominant livelihood adaption still consists of subsistence farming. In most of the country, infrastructure is extremely poorly developed, transport prices high and hence food markets very poorly developed. They estimated one medical doctor per 50,894 inhabitant, which is a fifth of the WHO recommendation of one per 10,000 inhabitants [167]. Between the DHS 2007 and 2014, infant mortality rates in Équateur fell from 102 to 65 per 1,000 live births, and under-five mortality rates fell from 168 to 132 per 1,000 live births. Despite this decrease those estimates are higher than the national average of DRC. In 2014, 38% of children under the age of five were stunted (19% severely), 6% wasted (2% severely), and 19% were underweight (5% severely). This is an improvement in absolute terms compared to 2007 and also relative to the national average of DRC in 2014 [170, 171]. The health zone of Bwamanda had a population of 215,583 in 2013. There is no newer data on health indicators of this specific health zone publicly available. With a continued absence of support by the Congolese state, health services are still run by CDI-Bwamanda [172]. While this NGO had activities in the areas of health, construction, education, drinking water access, production and trade during the study period, they currently had to lay down all activities other than health care.

Site 2: Nepal

According to the UNDP Human Development Index 2015 [169], Nepal was among the countries with a low human development, ranking 145 out of 188 countries. Nepal is divided into three ecological zones: the mountains, the hills, and the lowland plains (called terai) (Figure 3). Elevations in Nepal range from 90 to 8,848 meters above sea level. Administrational divisions include five regions with a total of 14 zones. The area of Bhaktapur is one of 75 districts in the country and is divided into six municipalities one of which is Bhaktapur municipality. It lies in the hills at about 1400m above sea level. The climate is sub-tropical with a pre-monsoon (March–May), a monsoon (June–September), a post-monsoon (October–November) and a winter season (December–February). Most of the annual precipitation of 1400 mm occurs during the monsoon season. The pre-monsoon is hot and humid and post-monsoon and winter are usually dry and cold.

Bhaktapur municipality lies in the Kathmandu valley, the most fertile and populated area in Nepal. In 2010, it had a population of 78,000 people [173]. It is one of the main tourist attractions in Nepal, offering traditional temples and buildings, which are on the UNESCO's World Heritage List. Tourism and agriculture are the main sources of livelihood in this peri-urban community, and there is also a considerable range of non-agricultural livelihoods. The main agricultural outputs are rice, wheat, maize and vegetables. Livestock also presents an important income in rural areas. People usually consume locally grown foods, with variation and availability heavily depending on the season. However, there is extensive horticultural production, and fresh, nutrient dense food is available year round, while prices may reflect whether certain crops are in or out of season. The main diet is *dal bhat*, with rice as a main staple, supplemented with vegetable curries and pulse soup, and eventually dairy products or meat. Animal source foods are consumed by most people, but restricted by affordability. In Nepal, there are substantial socio-cultural divides in the population, guided by a caste system and socioeconomic forces. These impact both dietary composition and child feeding.

The national literacy rate were estimated to be 67 % for women and 87 % for men in 2011 [174]. Estimates for Bhaktapur district are 73 % and 91 % respectively [175]. Infant and under-five mortality rates reported in the last DHS (2011) were 46 and 54 deaths per 1,000 live births respectively, with marked differences within the country. The most common diseases contributing to child mortality and morbidity were acute respiratory infections and diarrhea [174]. On a national level, 41 % of the children under five years of age were stunted, 11 % wasted and 29% underweight in 2010, with a decreasing trend since the last DHS in 2001 and 2006 [174].

Figure 3: Map of Nepal with ecological zones and administrative units and the Bhaktapur study site

4.2 Study designs

Site 1: The Democratic Republic of the Congo

The Bwamanda study was a prospective cohort study with a dynamic population as study base [176], carried out between August 1989 and March 1991. Out of 52 villages in the Bwamanda health zone, 16 villages were randomly selected for inclusion to the study (four from each of the four sub-areas). During a preliminary census rolled out between August and September 1989, all children under the age of five years and their mothers were enrolled into the study, in total 4,235 children. In six survey rounds, on average every three months, those children were followed and children that were born or had moved into the area were newly enrolled. Over the whole study period, 5,657 children were enrolled into the study (see Figure 4).

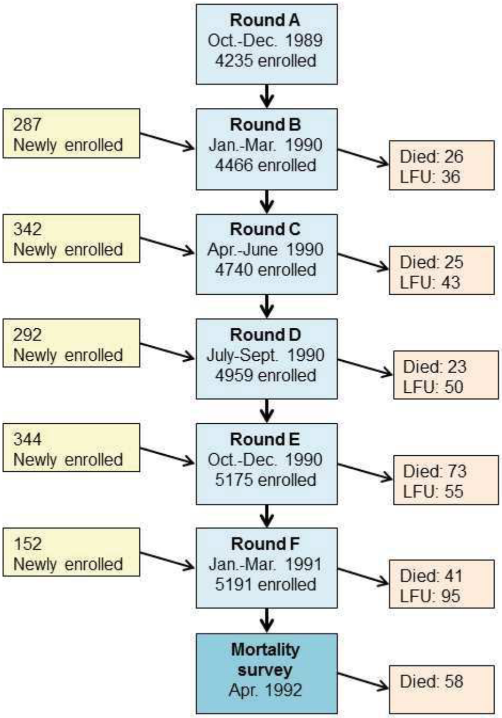

Figure 4: Study profile of the cohort study in Bwamanda, DRC. LFU = Lost to follow-up

Fifteen field staff were trained by a medical doctor. They performed interviews with the caregivers of the children, recording information on morbidity, mortality, harvest and feeding practices, socio-economic condition and environmental information. A clinical examination and anthropometric measurements were done by two medical doctors. Weight was measured with a spring scale (Continental Ltd., UK), height with a microtoise, length with a locally constructed measuring board and MUAC with a steel tape (Stanley). All measures were read to the nearest millimeter and in case of weight to the nearest 100 gram. Age was obtained using road to health charts or identity papers of the parents or in case these did not exist (in 10 %) by interviewing the parents with help of a local calendar. Date and cause of death were recorded in every survey round by interviewing the parents and checked against deaths registries in the health centers and churches. A special mortality survey was conducted in April 1992 to record all deaths up to that time point.

Site 2: Nepal

The Etiology, Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED) study was a prospective cohort study with a closed cohort as study base [176]. It was conducted in eight countries (Bangladesh, Brazil, India, Nepal, Pakistan, Peru, South Africa, and Tanzania). For our analysis, we used data from the Nepal site only. During the enrolment period (June 2010 to February 2012), 668 deliveries were identified in the Bhaktapur municipality. Households in which deliveries occurred were subsequently randomly selected for study participation. Consenting households were screened according to the following exclusion criteria: (1) The family had plans to move out of the catchment area for >30 consecutive days during the first 6 months of follow-up, (2) The mother was <16 years of age, (3) The mother had another child already enrolled in the MAL-ED cohort study, (4) The child was not a singleton (i.e., twins, triplets), (5) The infant had any of the following indications of serious disease: hospitalization for something other than a typical healthy birth; severe or chronic condition diagnosed by a medical doctor (e.g. neonatal disorder; renal, liver, lung, and/ or heart disease; congenital conditions); or enteropathies diagnosed by a medical doctor, (6) The child's guardian failed to provide signed informed consent, (7) Weight at birth or enrollment was <1500 gram. In total, 240 mother-child pairs were enrolled and followed for two years (Figure 5). Anthropometric measurements were taken monthly starting within 17 days after delivery until 24 months of age. Data on illnesses, diet, pathogen burden, gut function, micronutrient status, and cognitive development were also recorded, but not used for this thesis.

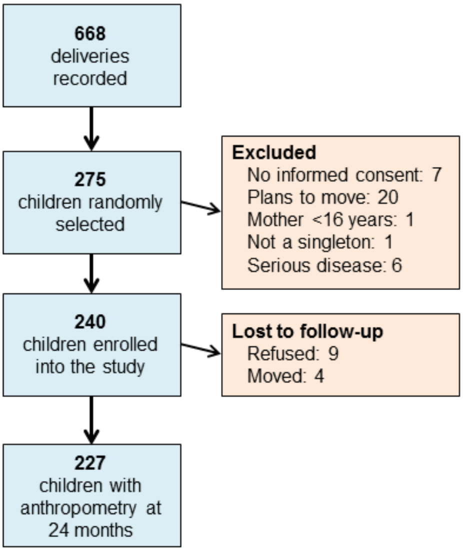

Figure 5: Study profile of the cohort study in Bhaktapur, Nepal

4.3 Data cleaning

The process of data cleaning in the analysis datasets was done in line with the description of Van den Broeck *et al.* [177]. This involved active screening before analysis of all variables needed, using amongst others description of ranges, logical order (e.g. increasing age in subsequent survey rounds) and graphical plots including scatter plots and histograms.

For anthropometrical data, hard cut-offs for plausible values of Z-scores according to the WHO Child Growth Standards [13-15] were set to <-6 and >6 for attained Z-scores (weight-for-age, weight-for-length/height, length/height-for-age, mid-upper arm circumference) and to <-10 and >10 for velocity Z-scores (weight and length velocity). For velocity Z-scores we chose more extreme cut-offs, because the spread is usually wider than in attained growth measures, even in the healthy child [15]. There are no standards or references for changes in MUAC available. Therefore we set values of changes within ± 5 cm within three months to missing if they were in contradiction with weight-based indices. Verification of suspicious values was difficult in the Bwamanda data, because original questionnaires were not available. Therefore, if a value was doubtful, we deleted it. In Paper 1 we regarded 0.16 % of all anthropometrical values as implausible, and 0.1 % in Paper 2. The MAL-ED data was already cleaned when we received it for analysis. A rigorous control system had been put into place during data collection, with instant plotting on growth charts, revision by the site data manager and external control by the Data Coordinating Center at Fogarty International Center, USA. Criteria for implausibility included Z-scores of <-7 and >7 as well as increments between subsequent measurements that exceeded 1.5 kg for weight or 3.5 cm for length. Additional checks before our analysis did not yield any implausible values.

4.4 Statistical methods

A plan of analysis was made for each paper by the author of the thesis in collaboration with the co-authors prior to analysis.

Baseline characteristics were described using summary measures together with measures of dispersion such as mean with standard deviation, median with interquartile range, and percentage, as appropriate.

Z-scores for attained growth (length-for-age, weight-for-age, weight-for-length and mid-upper-arm-circumference-for-age) were calculated according to the WHO Child Growth Standards 2006 and 2007 [13, 14]. Stunting, wasting and underweight were defined as Z-score of ≤-2 for length-for-age, weight-for-age and weight-for-length, respectively. Moderate forms of malnutrition were specified as Z-scores ≤-2 and >-3, and severe forms as ≤-3. Growth velocity Z-scores were calculated according to the WHO Child Growth Standards 2009 [15]. In general, growth velocity is the change of value expressed in units per time period. Due to a non-normal distribution of weight and height, individual Z-scores for weight and length velocity were calculated as:

Z-score = $\frac{\left[\frac{y}{M(t)}\right]^{L(t)}-1}{S(t)L(t)}$

for Z-scores between -3 and 3, where y is the raw value, L(t) the tabulated fitted value of Box-Cox, M(t) the median and S(t) the coefficient of variation at visit time *t*. As changes in weight can take negative values a constant δ is added for a shift to a positive value.

Weight velocity Z-scores = $\frac{\left[\frac{(y+\delta)}{M(t)}\right]^{L(t)}-1}{S(t)L(t)}$

If the Z-score was >3 the formula used was: $3+(\frac{y-SD3pos}{SD23pos})$, and

if the Z-score was <-3, we used: $-3+(\frac{y-SD3neg}{SD23neg})$,

always adding the constant δ for weight velocity, where:

SD3pos = $\mathrm{M(t)[1+L(t)*S(t)*(3)]}^{1/L(t)}$

SD3neg = $\mathrm{M(t)[1+L(t)*S(t)*(-3)]}^{1/L(t)}$

SD23pos = $\mathrm{M(t)[1+L(t)*S(t)*(3)]}^{1/L(t)} - \mathrm{M(t)[1+L(t)*S(t)*(2)]}^{1/L(t)}$

SD23neg = $\mathrm{M(t)[1+L(t)*S(t)*(-2)]}^{1/L(t)} - \mathrm{M(t)[1+L(t)*S(t)*(-3)]}^{1/L(t)}$

If ages at the beginning and the end of the interval did not match those in the WHO Growth Standards, we used the reference value for the next appropriate age. In Paper 3, the extremely thorough implementation allowed for a narrow target age definition with only ±3 days deviation from target ages. In Paper 1 and 2 we did not apply such a restriction.

We calculated changes in absolute MUAC and MUAC Z-scores (ΔMUAC and ΔMUACZ respectively) by dividing the difference in cm or Z-scores between two time points by the exact time interval and multiplying it by three to arrive at exact 3-month growth increments.

Differences in mean velocity Z-scores according to sex were analyzed with help of an unpaired t-test and differences according to age groups with a one-way ANOVA. We estimated associations of weight and length velocity Z-scores with distances to different sources of food and health care (distance to hospital, health center, market, fishing grounds, and forest) and village size with Pearson product-moment correlation coefficients. For Paper 1, we built multiple mixed effect regression models to account for the dependency of observations in subsequent survey rounds. We chose an unstructured correlation structure, because it is the most conservative, placing no constraints on the form of residual correlation. Weight and length velocity Z-scores were defined as the dependent variables. The choice of independent variables for model inclusion was guided by the process of purposeful variable selection described in Hosmer *et al.* [178]. Geographical determinants (distances to sources of food and health care and season) were tested in bivariate regression analyses and taken into the model if they were significant on a p-value level of 0.2. Other independent variables (age, sex, birth-rank, mother's age and breastfeeding status) were chosen on the basis of their clinical relevance and accessibility in the dataset.

Age at death was described using a Kaplan-Meier survival curve with 95 % confidence interval (CI). Generalized estimating equation (GEE) models with a log link informed the mortality risk within the next three months separately for each velocity index (WVZ, LVZ, ΔMUAC and ΔMUACZ). An autoregressive correlations structure was chosen, which assumes decreasing residual correlation with increasing time between measurements. This assumption was also confirmed with the quasi-likelihood under the independence model criterion (QIC) command in the statistical software Stata.

For Paper 3, we built simple linear and logistic regression models with WAZ, WLZ, LAZ or being wasted, stunted or underweight at 24 months as outcomes, respectively. Weight and length velocities were calculated for the following periods: 0–3, 0–6, 3–6, 6–9, 6–12, and 9–12 months. Z-scores for these periods were entered separately as predictors into the regression models. Other predictors tested one by one were WAZ, WLZ or LAZ at 0, 3, 6 or 12 months. For seven children birthweight was not available. For an approximation of these, we built a regression model with the available birthweights in this cohort as an outcome and the weight and age at the next measurement (within 17 days of birth) as predictor variables. With the slope and the intercept of this regression model, we imputed birthweight for the children lacking this information. Length at birth was not documented in this cohort and therefore length measured within 17 days of birth was used as a proxy. Additional analysis, estimating birth-length with the same procedure described for birthweight but using the length at one and two months of age, did not change the results.

The balance between sensitivity and specificity to predict child death (Paper 2) and nutritional status at two years (Paper 3) between different threshold levels was illustrated by receiver operating characteristic (ROC) curves. We calculated areas under the ROC curve (AUROC) to quantify the discriminative accuracy of the different growth measures. To formally compare the AUROC values, we used the roccomp function in Stata, which is based on the algorithm suggested by Delong *et al.* [179].

4.5 Ethics

For the Bwamanda study, ethical approval was obtained from the Tropical Childcare Health Working Group at the University of Leuven [168]. For all secondary analyses on the Bwamanda data in this thesis, ethical approval was granted by the Ethical Committee at the University of Kinshasa (approval number: ESP/CE/008/14).

All sites of the MAL-ED study obtained ethical approval from appropriate institutions. In Nepal, ethical approval was obtained from the Nepal Health Research Council and the Walter Reed Institute of Research (WRAIR), USA. The sub-analysis for Paper 3 was approved by the Central Board of the MAL-ED study and the local steering committee. Because the MAL-ED had approvals from several institutions, the institutional ethical review board at the University of Bergen did not find it necessary to have this study reviewed by a Norwegian committee.

In both studies, signed informed consent was given by the guardian of each participant. In case of illiteracy, oral consent was given in the DRC and a thumbprint in Nepal.

Funding bodies did not have any influence on the study design, implementation and analysis of the data. The author of this thesis and all co-authors of the papers on which this thesis is based have reported no conflicts of interest.

5 Results

In total 5,657 children were enrolled into the Bwamanda study during the study period (Paper 1 and 2). Study participants were comprised of 51 % male, and 98 % were from the ethnic group Ngbaka. Of all children, 2,223 children were under the age of two years at two or more time points and therefore eligible for growth velocity calculation.

The study sample of the MAL-ED study (Paper 3) comprised 240 children, of which 54% were male and 89 % from the Newar caste group. All children were enrolled into the study within 17 days of birth and followed monthly until 24 months of age.

5.1 Paper 1

Growth velocity Z-scores in the DRC cohort were lowest in the first months of life and gradually increased up to two years of age (see Paper 1, Table 2). Despite this increase, velocity Z-scores remained under what is expected in healthy children (Z-score of 0) and accumulated, resulting in a further deterioration in mean attained growth with age from an already low status at ages 0–6 months.

No association to spatial parameters i.e. distance to market, health center, hospital, fishing grounds and forest could be shown (Paper 1, Table 3). Weight and length velocity Z-scores showed a marked seasonal pattern, with Z-scores lowest before the main harvest and rising again in the post-harvest season (Figure 6, Panel A). Peak length velocity was lagged with two months after peak weight velocity. There was no clear seasonal pattern in attained growth indicators (Figure 6, Panel B). In multiple mixed effect regression models, age and season were independently associated with both weight and length velocity Z-scores.

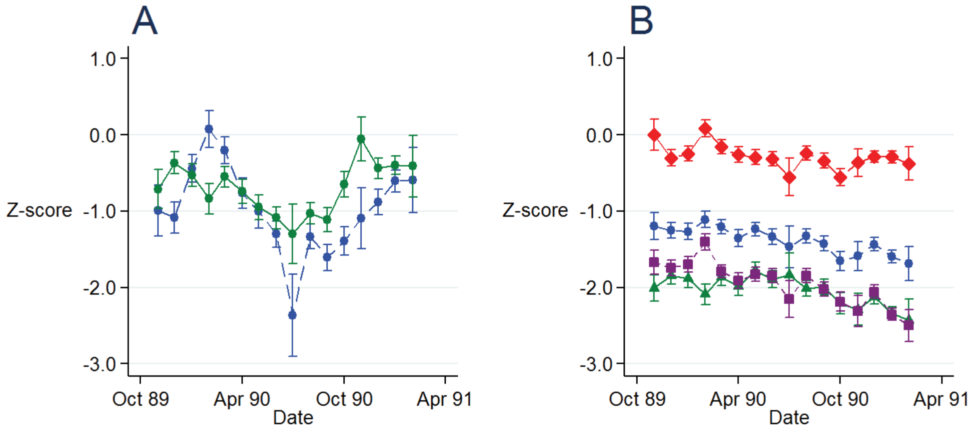

Figure 6: Mean and 95 % CI of various growth indicators according to the time of the year. Panel A: Mean growth velocity Z-scores with 95 % CI for weight (green solid line) and length (blue dashed line) according to date at midpoint of assessment period. Panel B: Mean attained growth Z-score with 95 % CI for weight-for-length (red diamonds), weight-for-age (blue circles), mid-upper-arm-circumference-for-age (purple squares) and length-for-age (green triangles).

5.2 Paper 2

During the study period 246 (4.3 %) children in the DRC cohort died, of whom 56 % were male. Fifty percent of the children died between the age of 5 and 26 months (median 12 months). The risk of death increased by a factor of 1.5 for every unit decrease in weight velocity under the Z-score of 0, and similarly by a factor of 1.2 for length velocity. A weight velocity Z-score of <-3 was associated with a 7.9 times higher risk of dying within the next three months (95 % CI: 3.9–36). The mortality risk for a length velocity Z-score of <-3 was 12 times higher (95 % CI: 3.9–16). If a MUAC Z-score decreased over the 3-month period, for each additional Z-score increase in the difference, the mortality risk increased by 2.3. Similarly, for every cm increase in the difference of absolute MUAC within three months, the risk of death was 2.4 times higher (see Paper 2, Table 2).

The receiver operating characteristic (ROC) curves to demonstrate the balance between sensitivity and specificity to predict child death at different threshold levels are presented in Figure 7. Length velocity, weight velocity and absolute MUAC featured the largest areas under the curve (AUROC), with values of 0.69, 0.67 and 0.63, respectively. Weight and length velocity Z-scores performed statistically better in predicting mortality than their attained counterparts WAZ (AUROC 0.57, p<0.05) and LAZ (AUROC 0.52, p<0.001). A longitudinal approach did not improve the predictive abilities of MUAC Z-score and absolute MUAC. If the children were already stunted (HAZ <-2) at the beginning of the assessment period, the AUROC increased to 0.74 for length velocity. If analysis was restricted to wasted children (WHZ <-2), the AUROC for weight velocity was 0.87 and for absolute MUAC it was 0.71. Mortality predicting abilities did not differ according to the age categories 0–6, 7–12, and 13–24 months.

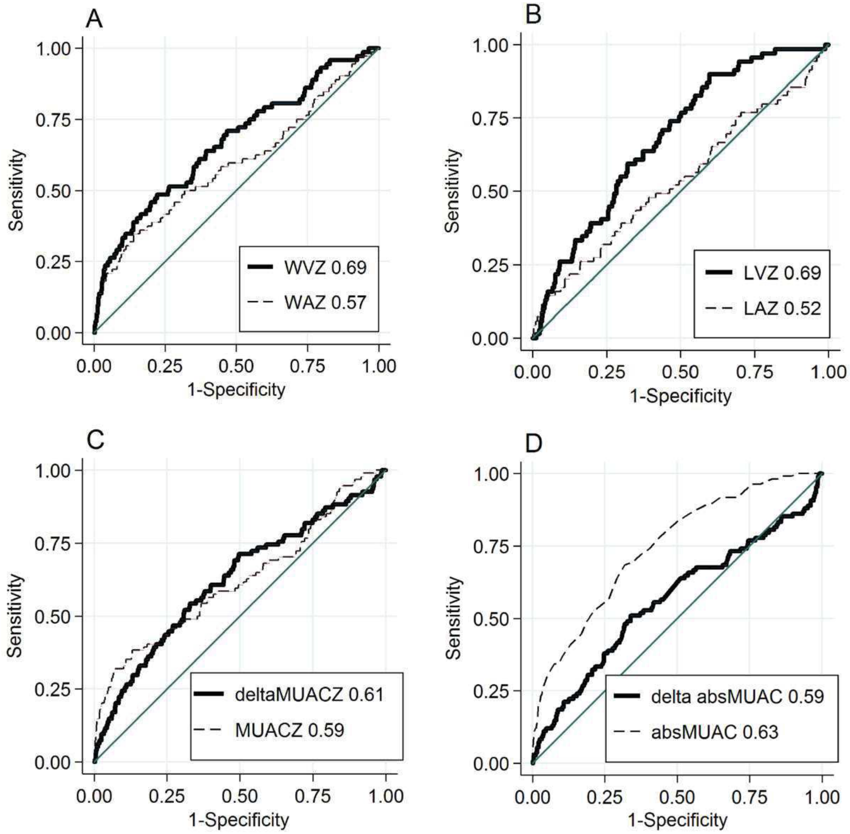

Figure 7: Receiver Operating Characteristic (ROC) curves indicating the ability to predict death within three months in children aged 3-24 months included in the cohort study in Bwamanda, DRC, for A) weight velocity Z-scores (WVZ) and weight-for-age Z-score (WAZ), B) length velocity Z-scores (LVZ) and length-for-age Z-score (LAZ), C) changes in mid-upper-arm-circumference-for-age Z-score (ΔMUACZ) and mid-upper-arm-circumference-for-age Z-score(MUACZ), D) changes in absolute mid-upper-arm-circumference (ΔabsMUAC) and absolute mid-upper-arm-circumference (absMUAC). Areas under the curve (AUROC) values of the individual predictors are given in the legend of each plot.

5.3 Paper 3

At the age of 24 months, 4 % of the 227 children in the Nepal cohort were wasted (WLZ ≤-2), 21 % stunted (LAZ ≤-2), and 13 % underweight (WAZ ≤-2). Those who were underweight at two years had a lower mean WAZ already at birth and throughout the whole study period compared to those whose Z-score was >-2 (Figure 8, Panel B). A similar pattern was seen in LAZ for those stunted at two years compared to those not stunted (Figure 8, Panel D). Weight and length velocity Z-scores were also lower for those wasted and stunted at two years, respectively (Figure 8, Panel A and C). This was especially pronounced for weight velocity in the first nine months of life.

Simple linear and logistic regression models showed that growth during most periods in infancy delineated by the different anthropometric indicators, significantly predicted growth at age two years. The highest values for the area under the ROC curves (AUROC) were observed for indicators of attained growth at 12 months. AUROC of weight and length velocity were somewhat lower (Paper 3, Table II, III and IV).

For this thesis we extended the analysis of Paper 3 by formally comparing the attained growth indicators and the growth velocity indicators with the highest AUROC (WLZ at 12 months vs. WVZ 0–3 months; LAZ at 12 months vs. LVZ 6–12 months; WAZ at 12 months vs. WVZ 0–6 months). We used the roccomp function in Stata as described for Paper 2. All comparisons showed that the attained indicator was significantly better to predict wasting (p=0.0432), stunting (p=0.0001) and underweight (p=0.001) respectively.

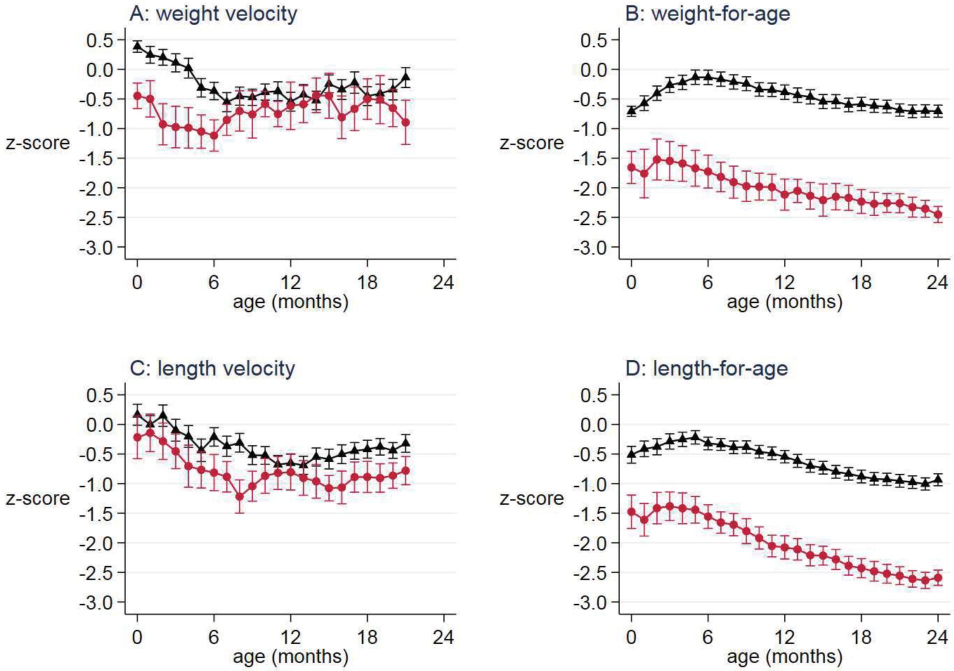

Figure 8: Mean Z-scores with 95 % CI over time from age 0-24 months according to underweight at 24 months (yes= red circles; no= black triangles) for A) weight velocity and B) weight-for-age, or according to stunting at 24 months for C) length velocity and D) length-for-age of 240 children enrolled in the MAL-ED study. All velocity Z-scores use a 3-month increment and are plotted at the beginning of the growth period.

6 Discussion

In this thesis, patterns of growth velocity according to season and its ability to predict mortality and morbidity have been described. This discussion will consider methodological aspects of this thesis and discuss its main findings in the light of the current scientific literature.

6.1 Discussion of the methods

6.1.1 Study design

For the calculation of growth velocity two or more anthropometric measurements and therefore studies with follow-up of children over time are needed. A cohort study was deemed suitable for the study objectives. Data for this thesis were taken from two studies, both of which were prospective cohort studies, recording the real time experience with positive etiologic time and individual follow-up [180].

6.1.2 Bias

A necessary basis for all research is internal validity, which is the ability to measure what the study aims to measure. Bias is a major threat to the validity. It arises from error which can occur at different stages in research (i.e. design of a study, collection, analyses, interpretation, publication or review of data) and leads to a systematic deviation from the truth [181]. It is also referred to as accuracy in this thesis. Inaccuracy can result in both over- and under-estimation of frequency, proportion or effect [182, 183]. Typically bias is classified into selection bias, information bias and confounding, all of which will be discussed below.

Selection bias

Selection bias results from erroneous procedures to select participants into the study or in a differential loss to follow-up of participants over the study period [182, 183]. Both our studies were community-based and used a statistical sampling method [184]. In Bwamanda a one-stage stratified cluster sampling was performed. All 54 villages in the administrative area of Bwamanda were divided into four clusters. Out of each cluster, four villages were randomly sampled. Subsequently, all children in these 16 villages were enrolled into the study. It is not documented how many participants refused to participate. Coverage of anthropometrical measurements in each round ranged from 81 % to 89 % with non-participation due to emigration, short-term travel, or absence of the mother [168]. If refusal or coverage would not be at random, this could have introduced selection bias. In the MAL-ED study, all births in the Bhaktapur municipality were recorded in the facilities and by home-visits of fieldworkers. Each week a pre-defined number of children were randomly selected for enrollment. Children born at home are at higher risk to be undocumented. If these children differ from those children delivered at the facility, this could have introduced bias. Nevertheless, this is unlikely to substantially affect our results, because most births are given at the facility in this population (97 % of those included in the MAL-ED study). In addition, parents of 7 out of 275 children refused to give informed consent. Again, if they differed from the study participants in a way that will distort the association of exposure and outcome, this could have introduced bias. In both studies, the lost-to-follow-up rate was very low, around 5% at the end in both studies. Some author suggest that <5 % attrition rate introduces little bias [185].

Information bias

Information bias results from differential measurement, documentation or classification of data between comparison groups. Information bias can occur due to problems recalling the information, social desirability, sub-optimal measurement equipment or measurer’s performance, inadequate phrasing of questions or answer possibilities [183]. In our studies, variables could have been mainly affected by recall bias and measurement error.

The classification of season into pre- and post-harvest for Paper 1 was based on recalling food items harvested in the past two months. Our study population in Bwamanda mainly consisted of subsistence farmers. Harvest is an annually reoccurring event that is quite salient to them and therefore more memorable. Beegle *et al.* [186] suggest that recall of agricultural data does not result in large bias even for periods of up to 12 months. In order to minimize errors in our analysis, the classification was additionally verified by informal talks to agricultural specialists residing in this area. Another potential source of bias in our study is the pooling of the study years for defining season. This will not take into account years with extraordinary events such as drought etc. Information bias would only occur if it would have been measured differently in compared groups, which is not very likely. Extraordinary events would have been observed by the principle investigator. However, our definition of season probably added some imprecision. An alternative explanation for the seasonal variation in weight and length velocities could be information bias with systematically shorter assessment periods during the pre-harvest season compared to the 3-months increments in the standards. This could have led to artificially low velocity Z-scores in this period and thus explain the dip in growth velocities. Nevertheless, a post-hoc analysis did not give any indication of this.

Retrieval of accurate age has been proven difficult in low resource settings [187, 188] and can have introduced some bias, especially for the procedure of scoring of anthropometrical data. In the MAL-ED study, 97 % of the study participants were born at facilities and therefore a valid birthdate was available. The remaining 3 % of the children were enrolled within 17 days after births, a period in which we believe the date of birth can be remembered accurately. In the Bwamanda study, birthdates were taken from road-to-health charts or identity papers, which were available for 90 % of the study participants. For the rest of the children, the birthdate was approximated in cooperation with the caretaker. This could have introduced some bias, if age of more children in one of the compared groups was documented incorrectly.

The most frequent sources of inaccuracy for anthropometric measurements are uncalibrated instruments and inadequate measurement technique. To measure the extent of inaccuracy in a study, the measurements need to be compared to a gold standard. In anthropometry the gold standard is usually the measurement of an expert. In the MAL-ED study, 10 % of the measurements were repeated by a supervisor. The inter-observer technical error of measurement (TEM) was 0.343 for weight and 0.070 for height, which reflects good quality of anthropometric data [181]. A comparison to an expert was not done in the Bwamanda study; hence a measure of accuracy cannot be stated. However, inaccuracy was sought to be minimalized by regular calibration of the instruments, and a thorough training of the two field staff with detailed measurement protocols. As both studies were conducted over a long time, the measurements could have become more accurate, improving with experience. However, this is not likely to be differential between groups. Intentional distortion of the values by the study subjects is unlikely in our case, because the participants were small children not being able of such behavior. Additionally, all children found sick were treated independent of nutritional status, not placing any “incentive” to report smaller values.

Confounding

Confounding, a third category of bias is not applicable to this thesis as none of the papers were causally oriented with an explanatory aim. Nevertheless, in Paper 1 we describe growth velocity for weight and length according to season, based on availability of food items and level of rainfall. Although Paper 1 did not aim to assess causal mechanisms through which season affects growth, one could get the impression that harvest is the main driver of growth velocity. Other mechanisms could contribute to these seasonal patterns, such as disease vector variability, differences in the caring for women and children, energy requirements due to varying work load, food prices, availability of bush foods etc. (compare chapter 1.3.2).

6.1.3 Random error

Another type of error is random error. This error relates to the extent of agreement of two repeated measurements and is also referred to as repeatability or precision in this thesis. Precision is the variance of measurement error. Imprecise measurements will always add on to the biological variability of the measurement [181, 189]. Biological variability is for example seen in human height, where a diurnal variation in height is due to compression of the spine during the day. Other examples are saltatory growth processes [190-194], and catch-up growth [195-198]. Random error, e.g. imprecise measurements, broadens the distribution of a variable measured. This can lead to exaggerated estimates of children falling below a certain cut-off, for example being defined as stunted or wasted (Z-score ≤-2) and can therefore jeopardize the internal validity of a study. Increasing sample size does not prevent this [189]. Random measurement error could have occurred in all the anthropometric measurements (weight, height, MUAC) in our study. In addition, factors such as measurer's fatigue and sub-optimal measurement environment could have imposed random error in our study, especially in the Bwamanda study. Digit preference was not observed in our studies, with exception of height measurements which show slight heaping to the next 0.5 cm in both studies. Random measurement error was sought to be minimized by thorough training in both studies and a rigorous data control system in Nepal. Intra-observer error could not be quantified in either of our studies as no measurements were repeated by the same observer. However, the standard deviations of WAZ, HAZ, WHZ give an indication of good data quality in Nepal (SD 1.09-1.11) [189]. The SD for WAZ and WLZ in the Bwamanda dataset are similar (SD between 1.06 and 1.10), but the distribution of LAZ is somewhat broader (SD 1.31).

We chose 3-month increments for growth velocity for all of our analyses to balance the proportionally higher variability of short increments, the proportion of measurement error compared to actual growth, and a preferred short period for timely identification of children at risk [181, 199]. The contribution of measurement error for growth velocity can be substantial for two reasons. The calculation of velocity is based on two measurements and therefore allows for two potential sources of error [33]. The other reason is that the difference in raw measurement for the same difference in Z-score is smaller for growth velocity than for attained growth. As an example, the difference between a length-for-age Z-score of -1 and 0 is 1.8 cm at birth and 3.2 cm at age 24 months. In contrast, the difference in length velocity of -1 and 0 is 1.2 cm for the age period 0–3 months and 0.9 cm for the age period 18–24 months. Also for changes in MUAC the degree of measurement error in relation to actual change in circumference is an issue. In the period of fastest growth, the median MUAC in the WHO growth standard increases only by 7 mm within three months (0–3 months of age) [14]. This decreases to 2 mm at the age 21–24 months. By comparison, the allowable difference between two readings in the MGRS study was 5 mm for MUAC [200].

6.1.4 Anthropometrical scoring

Raw anthropometric measurements need to be scored in relation to a reference population. A discussion among the scientific community exists if a prescriptive growth standard or a local reference distribution should be used for this purpose. Some studies show that children grew (partly) differently to those included for constructing the WHO standards (the Multicenter Growth Reference Study; MGRS study) [201-203]. Other researchers found an adequate fit to the growth of the MRGS children [147, 152, 204] and a good concordance with clinical assessment of nutritional status [205]. Despite this inconsistency, it is clear that estimates of malnutrition prevalence and associations with other factors will vary depending on which standard or reference is used [203, 206-209].

Also for growth velocity, several references and an international standard exist (see chapter 1.2.2). A comparison of the WHO velocity standard [15] and a velocity reference from the US [26] showed considerable differences, especially in the span of the distributions [210]. Differences were mainly attributed to varying inclusion criteria, frequency of measurements, and statistical approaches for construction of the growth curves. We decided to use the WHO growth velocity standards for our studies. Neither DRC nor Nepal has national velocity references, and for comparisons across different settings an international standard was considered the most suitable. As mentioned for the reference for attained Z-scores, also the choice of velocity reference or standard is likely to affect distribution of velocity Z-scores (Paper 1, 2, 3), associations with other factors (Paper 1) and predictive abilities (Paper 2, 3).

The use of the WHO growth velocity standards has some further methodological implications. In the construction of the WHO growth velocity standards, some flexibility concerning deviation from target intervals and ages were included. In the MGRS, allowable deviations at ages 0–6 months, 6–12 months and 12–24 months were ±3 days, ±5 days and ±7 days, respectively. If ages at the beginning and the end of the interval do not match those in the WHO standards, they suggest using the reference values for the next appropriate ages [15]. In the Bwamanda study, time points for measurements were not scheduled according to specific ages, and therefore do not tally target ages in the WHO standards. Also, measurement intervals were both longer and shorter than the allowable ranges. In these cases, we referred to the next appropriate age and/or interval. This is a limitation to the precision of our estimates. In the MAL-ED study, very strict measurement schedules allowed for a stringent definition of target ages, i.e. ±3 days at all ages up to 24 months. A more precise approach for both studies would have been to interpolate the interval and/or the L, M and S values to the exact age and interval. However, an interpolation limits the practical applicability.

For MUAC, there is no growth velocity standard available. Therefore, we calculated the difference in absolute MUAC (ΔMUAC) and the difference in MUAC-for-age Z-score (ΔMUACZ) and standardized them to a 3-month increment. These differences do not account for different growth rates at different ages.

6.1.5 Generalizability

Generalizability is defined as: *“The degree to which results of a study may apply, be generalized, or be transported to populations or groups that did not participate in the study”* [182, p. 118]. Pre-requisites for external validity are a high internal validity and informativeness.

In the MAL-ED study the proportion of children aged two years being classified as wasted, underweight and stunted were 4 %, 13 % and 21 % respectively. The numbers of children aged 18-23 months in the demographic health survey 2011 in Nepal [174] were 19 %, 37 % and 42 % respectively. However, these are numbers for the whole of Nepal. Malnutrition prevalence shows a considerable difference between geographical locations within Nepal. For example the under-5 stunting prevalence is 60 % in the western mountain regions compared to 31% in the central hill region where Bhaktapur is located [174]. Estimates according to region reflect the prevalence for children under five years. These are expected to be higher than our estimates at two years, because nutritional status is typically deteriorating with age in low-resource settings [2]. Unfortunately, there is no DHS available for the time of the study in the DRC. In the DHS 2007, the national prevalence estimates for wasting, underweight and stunting in the age group 18-23 months were 9 %, 23 % and 43 % respectively [170]. Estimates for children at the age of two years (23-25 months) in the Bwamanda study were 6 %, 33 % and 64 % respectively. Although some characteristics of the Bwamanda area will have changed over time, as for example the discontinuation of the services of CDI-Bwamanda as described in chapter 4.1, these malnutrition estimates show that the data might still be of relevance today. However, although direct comparisons with other estimates within these specific settings are not possible, both our studies were community-based studies with adequate selection of participants (see paragraph *selection bias* p. 31-32). We therefore think that the study populations were representative of the target population.

Both populations under consideration in this thesis are characterized by a low nutritional status. However, one context is highly dependent on seasonal subsistence agriculture, and the other one with a rather well developed market and year-round food availability but social differentiation. This might indicate a different set of causative determinants of malnutrition operating in the two study settings at various stages in the lifecycle. This is supported by the different mean velocity Z-scores according to age in the two study settings. While weight and length velocity Z-scores were already low at birth and improved with age in Bwamanda (Paper 1), they were above the WHO mean in the first months of life and deteriorated thereafter in the Nepali study children (Paper 3). A direct comparison of predictive abilities in the two study population was not possible within the scope of this thesis. The applicability of our study results is therefore limited to populations and environments with similar characteristics as described in chapter 4.1.

The main determinant of informativeness is sample size [211]. Sample size calculations for the studies were not based on our specific objectives. Confidence intervals for each individual outcome can be consulted for an indication of the adequacy of the sample size.

6.1.6 Statistical methods

For Paper 1 and 2, information from several periods of the same child was used for the analyses. Adjustments for the dependency of observations can be done using different longitudinal techniques, such as generalized estimating equations (GEE) and random coefficient analysis (RCA), also often called mixed effect model analysis. While GEE estimate the correlation within a subject (with an a priori defined correlation structure), RCA calculates the variance between subjects (e.g. the variance of intercepts) which is added to the regression model [212]. Another difference between the two techniques is the interpretation of the results; while GEE is a population average model, the RCA is a subject-specific approach. Due to the more sophisticated estimation procedure, RCA can lead to unstable results [212].

For Paper 1, the outcome was continuous (weight or length velocity Z-score). We used a RCA allowing for random intercepts. For continuous outcome variables, results from the two different techniques (GEE and RCA) are not expected to differ remarkably [212]. For Paper 2, where the outcome was death, a quite rare dichotomous event, we chose a GEE approach. For dichotomous outcomes, regression coefficients from RCA will always be greater than those of a GEE model [213].

For analyses in both Paper 1 and 2, a correlation structure was specified a priori. In Paper 1 we used an unstructured correlation structure as the least restrictive approach. In Paper 2, an autoregressive structure (AR1) was chosen based on the quasi-likelihood under the independence model criterion (QIC). GEE is said to be robust against false assumptions of the correlation structure. This is particularly true for GEE with dichotomous outcomes [213]. The choice of the correlation structures could have influenced the regression coefficients, standard errors and the statistical efficiency. However, choosing a different correlation structure did not result in substantial changes of estimates in our analyses (results not shown).

For Paper 3, only one growth period at a time was entered into the regression model to estimate the risk of being malnourished. Therefore the dependency of observations had not to be taken into account and simple linear and logistic regression models could be used.

6.2 Discussion of the main findings

Season and child growth

In our study (Paper 1), a clear annual cycle could be seen in weight and length velocity with a decrease towards the summer, which is the beginning of the rainy season and the time just before the main harvest. This annual pattern could not be observed in indicators of attained growth, for which means were gradually decreasing with increasing age.

In the scientific literature, nutritional status is described to be directly and indirectly affected by weather [160]. In rural regions, where rain-fed subsistence farming is often the prevailing livelihood, the reliance on weather is considered to be especially pronounced. In these regions, precipitation and temperature are suggested as important drivers of levels of disease vector occurrence, food production activities and thus food availability [214]. Mechanisms linking the seasonal reliance to undernutrition have been described [214]; yet, studies on the seasonality and child growth have reported inconsistent results [96-98, 100-113, 115, 215-217]. Reasons for this inconsistency can be different definitions and occurrence of seasons in the vast variety of settings, and the various ways in which child growth is assessed. Our results support the latter, showing a different effect of season on growth velocity indicators and indicators of attained growth. This is in line with other studies, in which measures of longitudinal growth were more strongly related to season than height-for-age or stunting prevalence [96, 101, 109, 112]. Our results therefore indicate a potential limitation of other studies that were not able to find an association between attained growth and seasonality.

Seasonal influences are supposed to affect child growth only during a defined period of the year. This period is often related to the terms hungry season or transitory food insecurity [74]. Also other seasonal mechanisms such as diarrhea were suggested to be transient [218]. But in our study population in the DRC, although weight and length velocity Z-scores are increasing in the post-harvest season, still they remain below the median of the growth standards throughout the year. This improvement is insufficient for the children to completely catch-up and is therefore not concurrent with an improvement in attained growth indicators, pointing to additional, more stable factors that affect growth in our study population.

With the current climate changes happening and the assumption that these amplify the negative effect of season and exacerbating already existing health problem such as undernutrition [160], there is a need to revisit this topic with updated definitions of child growth. Our study was of descriptive nature, not being able to discriminate causative pathways. However, our analysis highlights that growth velocity could be an important research tool to study effects of season and climate change in more detail, or to assess the success of mitigating interventions in the future.

Predictive abilities of child growth

In our study, we could show that weight and length velocity were better than indicators of attained growth in predicting death within the next three months (Paper 2). In contrast, there was no advantage of using weight and length velocity during infancy to predict undernutrition at the age of two years (Paper 3).

For attained growth it has been shown that the risk of mortality increased monotonically with a decrease in Z-score for WAZ, HAZ and WHZ [12]. Evidence for an association of growth velocity scored with the WHO standards and functional consequences is scarce. To our knowledge, only one study has assessed the mortality predicting abilities of growth velocity according to the WHO standards [219]. Although their findings were in line with our results, i.e. that low weight velocity predicts death within three months, they did not compare the predicting ability to that of other indices. Growth velocity over short periods shows no growth tracking [220-222], but a higher instability than attained growth with little correlation between successive periods [15, 33]. Nonetheless, 3-month increments used in our analysis predicted death within the following three months better than indicators of attained growth. The chosen growth period represents a balance between the relative influence of measurement error and short term fluctuations (as “noise”) on the one hand and the sensibility to show current growth and thus to capture fluctuations (as “risk factors under consideration”) on the other hand [181, 199]. This is also illustrated by studies in Bangladesh, where weight gain over periods between two and six months poorly discriminated children at risk of death within the following year [223, 224]. However, in one of the studies weight gain was reduced in the two months preceding death, indicating the ability to capture the current risk profile. Also other studies assessed the short-term mortality predicting abilities of different anthropometrical indicators. Authors from a study in Zaire found that a negative change of 0.5 or 1 SD in some attained indicators was significantly associated with mortality within the following 100 days. In contrast, there was no association with attained growth indicators measured at one time point in previous analyses in the same study population [225]. Briend *et al.* [226] found WAZ at one time point to better predict mortality within the following month than changes in weight or WAZ in the 1-month period before. However, WAZ was not significantly better than changes in weight over the period of three months.

We used 3- and 6-month growth period for estimating of the ability to predict attained growth and undernutrition at the age of two years. Although weight and length velocity during many periods in infancy were significantly associated with attained size at age 24 months, indicators of attained growth were better than indicators of longitudinal growth to predict nutritional status in the long-term. This is in accordance with other studies [227-229], although these studies differ in definitions of predictor and outcome variables. One study found that weight gain from age 3–6 months was as predictive of later stunting as weight status at 12 months. However, they used predicted weight gains over three months, artificially removing the effect of short-term fluctuations and measurement error. In our study (Paper 3), plotting mean velocity Z-scores for children being underweight at two years compared to those not being underweight revealed interesting information. While weight-for-age was lower already at birth and throughout the first two years of life (Figure 8 Panel B), weight velocity Z-scores were notably different only in the first nine months of life and quite similar thereafter (Figure 5, Panel A). Studying mean velocity Z-scores can therefore be valuable in assessing periods of vulnerability, in our case emphasizing early infancy besides the prenatal period to be important for hampering the occurrence and severity of malnutrition.

Our aim was to predict adverse health outcomes with a simple anthropometric index and not to establish a causal inference. Therefore, we did not include other parameters in the regression models that are known to influence growth. However, children with a low growth rate over a period of three months might have a worse prognosis if they are additionally already malnourished. Therefore we restricted analyses of predicting short-term mortality to those already malnourished at the beginning of the assessment period, which improved AUROC values as expected.

Arm-circumference to predict mortaltity

Mid-upper-arm-circumference (MUAC) without age standardization was the best predictor of death within three months among the attained growth indicators, and a longitudinal assessment of MUAC did not lead to better mortality predicting abilities (Paper 2).

The close relation between MUAC without age standardization and child mortality has been described earlier [230, 231]. One potential explanation of the lack of improved predictive abilities of MUAC-for-age is that absolute MUAC tends to identify young children, who have a higher risk of dying in general [230]. Another hypothesis emphasizes the role of muscle mass for child survival, which increases with age and is correlated with MUAC. Possible mechanisms of this hypothesis are summarized by Briend *et al.* [41].

Besides a low weight-for-height Z-score and the presence of edema, low MUAC has been specified as criterion for identifying acute malnutrition by WHO in 2009 [232]. The simplicity of absolute MUAC is alluring and it has gained importance in a decentralized treatment of malnutrition. Minimally trained health personnel and even caretakers were able to perform reliable measurements [233, 234]. However, MUAC is mostly used as one-time off criterion and a longitudinal assessment had not been studied yet.

Applicability of growth velocity

The applicability as a critical issue especially for clinical and field use has to be discussed. It is not disputed that longitudinal assessment over time provides valuable information. Nevertheless, the interpretation of growth curves is subjective. Some studies have underlined the difficulties even of trained health personnel to evaluate growth curves on common growth charts [235, 236]. Growth velocity Z-score is a measure that can objectively quantify deviations in growth. Unfortunately, there is no tool available which instantly calculates or plots velocity Z-scores according to the WHO Child Growth Standards. The development of a mobile application could be feasible, especially with the rapid global spread of smart phone users. Onyango *et al.* [237] suggest another solution on how to use growth velocity Z-scores. In their study they assessed if weight velocity in two successive 1-month periods could be used to screen for stunting. They propose a simple 3-column table showing the age interval and boys' and girls' increment at the 15th percentile of growth velocity. If a child has a weight velocity lower than the 15th percentile value for a given age interval, it would be reassessed after a months and if still under the corresponding value, a stunting prevention program should be initiated.

Approaches suggested above deal with the complexity in calculation and visualization of growth velocity. However, although growth monitoring is said to be almost universally practiced on a global scale, this picture is based on questionnaires filled out by the Ministries of Health in 178 countries [7]. At a smaller scale, irregular a performance of growth measurements in institutions in many low-resource settings suggest that other barriers exist. These include lack of measuring equipment, inadequate measurement training, limited capacity and motivation of health personnel [238]. Growth velocity necessitates several measurements (at least two), and thus more time investment both from the healthcare provider as well as the child's caretaker; time which often is precious for both of the groups. In addition, the comprehension of a single velocity Z-score is arguably more complicated and would need to be tested with the end-users. Another drawback is that WHO provides velocity standards only for ages 0–2 years, clearly limiting the potential target group.

7 Conclusions

Analyses undertaken for this thesis showed that in a poor, rural and predominantly subsistence farming area, seasonal variation of growth could be seen in weight and length velocity Z-scores, but not in indicators of attained growth (weight-for-age, length-for-age, weight-for-length and MUAC-for-age). Moreover, weight and length velocity over a 3-month period predicted child death within the next three months better than their more commonly used attained growth counterparts. However, attained growth indices predicted the level of the same index at two years better than velocity Z-scores.

Our results imply that measures of attained and longitudinal growth to a certain extent capture different aspects, and thus both of them are useful to understand and study optimal child growth and deviations thereof. There are different purposes for the use of child anthropometry. The indicator to be used should thus be selected carefully depending on the objective. Growth velocity might currently be limited for the use in clinical settings due to a higher complexity, but taken our results into account, they might have a significant value for short-term prediction of severe health outcomes and for epidemiological studies.

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RESEARCH ARTICLE **Open Access**

Seasonal and spatial factors related to longitudinal patterns of child growth in Bwamanda, DR Congo

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Abstract

Background: Studying the influence of geographical factors on child growth is important, especially given the increasing interest in climate change and health in resource-poor settings and the recognized importance of growth faltering as a general marker of population health. We describe patterns in children's weight and length velocity and relate them to seasonal and spatial factors in rural DR Congo. The study setting is a food-insecure area with a majority dependent on rain-fed subsistence farming and expected to be one of the regions most affected by climate change.

Methods: We studied the effect of selected geographical factors, i.e. season, village size and distances to hospital, health center, forest, fishing grounds and market on growth of children under two years old. We calculated individual growth velocity Z-scores according to the WHO-2009 growth velocity standards for up to five successive 3-month growth periods. Associations with geographical factors were examined in multivariate mixed effects regression models.

Results: For the study population of 2223 children is characterized by low nutritional status. Age and season were the only independent predictors of growth velocity in the multivariate regression analysis. Mean velocity Z-scores were already low in children aged 0-6 months for weight [-1.34 (95% CI: -1.45, -1.22)] and for length [-0.99 (95% CI: -1.13, -0.84)]. They increased with age, while Z-scores of attained growth gradually decreased. Mean growth velocities were lowest before the main harvest season with a mean improvement of 1.2 and 2.3 Z-scores for weight and length velocity thereafter. A seasonal pattern was not seen in attained growth. No relation to spatial factors was found.

Conclusions: In this rural subsistence economy area, geographical factors relating to distances to food sources and health services are less important determinants than harvest season, which is the major underlying determinant of child growth in these settings.

Keywords: Ecological factors; Growth velocity; Anthropometry; Climate; Nutritional status

Background and objectives

Experts are highly confident that existing high burdens of negative health outcomes associated with climate will be amplified by the expected climate change over the next decades (IPCC 2014; WHO and WMO 2012). Undernutrition, which is still a problem in many developing countries and, not only a major contributor to poor health (Black et al. 2008), but also associated with long-term consequences, such as cognitive impairment, immune defects etc. (Fishman et al. 2004; Schaible and Kaufmann 2007), is predicted to worsen globally, but especially in regions which are already food-insecure.

Undernutrition can be directly affected by climate, e.g. by drought, but also indirectly by a linkage to seasonal changes in weather and vegetation (Maleta et al. 2003). This is particularly pronounced in rural regions where subsistence farming is practiced and where energy intake as well as work intensity heavily depend on the seasonal cycle of agricultural production. Additionally, a higher morbidity load often coincides with the "hungry season", the season before harvest, when food stocks are running out. A complex of impaired immune system function, peaks

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of disease vectors in the environment as well as agricultural work competing with child care, adds to the seasonality of malnutrition (Gill 1991). Vaitla et al. (2009) states that most of the world's undernutrition occurs, not as expected during periods of conflicts and extreme weather conditions, but periodically during this "hungry season". With the background that the first years of life are the most important but also the most vulnerable in terms of growth, disturbances of these seasonal factors have the potential to lead to permanent negative consequences for child survival and development.

The Democratic Republic of Congo (DRC) is one of the regions where the Intergovernmental Panel on Climate Change (IPCC) predicts a rise in temperature and a shortening of the rainy season (IPCC 2014). It also belongs to one of the regions in which the emergence of climate signals relative to the natural climate variability will occur first (around 2020–2030) (Hawkins and Sutton 2012; Mahlstein et al. 2011) and where the ecosystem is particularly vulnerable to climate change (Mahlstein et al. 2011). With a majority relying on rain-fed subsistence agriculture this is an alarming issue (UNEP 2011; Kandala et al. 2011) and is reason to shed renewed light on the relationship between season and child malnutrition.

Spatial parameters have been found to explain a reasonable amount of the variation in childhood mortality on a large scale in West-Africa (Balk et al. 2004) as well as rates of malnutrition in the DRC (Kandala et al. 2011). Despite the improved possibilities available to assess spatial parameters, there is still a scarcity of research including them (De Sherbinin 2011). In the DRC, where the proportion of malnourished children under 5 years increased to an alarming level with 46% being stunted and 10% being wasted in 2007 (Ministère du Plan et Macro International 2008), and where continued conflict, land degradation and collapsing infrastructure worsens the capacity to produce and trade food, understanding regional differences in child malnutrition are important to effectively establish interventions and develop nutrition policies (Kandala et al. 2011). However, there is a difference in scale between the regional inequalities studied before (Kandala et al. 2011) and the spatial determinants we attempt to analyze in the present study.

In children, who are regarded as one of the populations most affected by climate change (IPCC 2014), undernutrition is reflected in restrained growth (UNICEF 1998). Growth can principally be measured with two main approaches: attained growth at a specific age or longitudinal growth over a period of time. Longitudinal growth measured over a short period is considered to have the advantage over attained growth, in that it represents what is currently happening and not, as in attained growth, what has happened in the entire past up to the point in time of measurement. This offers the opportunity to detect faster any unusual growth in children, but also to study associations with potential risk factors while the child is in the actual process of growth faltering and not when the child has already faltered (Argyle 2003). One method to assess longitudinal growth is growth velocity. The WHO released growth velocity standards in 2009 (WHO 2009), which scores anthropometric measurements in reference to normal growth velocity in the specific age period. Despite the recognized advantages, these standards are rarely used in research yet.

Although the impact of geographical factors, particularly season, on the nutritional status and growth of children is not a new research questions, some authors advise caution as over-generalizations, due to a wide variation in microclimates and ecologies, can affect causal pathways and the degree of impact of seasonality (Ferro-Luzzi et al. 2001; Prentice and Cole 1994). Previous studies on seasonality of nutritional status and growth have been conducted in Asia (Brown et al. 1982; Carlquist et al. 1999; Hillbruner and Egan 2008; Jalil et al. 1989; Karlberg et al. 1993; Miller et al. 2013; Panter-Brick 1997; Xu et al. 2001), Africa (Maleta et al. 2003; Ferro-Luzzi et al. 2001; Chotard et al. 2010; Hauspie and Pagezy 1989; Kigutha et al. 1995; Loutan and Lamotte 1984; Rosetta 1988; Tomkins et al. 1986; McGregor et al. 1968; Wright et al. 2001; Lindtjorn et al. 1993) and South-America (Marin et al. 1996), but they report inconsistent findings. Additionally, only one of the above-mentioned studies used the WHO standards to score growth (Miller et al. 2013). That study finds irregular associations with season depending on the anthropometrical measure used. They argue that even significant differences between seasons were small in absolute terms and should be interpreted cautiously due to possible bias, for example by the state of hydration, clothing etc. influencing weight-based indices. Comparisons of the WHO standards and previously used growth references show that important differences exist in identifying malnourished children, but also in age patterns of growth (de Onis et al. 2011).

This work aims to contribute to the understanding of growth velocity in children in relation to geographical factors in rural Africa. The objectives of this paper are to describe age- and sex-dependent patterns in weight and length velocity of children younger than two years living in the DRC using the WHO Child Growth Standards (WHO 2009) and to relate these patterns to selected climatic and spatial determinants, with a main focus on season and distances to sources of food and health care, and with the specific concern to examine the relative importance of those.

Methods

The original Bwamanda study

To address our research question, we did a secondary analysis of data collected in the Democratic Republic of Congo (DRC; formerly Zaire). Research setting and methods of participant enrollment and data collection are described in detail elsewhere (Van den Broeck 1994). In brief, a dynamic population study was conducted in the health zone of Bwamanda from August 1989 to March 1991. This health zone is one of 16 administrational zones within the Sud-Ubangi district, which is one of four districts in the Equateur province in the northwest of the country. Bwamanda has a tropical climate with two main seasons - a rainy season from March to November and a dry season from December to February. Up until today it is a rural area and over 90% of households practice traditional subsistence farming with maize and cassava as the main staple foods. Subsistence farming is highly dependent on geographical factors, such as soil quality, infrastructure and water availability (UNEP 2011; Morton 2007). Diets are rather monotonous, typically consisting of gruels from cassava and maize. The carbohydrate rich staples are to various degrees supplemented with smaller amounts of more nutrient dense green leaves, vegetables, legumes and animal source foods, and we anticipate that the main difference between adequately nourished and malnourished households is found in access to these nutrient dense foods. These factors, amongst others, contribute to the common problem of malnutrition in this community (Van den Broeck 1994).

Sixteen out of 52 villages in the Bwamanda health zone were selected in a random cluster sample procedure. A preliminary census based on home visits was carried out in August and September 1989 and 4238 children aged 0–5 years and their mothers were enrolled in the study. Simultaneous training of 15 interviewers, holding a secondary school certificate, was done at Bwamanda hospital by a medical doctor. Between October 1989 and March 1991 six surveys were carried out measuring each child at three-month intervals (rounds A-F), all at special under-5 clinics, or, if children were not present at the clinics, at house-to-house visits. In total 5657 children under the age of 5 were enrolled during the study period. Variables recorded in each of the six quarterly surveys included the results of a clinical examination, anthropometric measures (including weight, height or length and mid-upper-arm-circumference), data on interval-morbidity, mortality, harvest and feeding practices, socioeconomic conditions, and environmental information, such as distances from the village to health care and food sources. In addition emigration and temporary absence during the study period was recorded. Data collection was continuously overseen by two medical doctors. Age was obtained using the birthdates documented on the 'road to health charts' or the identity papers of the parents. If this information was lacking (in ca. 10% of the children), careful interviews of the mothers were used in combination with a local calendar to estimate the child's date of birth.

Geographical factors

According to the conceptual framework of child malnutrition developed by UNICEF (1998), risk factors can be assigned to basic, underlying and immediate level, all of which are interrelated with each other. In Bwamanda, the study area, characteristics reflecting the basic cause level (cultural, political, and economical structures) are considered to be relatively homogeneous. We selected geographical location and season as a proxy for underlying factors such as access to and availability of different sources of food and health care, and a healthy environment due to varying amount of germs and pathogens in different seasons. Spatial factors considered were village size and distance from the village to health center, hospital, market, fishing grounds, and the forest, as a proxy for access to bush foods. Inter-individual differences due to varying dietary patterns and morbidity, the immediate causes, are not accounted for in this analysis as they are mediators of the underlying causes in our epidemiological understanding. Including them would dilute the relationship between underlying factors and malnutrition.

Season in this setting is best described in terms of variation in precipitation, since temperature and daily sunshine hours do not differ much throughout the year. Seasons were defined as rainy season (1st March–30th November) and dry season (1st December–28th February). This definition differs from former analyses on this dataset (Van den Broeck 1994; Garenne et al. 2009). The adjustment was performed after analyzing data on precipitation obtained from a local weather station, which were additionally supported by satellite estimates (see Additional file 1), and published precipitation data from a nearby weather station (Franquin et al. 1988). The classification into pre- and post-harvest was based on information from the original study on harvest of the main food items cassava, cassava leaves, maize, sweet potato, taro, peanuts and bananas in the last two months. Although harvest is possible twice a year for maize and several times for cassava and cassava leaves, we used timing of the first main harvest for the classification of sub-season. This classification was confirmed by informal talks to local farmers and the responsible person for agricultural development in the NGO CDI Bwamanda, which specializes in integrated sustainable livelihood development and has been working in the study area since 1969.

Anthropometric measurements

Anthropometric measurements were taken following a standardized procedure by two experienced observers. Weight was taken with spring scales (Continental Ltd., United Kingdom) to the nearest 100 grams. Height was measured with a microtoise reading to the nearest millimeter while length was measured with a locally built measuring board. Mid-upper-arm circumference (MUAC) was taken by the same medical doctor with a steel tape measure (Stanley) to the nearest millimeter.

Anthropometric scoring

Weight and length velocity were calculated for each successive 3-month follow-up period. Raw values were scored according to the WHO Child Growth Standards (WHO 2009) using a macro provided by O'Neill et al. (2012). The analysis was restricted to children of the age 0–24 months, because the WHO-2009 standards are only available for this age range. Weight and length velocity were categorized on the basis of whether and when Z-scores were higher or lower the −2 to +2 normal Z-score range. Growth was defined as "slow" when the Z-score was ≤ −2, as "normal" when the Z-score was > −2 and <2 and as "rapid" when it was ≥2.

In order to compare the velocity Z-scores to indices of attained growth, we also calculated Z-scores for attained weight-for-age (WAZ), length-for-age (LAZ), weight-for-length (WLZ) and mid-upper-arm-circumference-for-age (MUAZ) according to the corresponding WHO child growth standards (WHO 2006, 2007). Wasting is defined as WAZ < −2 and stunting as LAZ < −2.

Statistical methods

For this analysis the original dataset was imported into SPSS (Statistical Package for the Social Sciences) version 19.0.0 and kept in a secure place to ensure confidentiality. Data cleaning was performed before commencing the analysis. Attained growth Z-scores < −6 and >6 as well as 3-month velocity Z-scores in weight and length of <10 and > −10 were defined as implausible and set as missing. Of a total of 46694 measurements 69 values for WAZ, LAZ, WLZ and MUAZ and eight values for weight and length velocity Z-scores were set as missing.

A bivariate analysis was carried out to establish the associations between growth velocity and the geographical determinants. In addition, multivariate mixed effect regression models, with an unstructured variance-covariance matrix, were developed. These models differed from conventional mixed effect models in growth analysis in that they do not use attained growth Z-scores but instead growth velocity Z-scores in successive periods. Modeling growth velocity Z-scores has the advantage that it accounts for different growth rates at different ages. That is important, because infants grow faster the younger they are, so that the same differences in attained Z-score for a certain period of time has a different meaning for different ages. For example a change of +0.25 Z-scores from age 0–3 months and from 3–6 months indicates a greater change in the older infant, since growth is normally slower compared to the younger infant. However, when modeling attained growth Z-scores this differences of +0.25 would be treated as equal acceleration of growth, when in reality it is not.

Variables for age, sex, birth-rank, mother's age and breastfeeding status (no breastfeeding, exclusive or complementary breastfeeding) were initially taken into the model as covariates, but omitted if they were not statistically significant.

Ethics

Ethical approval for the original study was obtained by the University of Leuven's Tropical Childcare Health Working Group. This current analysis was approved by the Ethical Committee at the University of Kinshasa (approval number: ESP/CE/008/14).

Results

Of the 5657 children enrolled in the study, 2223 were under the age of two years at two or more measurement points and eligible for growth velocity calculations. The sample was homogeneous in ethnicity (97.7% were Ngbaka) and balanced in sex (49.3% female). Birth-rank ranged from 1 till 15. The age of the mother at the time of child birth varied between 13 and 56 years with a median of 27 years (interquartile range 22–32). Other demographic and anthropometric characteristics are summarized in Table 1. The 16 selected villages had on average about 1600 inhabitants each (between 900 and 2000). The distance from the village to the market was between 200 m and 30 km, to the hospital between 500 m and 65 km, to fishing grounds between 150 m and 6 km and to the forest between 150 m and 15 km.

Growth velocity patterns

Mean (SD) velocity Z-scores according to the WHO-2009 standards were −0.70 (1.55) for weight and −0.87 (1.90) for length for all children included and all five study periods taken into account.

Indices of attained growth clearly showed tracking in individuals, i.e. measurements were strongly positively correlated with consecutive measurements throughout the study period. In contrast, growth velocities varied in consecutive periods, so that velocities in one 3-month period were negatively correlated with the velocities in the adjacent 3-month period, both before and after. These correlations were significant for all periods for length velocity. Weight velocities showed the same pattern, but the negative correlations were weaker and partly insignificant. Growth velocities showed an association with corresponding indices of attained growth, in that they correlated negatively with the attained Z-score in up to four periods before and positively in up to five periods after the velocity measurement.

Growth velocities were categorized as "slow", "normal" and "rapid" growth according to the criteria described in the Methods section. Over the total study period, 16.5% of the 3-month growth periods for weight of all children

Table 1 Demographical and anthropometrical characteristics of the study sample (N = 2223) in the different survey rounds

		Round A	Round B	Round C	Round D	Round E	Round F
Number of children analyzed		1293	1505	1734	1957	2223	2223
Average age in months (SD)		11.2 (6.4)	12.3 (7.0)	13.3 (7.7)	14.6 (8.4)	16.8 (9.5)	20.0 (9.6)
Mean LAZ (SD)		−1.86 (1.39)	−1.98 (1.35)	−1.87 (1.33)	−2.03 (1.29)	−2.26 (1.25)	−2.34 (1.17)
Mean WAZ (SD)		−1.24 (1.23)	−1.24 (1.18)	−1.30 (1.18)	−1.44 (1.20)	−1.54 (1.16)	−1.52 (1.06)
Mean WLZ (SD)		−0.24 (1.20)	−0.12 (1.15)	−0.30 (1.17)	−0.37 (1.14)	−0.31 (1.11)	−0.26 (1.01)
Mean MUAZ (SD)		−1.72 (1.10)	−1.72 (1.06)	−1,84 (1.08)	−2.01 (1.11)	−2.23 (1.12)	−2.12 (1.00)
Stunted (%)	Moderate	25.7	28.2	28.5	29.0	32.3	33.1
	Severely	19.6	22.1	18.4	21.8	27.1	27.8
Underweight (%)	Moderate	17.6	16.3	18.6	20.9	23.8	22.6
	Severely	7.1	7.2	7.7	10.1	10.5	8.3
Wasted (%)	Moderate	5.4	4.6	5.3	5.2	5.0	4.2
	Severely	1.5	0.9	0.9	1.7	1.4	0.5
Low MUAZ (%)	Moderate	28.5	27.6	27.8	31.0	34.4	36.9
	Severely	11.8	10.9	14.8	18.2	23.6	17.8

Stunting is defined as low length-for-age Z-score (LAZ), underweight as low weight-for-age Z-score (WAZ), wasting as low weight-for-length Z-score (WLZ) and low MUAC as low mid-upper-arm-circumference-for-age Z-score (MUAZ) according to the WHO Child Growth Standards. Cut-offs for moderate malnutrition were set to ≤ −2 and > −3 Z-score, and for severe malnutrition to ≤ −3 Z-score.

were within the slow growth category, 81.4% within the normal range and 2.1% within the rapid growth category. For length velocity Z-scores 24.1%, 70.9% and 5% of the periods were within the slow, normal and rapid category, respectively.

Further we were interested to see if children were able to counterbalance slow growth in one period by fast growth in the next period or the other way around, i.e. rapid growth in one period followed by slow growth in the next period. Therefore, we looked at two subsequent assessment periods of growth velocity. For weight it was observed that slow growth was infrequently followed by rapid growth (in 5% of the children). Mostly the second value was within the range of normal growth (82%) or stayed slow (13%). If a child had a normal growth velocity, it was more likely that in the following period the velocity would also be normal (86%), with 13% showing slow growth and 1% rapid growth. And after a period of rapid growth, the children were showing either slow or normal growth in the next period (39% and 59%). In summary, weight did not show distinct catch-up growth, defined as growth velocity exceeding statistical limits of normal growth, after a period of restrained growth. In contrast, length velocities showed more "balancing". After a period of slow linear growth it was more common that children had a rapid length growth in the following period (30%) compared to weight, and periods with rapid length growth were mostly followed by one with slow growth (55%).

Growth velocity according to age and sex

After stratifying according to ages 0–6, 7–12 and 13–24 months, mean velocities were compared (Table 2). Children in the oldest age category had the highest velocity Z-scores for weight and length compared to the two other age categories. The differences in mean velocities were not statistically significant between ages 0–6 and 7–12 for

Table 2 Indices of growth in three age-categories and according to sex for all survey rounds combined

Age category (in months)	Attained growth mean Z-score (95% CI)				Longitudinal growth mean Z-score (95% CI)	
	WAZ	LAZ	WLZ	MUAZ	Weight velocity	Length velocity
0–6	−0.96 (−1.03, −0.89)	−1.41 (−1.48, −1.33)	0.16 (0.09,0.23)	−1.54 (−1.60, −1.48)	−1.34 (−1.45, −1.22)	−0.99 (−1.13, −0.84)
7–12	−1.49 (−1.55, −1.44)	−2.00 (−2.05, −1.93)	−0.46 (−0.51, −0.40)	−1.95 (−2.00, −1.89)	−0.77 (−0.84, −0.69)	−1.01 (−1.12, −0.91)
13–24	−1.50 (−1.54, −1.47)	−2.38 (−2.42, −2.34)	−0.44 (−0.48, −0.41)	−1.97 (−2.00, −1.94)	−0.38 (−0.44, −0.32)	−0.67 (−0.74, −0.60)
Female (all ages)					−0.64 (−0.70, −0.58)	−0.85 (−0.93, −0.77)
Male (all ages)					−0.69 (−0.75, −0.62)	−0.81 (−0.89, −0.73)

Reported are mean Z-scores with 95% confidence intervals. Z-scores for weight-for-age (WAZ), length-for-age (LAZ), weight-for-length (WLZ), mid-upper-arm-circumference-for-age (MUAZ), weight velocity and length velocity are scored according to WHO Child Growth Standards (WHO 2006, WHO 2007, WHO 2009). Age is given in months.

length velocities. Attained Z-scores showed a downwards trends, i.e. the youngest age category had a significantly higher mean Z-score in all four indices (WAZ, LAZ, WLZ, MUAZ) than the older age categories. The two older age categories did not differ except in mean LAZ.

Weight and length velocity Z-scores did not differ significantly according to sex (Table 2). Figure 1 shows mean velocities according to sex and age category. Although error bars indicating the 95% CI overlap at all ages, the difference in sex for the age group 7–12 months is significantly different for weight velocity (t =2.622, p =0.009).

Associations between growth velocity and spatial parameters

There were no significant associations between growth velocity Z-scores for weight and length and the variables indicating the size of the village, and the distances to health center, market, hospital, fishing grounds, and the forest (Table 3). No differences were seen when stratified according to sex and age category. Also the occurrence of catch-up growth did not differ when comparing the quintile nearest to the hospital, market, fishing grounds and forest with the quintile farthest from those points.

Associations between growth velocity and season

Mean growth velocity Z-scores were lowest in the pre-harvest season, namely between March and July, and improved after the first main harvest in July (Figure 2) with a mean improvement of 1.2 and 2.3 Z-scores for weight and length velocity. This was also seen by a rise in the portion of growth velocity Z-scores categorized as slow growth and a decrease in the portion of rapid growth until the harvest season. Although weight and length velocities showed the same general pattern, mean length velocities deteriorated more markedly than mean values in weight velocity and the increase in mean length velocity at the beginning of the post-harvest season was slower than the increase of weight velocity. Length velocity peaked about two months after weight velocity.

A seasonal pattern could not be clearly seen in attained growth. No differences in the effect of season on longitudinal growth between the sexes were observable (Figure 2), nor between age categories. There was no seasonality in the occurrence of catch-up growth when defined as growth velocity Z-score > +2.

Multivariate analysis

We built mixed models with an unstructured variance-covariance matrix allowing for random intercepts for each individual child. Velocity Z-scores in weight or length were entered as dependent variables. Independent variables were season, size of village, distance to hospital, health center, market, fishing grounds and forest, age, sex, breastfeeding status, birth-rank and mother's age at birth. This multivariate analysis confirmed our findings from bivariate analysis, i.e. that age and season were the only independent predictors. Breastfeeding was a significant predictor, but did not improve the fit of the model significantly.

Discussion

The data from the Bwamanda study, which are still of high relevance today, and the newly published WHO growth velocity standards offered a unique opportunity to study longitudinal growth over up to five successive 3-month periods of 2223 children between 0–2 years in relation to seasonal and spatial factors, which are of increasing interest.

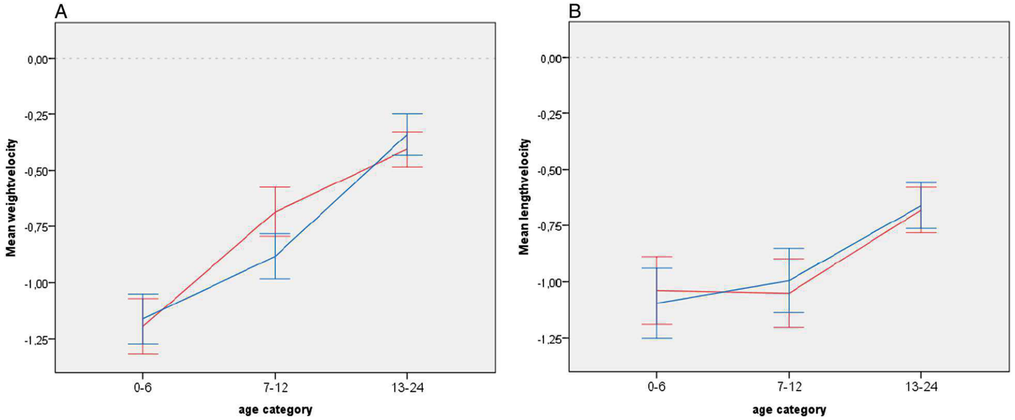

Figure 1 Mean weight velocity (A), mean length velocity (B) according to age-category and sex. Error bars indicate the 95% confidence interval. Girls are represented by a red line and boys by a blue line. Age is given in months.

Table 3 Correlations between indices of longitudinal growth and spatial parameters

	Weight velocity	p	Length velocity	p
Village size	0.006	0.683	0.024	0.083
Distance to market	0.000	0.991	−0.015	0.293
Distance to hospital	0.016	0.240	−0.010	0.494
Distance to fishing ground	0.004	0.790	−0.015	0.298
Distance to forest	0.009	0.501	−0.026	0.060

In order to study longitudinal growth of children, we described patterns for age- and sex-dependent growth velocity Z-scores for weight and length. We find that growth velocity Z-scores for weight and length were strongly related to season while no index was related to the selected spatial parameters in our sample. The seasonal impact could not be demonstrated in attained growth. This and the fact that a restriction in growth showed much earlier when studying growth velocity Z-scores, argue for longitudinal growth as an important tool in the timely detection of growth faltering. It also points to a limitation of many previous studies of the relation between geographical factors and growth.

Patterns of longitudinal growth

Poor nutritional status was common in our sample, reflected by around 52% stunted and 6% wasted children in each survey round. This was also observable in the percentage of children with velocity Z-scores under what is usually defined as the normal range (Z-score < −2). 16.5% and 24.1% had a slow growth in weight and length respectively. Analyses of child growth in low- and middle-income countries show that growth faltering starts early in life and worsens up to the age of two years (Victora et al. 2010). In our sample we also see continuous deteriorating indices of attained growth despite increasing velocities with age. This finding underlines the importance of early interventions.

Length velocities of successive periods were more strongly negatively correlated than weight velocities and when looking at two consecutive periods, we found that periods with slow length velocities were more often followed by rapid growth (indicating catch-up growth) and vice versa (catch-down growth) than in ponderal growth. This suggests that length velocity is more variable than weight velocity. Nevertheless, the corresponding index for attained growth (LAZ) still deteriorated over time. Catch-up growth can be defined as growth that statistically exceeds normal growth (i.e. > + 2 Z-scores). The periods with rapid growth following those with slow growth were probably not strong enough, and there were still many more children who after a period with slow growth had growth velocities within the normal growth range and therefore no catch-up growth, as defined above. It has to be mentioned that this description does not take into account any confounding factors and cannot therefore suggest any causes of the longitudinal behavior. Physiological growth is characterized by variation within the normal range in growth velocities in subsequent periods (WHO 2009), so it is difficult to interpret only a single growth velocity of an individual. It is thus necessary to study further patterns of growth velocity for individual children in consecutive growth periods to gain insight and guidance in the evaluation of longitudinal growth for clinical use and research.

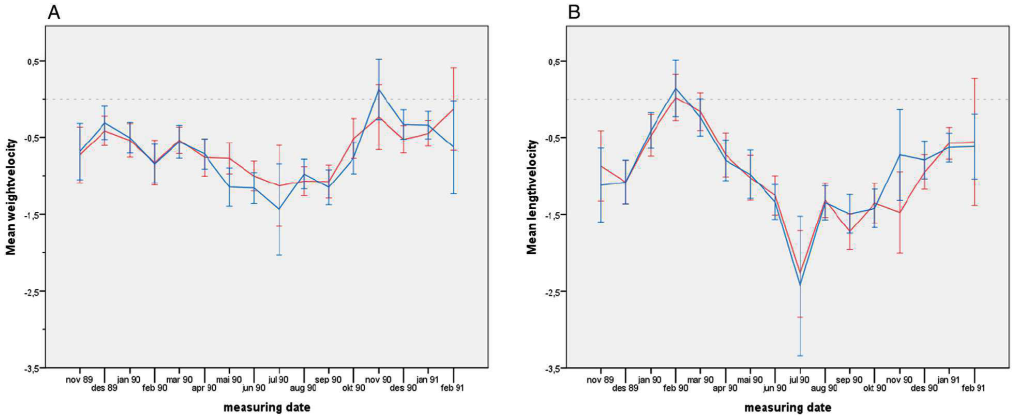

Figure 2 Mean weight velocity (A), mean length velocity (B) according to measuring date and sex. Error bars indicate the 95% confidence interval. Girls are represented by a red line and boys by a blue line.

Longitudinal growth according to sex, breastfeeding status and birth rank

When comparing mean growth velocities no differences were seen between boys and girls. After stratifying for age, boys aged 7–12 month had a significantly lower mean weight velocity Z-score than girls. This difference was not observed in the older age group. This could either illustrate a better ability for the boys to catch-up or a survivor bias. But neither mortality nor catch-up growth showed a difference between the sexes in this sample. We do not have any information about intra-household and gender disparities in food and dietary composition for our sample. Olusanya and Renner (2011) found in their study sample composed of 658 Nigerian children 0–8 weeks old that male gender is an independent predictor of higher weight velocity. They argue that boys usually have larger growth increments than the same aged girls (WHO 2009; Guo et al. 1991; van't Hof et al. 2000), but since weight and length gains were not scored according to the WHO-2009 standards, this argument is invalid for our sample.

Breastfeeding status was significantly associated with growth velocities, but did not improve the multivariate model. This could be explained by almost universal exclusive breastfeeding up to the age of four months in our study sample and a weaning period thereafter as described previously (Van den Broeck et al. 1996). Therefore breastfeeding status might not add to the fit of the model as there is too little variation and the mechanism is already captured by the age variable.

Birth-rank was not associated with growth velocity Z-scores and did not mitigate the effect of season in our study. In Bwamanda large household usually divide into three groups during the major meals: (i) children below the age of three, who eat with their mothers and other females in the household, (ii) those children above three years, who eat with other children, and (iii) adult males. A problem could arise in the group of children eating together (group ii), where there is competition and some discrimination against younger children, but for the age span we analyzed (0–24 months) this is not considered to be likely. Even if the younger family members did lose out during family meals, this is likely to be constant throughout the year independent of the total amount of food available and would therefore not affect the relation between season and growth.

Associations with season

The analysis of mean weight velocities shows that Z-scores decreased in pre-harvest and increased in post-harvest season. The same is true for length velocities, only peak velocity lagged by about two months. This lag is also described by Maleta et al. (2003) and Xu et al. (2001), who find that height gains peaked three months after weight gain. Some authors explained the lag as an effect of wasting on subsequent stunting, i.e. that a certain cut-off in weight-for-height has to be reached before compensatory linear growth appears (Costello 1989; Walker and Golden 1988). Although weight-for-height is also associated with weight gain in the study of Maleta et al. (2003), it only explains very little of the variation in height gain. Therefore other factors might play a more central role in linear growth.

We could not demonstrate a different impact of season in the age three groups 0–6, 7–12 months and 13–24 months. This is in accordance with the study by Hauspie and Pagezy (1989) in Zaire, who saw the same seasonal pattern in all age groups of 0–4 years. Age-dependency is reported by other studies (Maleta et al. 2003; Jalil et al. 1989; Karlberg et al. 1993; Miller et al. 2013; Rosetta 1988; McGregor et al. 1968), but with inconsistent results. The lack of differences related to age in our study might be due to the typical early weaning of children at around four month of age on average, resulting in less protection from environmental vectors and less mediation through maternal health.

Seasonality was not seen in indices of attained growth (WAZ, LAZ, WLZ). Our analysis suggests that it is important to study longitudinal growth and to associate factors when the growth of a child is actually faltering. This is supported by the work of Kismul et al. (2014) who find a seasonality in the incidence of wasting and stunting in children under five years in the same area. The lower responsiveness to season of length-for-age in comparison to length gains has been identified by others (Brown et al. 1982; Miller et al. 2013; Tomkins et al. 1986), but not for weight-based indices.

Associations with spatial parameters

Spatial parameters selected for this analysis were village size and distance from the village to health center, to the hospital, to a market, to fishing grounds and to the forest. None of them contributed essentially to differences in growth velocities in our sample, although they differed substantially for individual participants and could be expected to be of importance, especially in areas like the study setting, where only restricted motorized transport is available for local people.

Other studies, have found that population density has a close relationship with child malnutrition, explained by lower market penetration, and more limited access to health facilities and nutrition-related information (De Sherbinin 2011; Nikoi and Anthamatten 2013). In our setting, the scale was very different with a relatively homogenous village size, ranging from about 900 inhabitants to about 2000. Nevertheless, accessibility was different with some villages near the main road and local markets and others far off and difficult to reach, due to almost impassible roads, especially during the rains. Nevertheless, the whole region mainly comprises subsistence farmers producing only a minimal portion of cash crops. Therefore distance to market as well as size of village as an indication of connectivity or food availability, seem less important than size of the extended family, forming the working capacity to cultivate the fields. Quantity of cultivatable land is only of relevance if adequate working capacity exist, also having an impact on the quality of the harvested foods.

Low cash income may be one of the reasons why distance to the hospital, which varied greatly, did not have an impact on growth velocities, for even if the hospital was accessible, it is of no benefit if one cannot afford it. Local health centers, which where more accessible for all children and less expensive, did not show any impact on child growth velocities either. From our own experience in this region, health centers have variable resources in terms of medical equipment, medication, and training of their staff. Also the use of traditional healers has not been adjusted for in this analysis.

Similar arguments could be used for the association of distance to fishing grounds, which we were not able to show. Distance to fishing grounds was included in the analysis as a proxy for the availability of fish and therefore a source of animal protein-rich food. Although distance might determine the possibility for fishing, informal talks to people in the area indicated that even if people lived near fishing grounds, the lack of money to purchase fishing equipment stopped them from fishing.

Using distance to forests as a proxy for bush food did not generate correlations. Since fallow fields and other areas may be important sources of nutrient-dense supplementary foods, other measures of access to these resources should be developed.

Limitations

In addition to the limitations already discussed above, some uncertainties in measuring age, date and climatic data have to be reported. The exact age was documented for 90% of the 5657 children; in the remaining 10% it was obtained through careful interviews with the help of local calendars. Even if some inaccuracy persists in this small portion of the children, it is not expected to substantially influence the results.

Data on the date of measuring was derived from adding the age in days to the birthdate, assuming that every month has 30.43 days. This will add some minor inaccuracies, but measuring date was only used to categorize the timing of measurements into seasons. Season is not a construct with clear borders, going from dry season to rainy in one day, and therefore only a few misclassifications with no substantial effects are expected.

Precipitation data was derived from triangulation of data from a local weather station, satellite data and published data from a nearby meteorological station. Nevertheless, no data for the specific study years were available, only long-term data from 1941–2005 and detailed data for the years 2001–2005. Weather conditions deviating from the normal in the study years could not therefore be accounted for.

The measure of harvest to define sub-seasons also has to be evaluated critically. Data on harvest was obtained by asking the interviewee if they had harvested a specific food item in the past two months. This rather long recall period is susceptible to recall bias. Further the possibility of information bias exists, since only two months of the average 3-month period between survey rounds are covered. However, the estimate still gives a good idea of the timing of harvest, since different households were interviewed every day and the purpose was not to assess the exact amount of harvest, but the timing, which we believe can be adequately recalled for the last two months. In addition, timing was confirmed by informal talks to local specialists. Analysis of the amount harvested compared to the amount eaten or sold assessed with a 24-hour recall, confirmed that it is an adequate indicator of food availability, because neither storing nor selling was common (data not shown).

A weakness in our study is the fact, that we did not include birth weight in our analysis. As mentioned in previous work (Van den Broeck et al. 1996), the majority of births took place at home with the help of a traditional birth attendant and it was therefore impossible to record birth weight for our study sample. Birth weight deviating from the normal is known to affect early child growth rates, representing catch-up or catch-down growth (WHO 2009). Births were almost evenly distributed throughout the year in our study, so varying growth rates in early childhood are not expected to change the relationship between season and growth velocities to a substantial extent.

Conclusions

In our analysis, we demonstrate that studying growth velocities instead of attained Z-scores can provide an important perspective concerning the early detection of growth faltering, because even if nutritional status measured by attained growth was deteriorating with age in our study sample, a restriction in growth could already be seen in much younger ages. Looking at growth velocities also revealed a clear seasonal impact on growth, which was not observable in attained growth.

In our study area, a rural subsistence economy, geographical factors relating to distances to food sources and health services seem less important determinants of child growth than harvest season, which is the major underlying determinant of child growth in these settings and is in turn is a geographical factor expected to be influenced greatly by climate change. Having such a negative impact on child growth in a supposedly pre-climate change situation, the perspective of climate changes taking place in this area and thus a change in the seasonal conditions for agricultural success is alarming. Additionally, the term transitory food-insecurity is often used for non-permanent, short-term lack of food (Pinstrup-Andersen 2009) as in our described setting. But only in a few areas was it shown that weight gain exceeded the reference mean in seasons with less nutritional stress or morbidity burden and children thus maintained a satisfactory nutritional status in the long-term (Loutan and Lamotte 1984; Tomkins et al. 1986). In most other areas a further deterioration of nutritional status and long-term consequences are expected from those seasonal variations and therefore the expression transitory food-insecurity might be misleading.

As Wand et al. (2012) state, prevention and treatment of restricted growth in early childhood is central to enhancing social and economic development in low income countries, and approaches are likely to be successful if they allow for local factors. Our study indicates that agricultural season is an important factor for child growth, and thus targeting of local strategies to cope with seasonal conditions are crucial, especially in the light of predicted future risk related to climate change.

Additional file

Additional file 1: Monthly mean precipitation from observations and satellite estimates in the area of Bwamanda, DR Congo.

Abbreviations

DRC: Democratic Republic of the Congo; LAZ: Length-for-age- Z-score; IPCC: Intergovernmental Panel for Climate Change; km: Kilometer; LVZ: Length-velocity Z-score; m: Meter; MUAC: Mid-upper-arm-circumference; MUAZ: Mid-upper-arm-circumference-for-age Z-score; SD: Standard deviation; WAZ: Weight-for-age-Z-score; WHO: World Health Organization; WLZ: Weight-for-length Z-score; WVZ: Weight velocity Z-score.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

CS conducted the analysis and wrote the first draft of the manuscript. TML provided the supplementary material. All authors edited the manuscript and contributed in the interpretation of the results. All authors read and approved the final manuscript.

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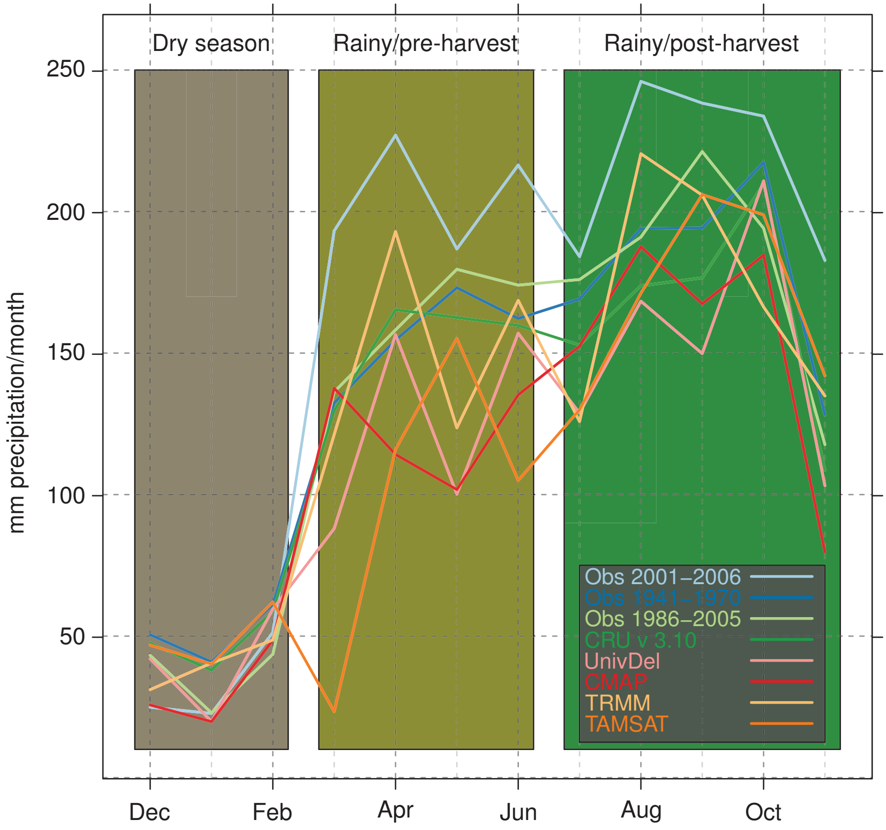

Monthly mean precipitation from observations and satellite estimates. Obs 2001-2006 is observations from Bwmanda (3.174 N, 19.242 E), Obs 1941-1970 shows monthly climatology from Zingo (2.4456 N 17.4269 E), and Obs 1986-2005 monthly climatology from Boketa (1.8069 N 18.0119 E). CRU v 3.10 [1] and UnivDel (University of Delware precipitation [2]) are gridded precipitation data sets based on observations, CMAP (CPC Merged Analysis of Precipitation [3]) includes satellite and station data, while TRMM (3B43 [4]) and TAMSAT [5] are based on satellite data only. For the gridded data sets, the closest pixel were selected.

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II

The American Journal of Clinical Nutrition

See corresponding editorial on page 681.

Using growth velocity to predict child mortality[1,2]

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ABSTRACT

Background: Growth assessment based on the WHO child growth velocity standards can potentially be used to predict adverse health outcomes. Nevertheless, there are very few studies on growth velocity to predict mortality.

Objectives: We aimed to determine the ability of various growth velocity measures to predict child death within 3 mo and to compare it with those of attained growth measures.

Design: Data from 5657 children <5 y old who were enrolled in a cohort study in the Democratic Republic of Congo were used. Children were measured up to 6 times in 3-mo intervals, and 246 (4.3%) children died during the study period. Generalized estimating equation (GEE) models informed the mortality risk within 3 mo for weight and length velocity z scores and 3-mo changes in midupper arm circumference (MUAC). We used receiver operating characteristic (ROC) curves to present balance in sensitivity and specificity to predict child death.

Results: GEE models showed that children had an exponential increase in the risk of dying with decreasing growth velocity in all 4 indexes (1.2- to 2.4-fold for every unit decrease). A length and weight velocity z score of <-3 was associated with an 11.8- and a 7.9-fold increase, respectively, in the RR of death in the subsequent 3-mo period (95% CIs: 3.9, 35.5, and 3.9, 16.2, respectively). Weight and length velocity z scores had better predictive abilities [area under the ROC curves (AUCs) of 0.67 and 0.69] than did weight-for-age (AUC: 0.57) and length-for-age (AUC: 0.52) z scores. Among wasted children (weight-for-height z score <-2), the AUC of weight velocity z scores was 0.87. Absolute MUAC performed best among the attained indexes (AUC: 0.63), but longitudinal assessment of MUAC-based indexes did not increase the predictive value.

Conclusion: Although repeated growth measures are slightly more complex to implement, their superiority in mortality-predictive abilities suggests that these could be used more for identifying children at increased risk of death. *Am J Clin Nutr* 2016;103:801–7.

Keywords: anthropometry, longitudinal growth, mortality, prediction, WHO growth velocity standards

INTRODUCTION

Growth monitoring is nearly universally practiced in pediatric care worldwide (1) to detect growth faltering and thus intervene accordingly. Various anthropometric indexes, such as indexes based on weight, height, or midupper arm circumference (MUAC),[6] have been suggested, but somewhat different abilities to predict the risk of child deaths were reported (2–8). Despite their hypothesized advantages for early detection of growth problems (9), and thus the possibility to direct life-saving interventions, currently only a few studies have assessed the mortality-predictive ability of longitudinal indicators of poor growth (i.e., growth velocities) (4, 10–12). Those studies used various approaches to define and score growth velocity. To our knowledge, only 1 study (4) looked at the predictive ability of weight velocity z scores (WVZs) by using the WHO standards. O'Neill et al. (4) found that very low weight velocity (z scores <-3) predicted death within 3 mo to some degree. However, they did not include WVZs in their comparative analysis and did not assess length velocity. In addition, changes in MUAC and MUAC z scores were not explored. This encouraged us to expand on the analysis of O'Neill et al. (4) within the same study population to further explore how various velocity measures could predict the risk of death.

We aimed to determine the ability of WVZs and length velocity z scores (LVZs) as well as changes in MUACZ and absolute MUAC (absMUAC) with the use of the WHO Child Growth Standards to predict child death within 3 mo in a cohort of children under the age of 5 y in the Democratic Republic of

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[2] Supplemental Tables 1–4 and Supplemental Figure 1 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

[5] JVdB is deceased.

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[6] Abbreviations used: absMUAC, absolute midupper arm circumference; DRC, Democratic Republic of Congo; LAZ, length-for-age z score (also applied for height-for-age); LVZ, length velocity z score; MUAC, midupper arm circumference; MUACZ, midupper arm circumference z score; ROC, receiver operating characteristic; WAZ, weight-for-age z score; WLZ, weight-for-length z score (also applied for weight-for-height); WVZ, weight velocity z score; Δ, change.

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Congo (DRC). Second, we aimed to compare the mortality-predictive abilities of these indicators with those of attained growth.

METHODS

The primary study was a cohort study carried out in the health zone of Bwamanda in the northwest of the DRC from August 1989 to April 1991. The Bwamanda health zone is 1 of 16 administrative zones within the district of Sud-Ubangi, covering $\sim$10,000 km^2. Details can be found elsewhere (13). In brief, 16 of a total of 52 villages in this health zone were randomly selected and all children $<$5 y living in the selected villages were enrolled. In 6 trimestral survey rounds a total of 5657 children were included (**Figure 1**).

Two trained field staff performed all anthropometric measurements according to a standardized protocol. Birth dates were available from road to health charts (a parent-held record of the child's identify, health, and development) or parent identity papers in 90% of the children. If these records were missing, the birth date was approximated after interviews with the mothers by using a local events calendar. Deaths were recorded in each survey round by interview of the caretakers and checked against death registries in the health centers and funeral registers kept by members of the clergy. After the sixth survey, in April 1991, a special mortality survey was conducted in April 1992 to record deaths up to that time.

Ethics

The Bwamanda study was granted ethical approval from the Tropical Childcare Health Working Group at the University of Leuven (13). For this secondary analysis, ethical approval was obtained from the Ethical Committee at the University of Kinshasa (approval number: ESP/CE/008/14).

Statistical analysis

Data were prepared with SPSS (version 19; IBM Corporation) and analyzed with Stata (version 13; StataCorp LP). We calculated z scores for weight-for-age (WAZ), height/length-for-age (LAZ), weight-for-height/length (WLZ), MUAC-for-age (MUACZ), weight velocity (WVZ), and length velocity (LVZ) using the WHO Child Growth Standards (9, 14, 15). To capture changes in absolute MUAC and MUACZs, the difference between 2 succeeding values was calculated, divided by the exact time period (in mo) between these values, and standardized to an exact 3-mo interval (multiplying the results by 3) [change in absMUAC (ΔabsMUAC), change in MUACZ (ΔMUACZ)]. During checks of data integrity, z scores of attained growth (WAZ, LAZ, WLZ, and MUACZ) exceeding ± 6 z scores and z scores of longitudinal growth (WVZ, LVZ, and ΔMUACZ) exceeding ± 10 z scores were considered implausible and set to missing. Higher cutoffs for weight and length velocity z scores were chosen, because the spread in growth velocity z scores usually is wider than in attained growth measures, even in healthy children (9). Values for ΔabsMUAC were set to missing if they were ± 5 cm within 3 mo and were contrary to weight-based indexes. A total of 154 of 116,452 values (0.1%) for all indexes were discarded. We describe characteristics of nutritional status using median z scores (IQR). A Kaplan-Meier plot was constructed to present survival in this cohort. Reported P values are 2-sided, and $P < 0.05$ was considered significant.

A generalized estimating equation model with a log link, a binomial distribution, an autoregressive correlation structure, and the unique child identification number as a cluster variable was constructed separately for each anthropometric index to assess the risk of death within 3 mo. In line with Briend et al. (16) that negative changes in growth could have negative health consequences even within the "normal range," which was also indicated from a graphical assessment of the observed mortality risk in our data (**Figure 2**), we assessed the distance between expected values (z scores of 0) and observed anthropometric indexes in children with negative growth z scores. Thus, a continuous measure with the degree of negative scores was used in the continuous models. For the categorical models, we used the following categories for WVZ and LVZ: <-3 (severe), ≥ -3 but <-2 (moderate), ≥ -2 but <0 (mild), and ≥ 0 (reference). The Kasongo Project Team (17) found a higher risk of death if deceleration in MUAC was >1 SD. For comparative purposes, we chose the following categories for ΔMUACZ and ΔabsMUAC: <-1 (severe), ≥ -1 but <-0.5 (moderate), ≥ -0.5 but <0 (mild), and ≥ 0 (reference). Because a different effect of growth velocity on mortality would be expected when a child is well nourished compared with when he or she is malnourished already, we additionally report RRs adjusted for nutritional status at the beginning of the assessment period. In addition, the risk according to the age groups 0–6, 7–12, and 13–24 mo was assessed. Receiver operating characteristic (ROC) curves were used to present balance in sensitivity and specificity to predict child death between different thresholds of various growth measures. Analyses were restricted to age ranges available in the WHO standards (WVZ and LVZ: 0–24 mo; ΔMUACZ: 3–60 mo). It is recommended to interpret growth velocity in combination with attained growth. Therefore, we also calculated AUC values according to attained growth (stunted: LAZ <-2; wasted: WLZ <-2) at the beginning of the increment period. For the comparative analysis, we restricted

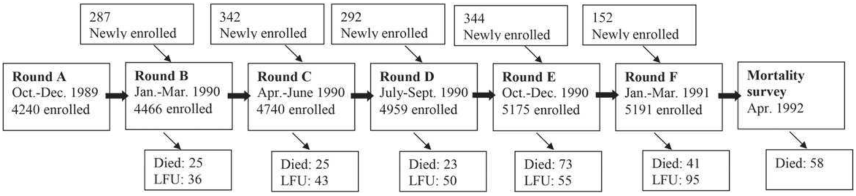

FIGURE 1 Study profile of the cohort study in Bwamanda, Democratic Republic of Congo: 1989–1991. LFU, lost to follow-up.

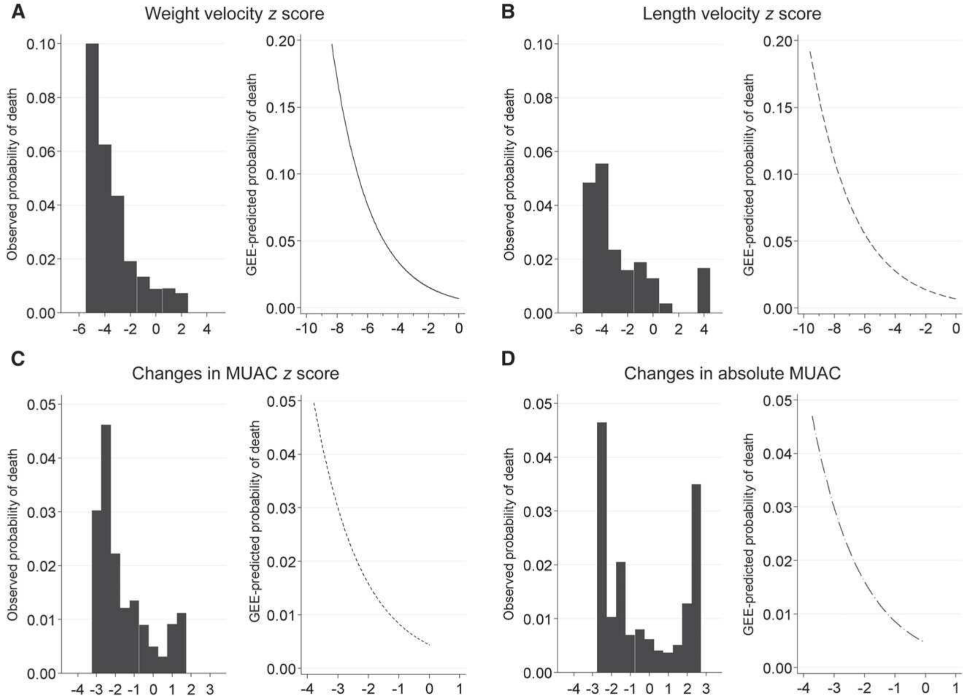

FIGURE 2 Observed and predicted (by using a GEE model) probabilities of death within 3 mo for children included in a cohort study in Bwamanda, Democratic Republic of Congo (1989–1991), for weight velocity *z* score (A; *n* = 2296), length velocity *z* score (B; *n* = 2296), change in MUAC-for-age *z* score (C; *n* = 4451), and changes in absolute MUAC (D; *n* = 4451). GEE, generalized estimating equation; MUAC, midupper arm circumference.

analysis to the age range that is common for all indexes (3–24 mo). AUCs of the different prediction models with the individual child as a cluster variable were contrasted with the "roccomp" function in Stata. Sensitivity (i.e., percentage of children below the threshold among those who are dying), specificity (i.e., percentage of children above the threshold among those who are not dying), positive-predictive value (i.e., percentage of children who are dying among those who are below the threshold), and negative-predictive value (i.e., percentage of children who are not dying among those who are above the threshold) for certain cutoffs are presented. Optimal cutoffs for velocity indexes are defined as the value with the largest product of sensitivity and specificity.

RESULTS

Description of the sample

The study sample comprised 5657 children, of whom 51.3% were male and 98% were from the ethnic group Ngbaka. They were, on average, 36 mo old (SD: 21 mo). Children were measured up to 6 times with, on average, 3 mo between measurements. The median follow-up time was 15 mo. This provided 5294 WVZs, 5086 LVZs, 14,065 changes in MUACZs (*Δ*MUACZ), and 17,851 changes in absMUAC (*Δ*absMUAC) for analysis. The nutritional status of the study sample is summarized in **Table 1**.

Of all of the children, 246 (4.3%) died, 56% of whom were male. For 40 (16%) of these children anthropometric data in the 3-mo period before death were not available. The median age of death was 12 mo (IQR: 5.3, 26.1 mo; **Figure 3**). Causes of death are described elsewhere (18).

Mortality risk by level of anthropometric index

For each anthropometric index, a separate generalized estimating equation regression model was constructed. **Table 2** summarizes the results for all velocity indexes either as continuous or as categorical variables. Independent of the attained growth status at the beginning of the increment period, there was a 1.5-fold increase in the risk of dying for weight velocity, a 1.2-fold increase for length velocity, and a 2.3-fold increase for *Δ*MUACZ for every *z* score falling under the *z* score of 0. For every centimeter negative change in absMUAC within 3 mo, the risk of dying increased by 2.4. An LVZ and a WVZ of less than −3 were associated with 11.8- and 7.9-fold increases, respectively, in the RR of death in the subsequent 3-mo period (95% CIs: 3.9, 35.5, and 3.9, 16.2, respectively). For velocity measures there was no trend in risk of dying according to age category. Estimates according to age category

TABLE 1
Mean nutritional status according to age category of 5657 children <5 y included in a cohort study in Bwamanda, Democratic Republic of Congo: 1989–1991[1]

	0–6 mo		7–12 mo		13–24 mo	
	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*
WAZ	−0.8 ± 1.2	1977	−1.5 ± 1.2	2015	−1.5 ± 1.1	4405
LAZ	−1.2 ± 1.4	1951	−1.9 ± 1.3	1985	−2.4 ± 1.2	4361
WLZ	0.2 ± 1.4	1945	−0.4 ± 1.2	1983	−0.4 ± 1.0	4349
MUACZ	−1.5 ± 1.1	1219	−1.9 ± 1.1	2015	−2.0 ± 1.1	4416
absMUAC	11.6 ± 1.3	1980	12.3 ± 1.1	2015	12.6 ± 1.1	4416
WVZ	−1.0 ± 1.6	700	−1.1 ± 1.5	1501	−0.4 ± 1.5	3092
LVZ	−1.1 ± 2.1	679	−1.0 ± 2.0	1454	−0.8 ± 1.8	2952
ΔMUACZ	−0.4 ± 1.1	157	−0.2 ± 0.8	1472	−0.1 ± 0.8	3246
ΔabsMUAC	1.1 ± 1.4	704	0.1 ± 0.8	1503	−0.01 ± 0.8	3246

[1] absMUAC, absolute midupper arm circumference; LAZ, height/length-for-age *z* score; LVZ, length velocity *z* score; MUACZ, midupper arm circumference-for-age *z* score; WAZ, weight-for-age *z* score; WLZ, weight-for-height/length *z* score; WVZ, weight velocity *z* score; ΔabsMUAC, change in absolute midupper arm circumference; ΔMUACZ, change in midupper arm circumference-for-age *z* score.

and for attained growth indexes can be found in the **Supplemental Tables 1** and **2**). Figure 2 shows the observed and predicted risk curves for all velocity indexes, and **Supplemental Figure 1** shows the predicted risk curves for all attained and velocity indexes.

Comparison of abilities to predict death

Balances between sensitivity and specificity to predict child death at different thresholds are presented with ROC curves in **Figure 4**. Length and weight velocities showed the largest AUCs, with 0.69 and 0.67, respectively. The corresponding values for ΔMUACZ (0.61) and ΔabsMUAC (0.59) were slightly lower ($P < 0.05$). A comparative analysis showed that velocity *z* scores for weight and length performed significantly better in predicting deaths than did their attained counterparts (WAZ: 0.57; $P < 0.05$; LAZ: 0.52; $P < 0.001$). For absMUAC, the attained index was superior to the changes in absMUAC ($P < 0.001$), and for MUACZ no difference was shown ($P = 0.97$) (see Figure 4). AUC values did not differ between those who were ≤6 mo and those who were 7–24 mo old. Restricting analysis to the group of children who were stunted (LAZ <-2) at the beginning of the assessment period, the AUC for length velocity increased to 0.74. In the group of wasted children (WLZ <-2), the AUC for weight velocity increased to 0.87 and for absMUAC to 0.71. Exact AUC values with 95% CIs can be found in **Supplemental Table 3**. Sensitivity, specificity, and positive- and negative-predictive values extended the ROC curve analysis and are presented in **Supplemental Table 4**.

DISCUSSION

This article showed that growth velocity measures can be useful in identifying a high risk of dying among children <5 y old living in the DRC. There was an exponential increase in the risk of dying with decreasing growth velocity in all 4 indexes. Comparing the mortality-predictive abilities of the 4 velocity indexes with the help of ROC curves and contrasting them to those of attained indexes, LVZ, WVZ, and absMUAC performed best. The predictive ability could be improved if attained growth at the beginning of the increment period was taken into account.

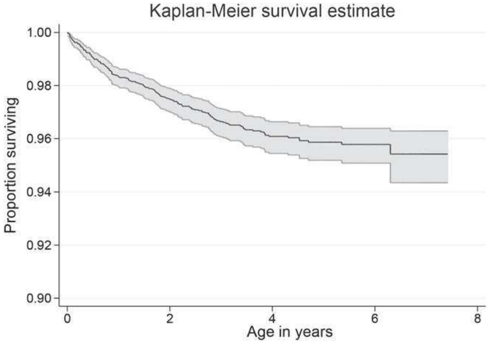

FIGURE 3 Kaplan-Meier survival curve showing survival for all 5657 children under the age of 5 y included in a cohort study in Bwamanda, Democratic Republic of Congo (1989–1991), at different ages (with 95% CIs).

We are aware of only one other publication on the mortality-predictive ability of growth velocity that used WHO Child Growth Standards (4). Although the authors used the same study population as we did, their objective was restricted to weight velocity and noncomparative analyses only. Nevertheless, it is important to compare the velocity indexes to the more traditionally used indexes of attained growth (WAZ, LAZ, and WLZ) to provide a basis for a discussion about their usefulness. Two other studies that investigated the relation between mortality and weight velocity found a superiority of attained indexes (10, 11). Neither of the studies scored velocity according to an external reference and both were carried out within the framework of treatment programs, which could have biased the growth velocities, especially of those children with the worst nutritional status at baseline.

With growth velocities there is usually a trade-off concerning the length of the assessment period. The shorter the period, the higher the (physiologic) variability in growth velocity and the higher the measurement error compared with the actual growth. But the longer a growth velocity period extends, the less relevant it is for the current situation and the more it approaches attained growth, which is more of a cumulative growth measure. This is exemplified and discussed by Bairagi et al. (10), who looked at 1-y growth increments and found an inferiority of weight and height velocities compared with weight-for-age, height-for-age, and weight-for-height. However, they also found that weight velocity was reduced just before death and stated that velocities might be a good discriminator of short-term mortality. This was also emphasized by the Kasongo Project Team (17), where growth deceleration over 2–4 mo increased the mortality risk within the subsequent 100 d, whereas an association between death and attained indexes could not be shown with the same study population (19). Although single velocity measures are often critiqued because of their high variability in consecutive periods, in our analysis the discriminating power of 3-mo velocity *z* scores

TABLE 2

RRs (95% CIs) for mortality for continuous and categorical growth velocity *z* scores of 5657 children <5 y of age included in a cohort study in Bwamanda, Democratic Republic of Congo (1989–1991), after GEE-based regression[1]

Index and category	*n*	RR (95% CI)[2]	Adjusted RR (95% CI)[3]
Continuous			
WVZ	—	1.49 (1.37, 1.62)	1.49 (1.30, 1.71)
LVZ	—	1.41 (1.30, 1.53)	1.24 (1.06, 1.45)
ΔMUACZ	—	1.90 (1.60, 2.26)	2.28 (1.74, 2.99)
ΔabsMUAC	—	1.87 (1.51, 2.31)	2.40 (1.84, 3.14)
WVZ			
Reference	1736	1	1
Mild	2688	1.34 (0.72, 2.51)	1.39 (0.73, 2.66)
Moderate	521	2.36 (1.06, 5.25)	2.65 (1.17, 6.04)
Severe	349	6.70 (3.42, 13.12)	7.92 (3.87, 16.19)
LVZ			
Reference	2741	1	1
Mild	1106	5.81 (2.14, 15.73)	5.82 (2.13, 15.94)
Moderate	622	5.82 (1.89, 17.97)	5.86 (1.86, 18.48)
Severe	603	11.70 (4.13, 33.17)	11.80 (3.92, 35.54)
ΔMUACZ			
Reference	6199	1	1
Mild	4029	1.42 (0.82, 2.46)	1.80 (1.03, 3.15)
Moderate	2347	2.12 (1.20, 3.75)	3.10 (1.69, 5.68)
Severe	1486	3.66 (2.10, 6.38)	6.25 (3.26, 11.98)
ΔabsMUAC			
Reference	8718	1	1
Mild	4214	1.68 (1.01, 2.79)	2.59 (1.54, 4.37)
Moderate	2504	1.97 (1.13, 3.43)	3.80 (2.08, 6.98)
Severe	1325	2.74 (1.50, 5.01)	6.13 (3.18, 11.82)

[1] *z* Score categories for WVZ and LVZ are defined as follows: reference group, ≥ 0; mild, <0 but ≥ -2; moderate, <-2 but ≥ -3; and severe, <-3. For the MUAC-based indexes, these are as follows: reference, ≥ 0; mild, <0 but ≥ -0.5; moderate, <-0.5 but ≥ -1; and severe, <-1. GEE, generalized estimating equation; LAZ, length-for-age *z* score; LVZ, length velocity *z* score; MUAC, midupper arm circumference; WLZ, weight-for-length *z* score; WVZ, weight velocity *z* score; ΔabsMUAC, change in absolute midupper arm circumference; ΔMUACZ, change in midupper arm circumference-for-age *z* score.

[2] For simplicity, continuous variables are converted so that 1 unit is a decrease in 1 *z* score. The RR represents the risk of death with each *z* score falling under the *z* score of 0. For absolute MUAC, the RR represents the risk of death for every centimeter decrease compared with an MUAC of ≥ 12.5 cm.

[3] Adjusted for attained growth (WLZ, LAZ, or MUAC, respectively) at the beginning of the increment period.

for weight and length to predict short-term death was better than that of conventionally used approaches.

It could be argued that growth velocity is more complex than attained growth measures, which could be a challenge for the applicability in the field. For the calculation, at least 2 measurements are needed. This requires more effort and might not be possible in some situations [e.g., in acute (clinical) settings]. Still, even with attained growth measures, assessing a trend of the individual's growth measures rather than 1 separate value alone is more valuable for different reasons (20). A low value at 1 time point cannot discriminate those who are small by constitution from those whose growth curve has decreased recently. In addition, a single low measurement indicates that the child is already obviously malnourished and therefore treatment would be unnecessarily delayed (21). The first signs of growth faltering are growth curves that cross a *z* score line that are decreasing sharply or are flattening (22). However, a visual assessment of growth faltering can be more difficult to perform objectively, especially for those with less experience. This again leads to a disproportionate focus on attained values rather than the development over time (23). Growth velocity scores, however, could be an objective measure to quantify these trends.

Another disadvantage of growth velocity is that, currently, mostly statistical packages have been used to calculate velocity scores. There is also a scarcity of programs and tools for instant plotting of scores. Nevertheless, with rapid advances in the field of mobile technology and the spread of smart-phone use, it should be feasible to create an easy-to-use application to calculate and visualize growth velocity *z* scores, which could guide clinical decision making.

There are methodologic limitations that need to be mentioned. One relates to our definition of velocity in MUAC. No velocity standards for MUAC are available in the currently recommended set of WHO standards and therefore we standardized changes to a 3-mo period. This does not account for the different growth rates at different ages and could dilute our estimates. The absMUAC had a higher AUC than changes in absMUAC or MUACZs in our study. In addition, other studies have not found any advantages of scoring MUAC according to age (24, 25), assuming that a higher selection of younger children, who are also more vulnerable to deaths partly unrelated to nutritional status, adds to the mortality-predictive ability (3, 4). The mechanisms that put younger children at higher risk of dying unrelated to nutritional status might also be one of the reasons for the relatively low AUC values as well as low sensitivity and specificity in our study. However, with a threshold in LVZ of <-1, the sensitivity of death as an outcome was 71% and the specificity 54%. We are not aware of other feasible tests applicable to the population level in this setting that are known to have better predictive effects. Due to the availability of the WHO growth standards we restricted analysis to ages 3–24 mo, thus assessing a relatively young study sample. In a hospital-based study in Niger, the prognostic accuracy of weight-for-height was better in older children (34–59 mo) (6). Within our sample, there was no difference in predictive ability between those aged <6 mo and those aged 7–24 mo. Previous analysis showed that for 13% of the deaths no cause could be cited (13). Those could have been from factors unrelated to nutritional status (e.g., accidents) and thereby dilute our estimates. The main causes of death in our sample were malaria and acute respiratory infections (43%). Even though malnutrition adds vulnerability to these children, these illnesses are not as strongly related to nutrition as, for example, diarrhea and might therefore slightly reduce the AUC, sensitivity, and specificity values in our analysis. To further generalize the findings, predictive abilities of the velocity scores need to be tested in other settings with a different disease pattern. The positive-predictive value is dependent on the prevalence of the outcome. Mortality, although relatively high in our study sample, is still a rare outcome and low positive-predictive values are expected.

The aim of this assessment was to predict the risk of child death on the basis of anthropometric measurements and not to establish a net of causal relations. Therefore, we did not adjust

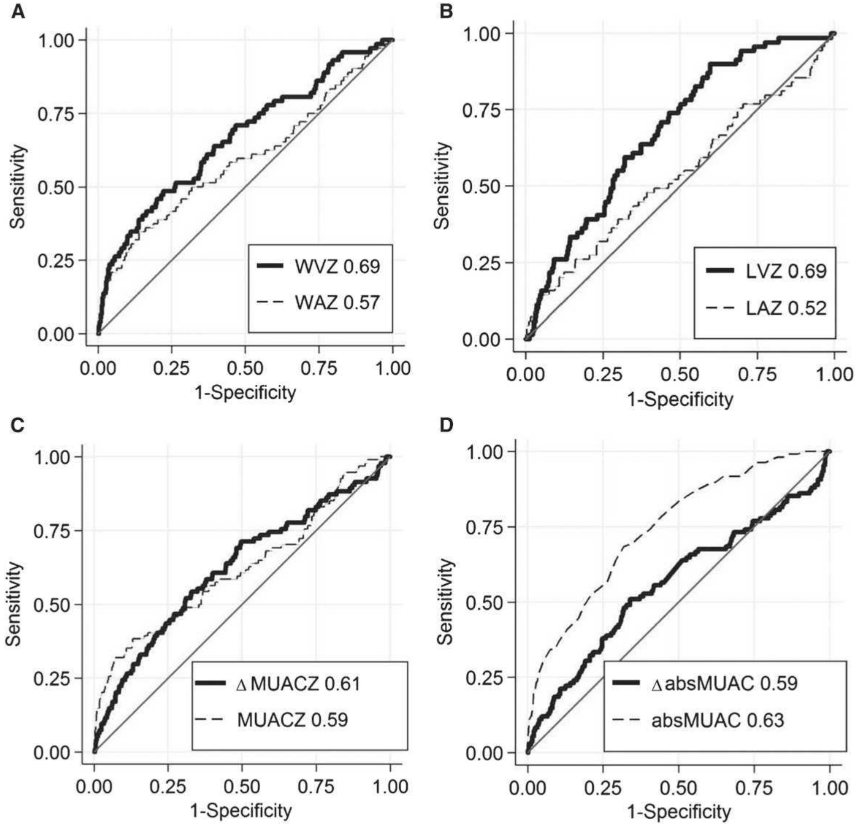

FIGURE 4 Receiver operating characteristic curves for ability to predict death within 3 mo in 2567 children aged 3–24 mo included in a cohort study in Bwamanda, Democratic Republic of Congo (1989–1991), by WVZ and WAZ (A), LVZ and LAZ (B), *Δ*MUACZ and MUACZ (C), and *Δ*absMUAC and absMUAC (D). *z* Scores are calculated with help of the WHO Child Growth Standard. AUC values of the individual predictors are given in the inserts of each plot. absMUAC, absolute midupper arm circumference; LAZ, length-for-age *z* score; LVZ, length velocity *z* score; MUAC, midupper arm circumference; MUACZ, midupper arm circumference *z* score; WAZ, weight-for-age *z* score; WVZ, weight velocity *z* score; *Δ*absMUAC, change in absolute values of midupper arm circumference; *Δ*MUACZ, change in midupper arm circumference *z* score.

our analyses for other factors, such as socioeconomic status or morbidity. The data used are relatively old and the risk of mortality could have changed slightly since then. However, there is a lack of recent studies available that could enable a similar assessment, related to the required methodologic rigor of the anthropometric measurements, sufficient frequency, and length of follow-up combined with a study size of required power to enable assessment of mortality. This study adds knowledge about children who are particularly vulnerable and important to reach with appropriate interventions to reduce child mortality.

In summary, our study provides evidence that growth velocity *z* scores according to WHO standards could be useful and important as a tool in identifying children at high risk of negative health consequences such as death. Growth velocity *z* scores were better able to predict death in the short term (i.e., within 3 mo) than the more conventionally used attained growth counterparts. The combination of growth velocity and attained growth produced the best results. This suggests that WVZs and LVZs could be used more to identify children at risk of dying. However, growth velocity assessment requires repeated measures and is thus slightly more complex to implement than the use of attained growth measures. Repeated anthropometric measurements might be difficult in some settings in which a lack of resources, such as material and competent and motivated staff, or a lack of infrastructure restrict effective actions.

JVdB: designed and conducted the research, provided the database, and consistently provided methodologic and contextual expertise; CS and LTF: performed the statistical analysis; CS: wrote the first draft of the manuscript; and all authors: authors edited the manuscript, contributed in the interpretation of the results, and read and approved the final manuscript (except for JVdB, who died recently). None of the authors had a conflict of interest.

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Online Supplemental Material

Supplemental Table 1: Relative risks for mortality (RR) with 95% confidence intervals (CI) by GEE regression models for continuous Z-scores according to age category for children under the age of five included in a cohort study in Bwamanda, DRC, 1989-1991

Index	**RR (95% CI)**[a]				
	All children	**0-6 months**[b]	**7-12 months**	**13-24 months**	**24-60 months**
WVZ	1.49 (1.37, 1.62)	1.54 (1.28, 1.84)	1.38 (1.10, 1.74)	1.41 (1.18, 1.68)	-
LVZ	1.41 (1.30, 1.53)	1.40 (1.22, 1.60)	1.48 (1.26, 1.74)	1.23 (1.00, 1.51)	-
ΔMUACZ	1.90 (1.60, 2.26)	0.68 (0.22, 2.14)	1.57 (0.89, 2.76)	1.58 (1.05, 2.39)	2.13 (1.63, 2.78)
ΔabsMUAC[c]	1.87 (1.51, 2.31)	-	-	-	-
WAZ	1.58 (1.32, 1.87)	1.50 (0.99, 2.30)	1.38 (0.95, 2.00)	1.05 (0.71, 1.56)	2.07 (1.58, 2.73)
LAZ	1.19 (0.02, 1.39)	1.27 (0.85, 1.88)	1.18 (0.84, 1.66)	0.92 (0.69, 1.24)	1.78 (1.29, 2.46)
WLZ	1.61 (1.44, 1.79)	1.23 (1.03, 1.47)	1.29 (0.74, 2.27)	1.46 (0.91, 2.34)	2.51 (1.80, 3.49)
MUACZ	1.59 (1.29, 1.95)	0.54 (0.36, 0.81)	1.33 (0.83, 2.13)	1.06 (0.74, 1.52)	2.14 (1.48, 3.11)
MUAC[c]	2.60 (2.26, 3.00)	-	-	-	-

[a] For simplicity, continuous variables are converted so that one unit is one Z-score decrease. RR represents risk of death with every Z-score falling under the Z-score of zero. For absolute MUAC RR represents risk of death for every centimeter decrease compared to a MUAC of 12.5 cm or above.

[b] For the indices ΔMUACZ and MUACZ this age category is 3-6 months, because the WHO Growth Standards for MUAC only starts from 3 months of age.

[c] The GEE model according to age category did not achieve convergence.

Abbreviations: GEE, generalized estimating equation; LAZ, height/length-for-age Z-score; MUAC, mid-upper-arm-circumference; MUACZ, mid-upper-arm-circumference-for-age Z-score; WAZ, weight-for-age Z-score; WLZ, weight-for-height/length Z-score

Online Supplemental Material

Supplemental Table 2: Relative risks for mortality (RR) with 95% confidence intervals (CI) by GEE regression models for categorical Z-scores for attained anthropometric indices of children under the age of five included in a cohort study in Bwamanda, DRC, 1989-1991

Index	Category[a]	n	RR [b]	95% CI
WAZ	Reference	1764	1	
	Mild	14112	0.70	0.39, 1.25
	Moderate	4560	0.79	0.41, 1.51
	Severe	1876	2.94	1.59, 5.42
LAZ	Reference	853	1	
	Mild	8202	0.51	0.27, 0.96
	Moderate	6969	0.33	0.17, 0.64
	Severe	6055	0.57	0.30, 1.09
WLZ	Reference	11404	1	
	Mild	11681	1.30	0.92, 1.85
	Moderate	693	3.45	1.89, 6.28
	Severe	169	16.57	9.55, 28.75
MUACZ	Reference	446	1	
	Mild	9695	2.35	0.33, 16.77
	Moderate	6372	2.09	0.29, 15.11
	Severe	3166	6.64	0.93, 47.47
MUAC	Reference	16774	1	
	Moderate	4201	1.98	1.3, 3.03
	Severe	2349	7.31	5.13, 10.42

[a] Z-score categories for WAZ, LAZ, WLZ, MUACZ are defined as: 1) reference group: ≥0; 2) mild: <0 but ≥-2; 3) moderate: <-2 but ≥-3; 4) severe: <-3; categories for MUAC are 1) reference: ≥12.5cm; 2) moderate: <12.5 but ≥11.5cm; 3) severe: <11.5cm

Abbreviations: GEE, generalized estimating equation; LAZ, height/length-for-age Z-score; MUAC, mid-upper-arm-circumference; MUACZ, mid-upper-arm-circumference-for-age Z-score; WAZ, weight-for-age Z-score; WLZ, weight-for-height/length Z-score

Online Supplemental Material

Supplemental Table 3: Area under the curves with 95% CI for various anthropometric indices to predict death within three months based on logistic regression models with individuals as clustering variable. Estimates are reported for all children 3-24 months and according to age category.

Index	**AUC (95%CI)**		
	All	**<6 months**	**>6months**
LVZ	0.69 (0.64, 0.75)	0.69 (0.53, 0.86)	0.69 (0.63, 0.75)
WVZ	0.67 (0.60, 0.74)	0.68 (0.48, 0.88)	0.67 (0.59, 0.75)
MUAC	0.63 (0.56, 0.69)	0.61 (0.48, 0.74)	0.62 (0.55, 0.69)
MUACZ	0.59 (0.53, 0.66)	0.61 (0.48, 0.73)	0.60 (0.53, 0.67)
WAZ	0.57 (0.50, 0.64)	0.51 (0.38, 0.64)	0.60 (0.53, 0.68)
WLZ	0.56 (0.49, 0.63)	0.56 (0.43, 0.69)	0.58 (0.50, 0.66)
ΔMUACZ	0.61 (0.53, 0.68)	0.63 (0.47, 0.79)	0.60 (0.52, 0.68)
ΔabsMUAC	0.59 (0.52, 0.66)	0.60 (0.38, 0.81)	0.59 (0.51, 0.67)
LAZ	0.52 (0.45, 0.58)	0.50 (0.37, 0.64)	0.54 (0.47, 0.62)

Abbreviations: ΔabsMUAC, changes in absolute mid-upper-arm-circumference; ΔMUACZ, changes in mid-upper-arm-circumference-for-age Z-score; AUC, area under the receiver operating characteristic curves; LAZ, height/length-for-age Z-score; LVZ, length velocity Z-score; MUAC, absolute mid-upper-arm-circumference; MUACZ, mid-upper-arm-circumference-for-age Z-score; WAZ, weight-for-age Z-score; WLZ, weight-for-height/length Z-score; WVZ, weight velocity Z-score

Supplemental Table 4: Sensitivity, specificity and predictive values for selected cut-off points in different anthropometric indices in children under the age of five included in a cohort study in Bwamanda, DRC, 1989-1991

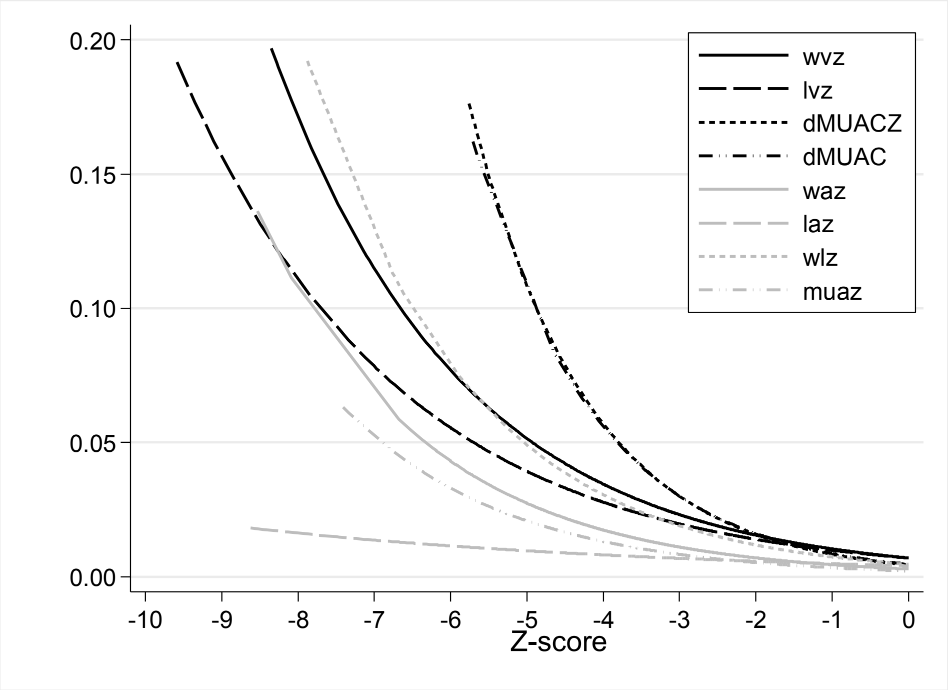
Index (cut-off[a])	Sensitivity	Specificity	Positive predictive value	Negative predictive Value
WVZ (-1) [a]	61.1	62.7	2.2	99.2
WVZ (-2)	40.3	83.9	3.3	99.0
LVZ (-1)	71.4	54.4	2.1	99.3
LVZ (-2) [a]	41.4	76.1	2.4	98.9
ΔabsMUAC (0) [a]	63.9	48.9	0.8	99.6
ΔabsMUAC (-1)	13.9	92.6	1.1	99.4
ΔMUACZ (0) [a]	72.3	44.2	0.9	99.6
ΔMUACZ (-1)	24.5	89.5	1.5	99.4
WAZ (-2)	46.2	71.3	1.1	99.5
LAZ (-2)	56.4	41.0	0.7	99.2
WLZ (-2)	17.7	96.5	3.2	99.4
MUACZ (-2)	59.0	51.6	0.8	99.5
MUAC(12.5)	64.8	71.9	1.5	99.7

[a] Statistically suggested cut-off threshold for WVZ (-1.11), LVZ (-1.92), ΔabsMUAC (0.29) and ΔMUACZ (-0.19) were approaching the cut-offs -1, -2 and 0 respectively and are therefore not reported separately. Optimal cut-offs for growth velocity indices are defined by the program cutpt in STATA as largest product of sensitivity and specificity. For attained indices the commonly used cut-off for malnutrition (-2 Z-score) is used for comparative purposes.

Abbreviations: ΔabsMUAC, changes in absolute mid-upper-arm-circumference; ΔMUACZ, changes in mid-upper-arm-circumference-for-age Z-score; LAZ, height/length-for-age Z-score; LVZ, length velocity Z-score; MUAC, absolute mid-upper-arm-circumference; MUACZ, mid-upper-arm-circumference-for-age Z-score; WAZ, weight-for-age Z-score; WLZ, weight-for-height/length Z-score; WVZ, weight velocity Z-score

Online Supplemental Material

Supplemental Figure 1: Predicted probabilities of death within three months by GEE model for children included in a cohort study in Bwamanda, DRC, 1989-1991 for all attained growth and growth velocity indices. Abbreviations: absMUAC, absolute mid-upper-arm-circumference; dMUAC, changes in absolute mid-upper-arm-circumference; dMUACZ, changes in mid-upper-arm-circumference-for-age Z-score; LAZ, height/length-for-age Z-score; LVZ, length velocity Z-score; MUACZ, mid-upper-arm-circumference-for-age Z-score; WAZ, weight-for-age Z-score; WLZ, weight-for-height/length Z-score; WVZ, weight velocity Z-score



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ORIGINAL ARTICLES

Predicting Undernutrition at Age 2 Years with Early Attained Weight and Length Compared with Weight and Length Velocity

Catherine Schwinger, MA[1], Lars T. Fadnes, PhD[1,2], Sanjaya K. Shrestha, MD[1,3], Prakash Sundar Shrestha, MD[4], Ram Krishna Chandyo, PhD[4], Binob Shrestha, BPH[3], Manjeswori Ulak, MD[4], Ladaporn Bodhidatta, MD[5], Carl Mason, PhD[5], and Tor A. Strand, PhD[1,6]

Objective To estimate the abilities of weight and length velocities vs attained growth measures to predict stunting, wasting, and underweight at age 2 years.

Study design We analyzed data from a community-based cohort study (The Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development study [MAL-ED] study) in Bhaktapur, Nepal. A total of 240 randomly selected children were enrolled at birth and followed up monthly up to age 24 months. Linear and logistic regression models were used to predict malnutrition at 2 years of age with growth velocity z scores at 0-3, 0-6, 3-6, 6-9, 6-12, and 9-12 months (using the World Health Organization Growth Standards) or attained growth at 0, 3, 6, and 12 months as predictors.

Results At age 2 years, 4% of the children were wasted, 13% underweight, and 21% stunted. Children who were malnourished at age 2 years had lower mean growth z scores already at birth and throughout the study period. Anthropometric indicators in infancy were significant predictors for growth at the age of 2 years during most periods and at most ages in infancy. Weight-for-age z score, length-for-age z score, and weight-for-length z score at age 12 months had excellent areas under the curve (91-95) to predict the value of the same indicator at age 24 months. Maximum area under the curve values for weight and length velocity were somewhat lower (70-84).

Conclusions Growth measured at one time point in infancy was better correlated with undernutrition at age 2 years than growth velocity. *(J Pediatr 2016;■■:■■-■■).*

The first 1000 days of life, starting from conception until around the child's second birthday, increasingly are recognized as essential for child growth, with inadequate growth often indicating serious and potentially irreversible consequences.[1-5] Childhood undernutrition is estimated to contribute to 45% of all the deaths of children younger than 5 years globally[6]; however, early anthropometric deficits also are associated with long-term consequences for health and educational attainment, extending into adulthood and even into the next generation.[3,4,7-9] Thus, the first 1000 days have been suggested to be critical for the prevention of malnutrition.

Any measure of inadequate attained growth used for identifying children at risk of adverse events has the inherent limitation that the child already is stunted or wasted to a varying degree, impeding possibilities for prevention and impacts of nutritional interventions. Longitudinal growth measures such as weight velocity or weight gain have a theoretical advantage as they present a picture of the current growth trend, whereas attained growth is a cumulative measure of an altered growth rate that leads to a recognizable malnourished state.[10,11] Few studies have estimated the extent to which measures of longitudinal growth early in life can predict future nutritional status. Although weight at 12 months predicted stunting at 36 months equally well as weight gain from 3 to 6 months in children living the Republic of Congo,[12] the detection at an earlier age with weight gain could be advantageous. Iannotti et al[13] found that weight gain during the first month of life predicted attained weight and length at 1 year of age, but they did not compare it with attained growth measures. In a study in Peru, no advantage of weight gain assessment to predict underweight at 24 months of age was found compared with attained weight assessment.[11] Length gain was not found predictive of wasting or stunting at later ages in Peru and Guatemala.[11,14] These studies

AUROC	Areas under the receiver operating characteristic curves
LAZ	Length-for-age z score
LVZ	Length velocity z score
MAL-ED	The Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development study
WAZ	Weight-for-age z score
WHO	World Health Organization
WLZ	Weight-for-length z score
WVZ	Weight velocity z score

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all had different approaches to define weight and length gain.

The World Health Organization (WHO) published growth velocity standards in 2009,[15] offering the opportunity to score weight and length gain according to age and sex. Two studies have used the WHO growth velocity standards to assess the relationship with future nutritional status, but one focused on the association with obesity and did not compare the predictive ability of weight velocity with other growth measures,[16] and the other studied children with cystic fibrosis in the US.[17] Studying growth velocities could help to identify critical time windows for prevention or early interventions of undernutrition.[7,8,18] We therefore aimed to estimate the abilities of weight and length velocity z scores in infancy (according to the WHO Child Growth Standards) to predict stunting, wasting, and underweight at the age of 2 years and compare them with those of the attained growth measures weight-for-age z score (WAZ), length-for-age z score (LAZ), and weight-for-length z score (WLZ).

Methods

The Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development study (MAL-ED) was conducted in 8 countries (Bangladesh, Brazil, India, Nepal, Pakistan, Peru, South Africa, and Tanzania). For this analysis, data from the Nepal site were used. The study in Nepal was carried out in the Bhaktapur municipality, located 15 km east of the capital Kathmandu and at about 1400 m above sea level. Bhaktapur had a population of about 78 000 people in 2010.[19] Hinduism and Buddhism are the predominant religions practiced in this municipality, and community members are primarily distinguished by the traditional caste system. Tourism and agriculture are the main sources of livelihoods. The climate is humid subtropical, with a hot and wet monsoon season from May to September and a cool and dry season from October to March. A pilot study in 2010 of 100 households with children 24-36 months of age showed that although socioeconomic indicators compared favorably with national averages, 40% of children were stunted.[19]

The MAL-ED study is a prospective cohort study. During enrollment from June 2010 to February 2012, 668 deliveries were recorded, with 97% occurring at the hospital. Deliveries outside the hospital were registered by fieldworkers surveying the households. Households with recent deliveries were selected randomly on a weekly basis. The number for children selected each week was based on a prestudy census, which informed the expected birth rate, and the target sample size defined for all 8 sites of the MAL-ED study (ie, to arrive at >200 children enrolled during a period of 2 years).[20]

With this weekly number, 275 children were selected, and all caretakers of were informed about the MAL-ED study. If informed consent was given, households were screened for enrollment. Participants were excluded if the family had plans to move out of the catchment area for >30 consecutive days during the first 6 months of follow-up; the mother was <16 years of age; the mother had another child already enrolled in the MAL-ED study; the child was not a singleton (ie, twins, triplets); the child's guardian failed to provide signed informed consent; weight at birth or enrollment was <1500 g; or the infant had any of the following indications of serious disease: hospitalization for something other than a typical healthy birth; severe or chronic condition diagnosed by a medical doctor (eg, neonatal disorder; renal, liver, lung, and/or heart disease; congenital conditions); or enteropathies diagnosed by a medical doctor. In total, 240 children were enrolled. Ethical approval for the study was obtained from the Nepal Health Research Council and the Walter Reed Institute of Research (Silver Spring, Maryland). All caretakers of the participating children provided informed consent. This subanalysis was approved by the Central Board of the MAL-ED study.

At enrollment (within 17 days after delivery), well-trained fieldworkers interviewed caretakers on the child's date of birth, birth weight (available for 97% of the children), breastfeeding status, and sociodemographic characteristics of the household and took anthropometric measurements using standardized techniques (length, weight, and head circumference). Thereafter, monthly anthropometric measurements were taken until the age of 2 years, resulting in 24 anthropometric measurements for each child. Length was measured with a standard length board (ShorrBoard; Weigh and Measure, LLC, Olney, Maryland), weight with an infant scale (seca, Chino, California), and head circumference with a nonstretch synthetic tape (seca). Each month a supervisor duplicated 10% of the measurements within 24 hours. The interobserver technical error of measurement for these repeated measurements was 0.343 for height and 0.070 for weight.

Data Management and Statistical Analyses

If concern or suspicion was articulated during measurements, raw values were plotted on growth curves. In case of implausible discrepancies to the previous values, measurements were redone immediately. All data were double-entered into a local database, and discrepancies and completeness were checked by the site data entry supervisor. If necessary, remeasurements were taken within the shortest time possible, generally within 2 days. Data were sent to and stored at the Data Coordinating Center at Fogarty International Center (Bethesda, Maryland), which did an external quality control and marked values that exceeded plausible ranges within subsequent measurements (increments >1.5 kg for weight, >3.5 cm for length, and >2 cm for head circumference) for review by the study site. The Data Coordinating Center made Web-based issue logs available to the local teams to enable prompt corrections. In addition, monthly reports provided the sites with feedback on data quality.

Data were analyzed with Stata (version 13; StataCorp LP, College Station, Texas). We calculated WAZ, WLZ, LAZ, weight velocity z score (WVZ), and length velocity z score (LVZ) according to the WHO Child Growth Standards.[15,21] We defined wasting, stunting, and underweight as z score ≤–2 for WLZ, LAZ, and WAZ, respectively.

For the description of the sample, we report percentages, means with SDs or medians with IQRs as appropriate. For each anthropometric index, we built a separate simple logistic or linear regression model, depending on the format of the outcome, ie, WAZ, WLZ, or LAZ at 2 years of age as continuous variable (linear) or as dichotomous variable with a cutoff at −2 z scores (logistic). The predictor variables, all tested in the regression models one at a time, were the individual growth velocity z scores, for 3- and 6-month increments at the ages 0-3, 0-6, 3-6, 6-9, 6-12, and 9-12 months as well as measures of attained growth at the ages 0, 3, 6, and 12 months. Because weight at birth was lacking for 7 children (3%), we imputed values for birth weight for those by regressing birth weight from the earliest weight measurements. Length was not measured at birth and therefore length within 17 days was used as proxy for birth-length for all 240 children. For all other target ages, we allowed for a deviation of ±3 days, eg, between 2.9 and 3.1 months at the 3-month visit.

For linear regression models, the R-square is reported in addition to the regression coefficients. For logistic regression models, receiver operating characteristic curves depict the balance between sensitivity and specificity at different threshold levels. ORs and areas under the receiver operating characteristic curves (AUROC) are reported.

Table I. **Selected characteristics of the study sample of 240 children aged 0-24 months living in Bhaktapur municipality, Nepal, enrolled into the MAL-ED study, 2010-2012**

	n	Values
Male sex, %	240	54
Education, father		
Ever gone to school, %	104	95
Median duration of education, y (IQR)	99	9 (6-10)
Education, mother		
Ever gone to school, %	236	94
Median duration of education, y (IQR)	221	10 (6-10)
Median household incomes, median (IQR)*	236	12 (8-20)
Electricity available, %	236	100
Access to flush toilet, %	236	94
Owning a television, %	236	94
Owning a computer, %	236	25
Owning a refrigerator, %	236	25
WAZ, mean (SD)		
0-6 mo	2088	−0.52 (1.00)
7-12 mo	1353	−0.52 (0.99)
13-24 mo	2653	−0.82 (0.93)
LAZ, mean (SD)		
0-6 mo	1855	−0.57 (0.98)
7-12 mo	1354	−0.77 (0.93)
13-24 mo	2653	−1.20 (0.93)
WLZ, mean (SD)		
0-6 mo	1851	−0.12 (1.11)
7-12 mo	1353	−0.15 (1.01)
13-24 mo	2653	−0.33 (0.91)

*Nepali rupees per month in thousands, corresponding to about 144 US$ (IQR 95-240).

Results

In total, 240 children were enrolled into the study, of which 130 (54%) were male and 233 (97%) delivered at a health facility. Characteristics of the study sample are summarized in Table I. The majority of the mothers (90%) initiated breastfeeding within the first 24 hours after childbirth. Introduction of solid foods was on average at 3 months, although supplementary liquids were given earlier. On an average, exclusive breastfeeding lasted 1 month (IQR 0.6-3.2 months) and total breastfeeding duration 24 months (IQR 23-26 months). A toilet with a flush to a piped sewer system was available in 94% of the households, although 46% of those shared facilities with up to 10 other households. The median monthly household income was approximately 12 000 Nepali rupees (IQR 8000-20 000), corresponding to about 144 US$ (IQR 95-240).

At the age of 2 years, 4% of the children were classified as wasted (WLZ ≤ -2), 13% as underweight (WAZ ≤ -2), and 21% as stunted (LAZ ≤ -2). Figure 1 displays the proportion of children who were wasted, underweight, and stunted according to age and correspondingly for low weight and length velocity z scores (≤ -2) in Figure 2 (available at www.jpeds.com). Mean weight and length velocity z scores for the whole study sample were above the standard mean in the first 3 months but declined with age until about 5 and 13 months, respectively, and improved marginally thereafter. Indicators for mean attained growth (WAZ, WLZ, and LAZ) were low already at birth, improved slightly until about 5 months of age, and deteriorated continuously after that age.

When we compared children who were underweight or stunted at 2 years of age with those who were not, it showed that differences in mean z scores for WAZ and LAZ were apparent already at birth and remained throughout the study period up to 2 years of age (Figure 3, B and D). For those underweight at 2 years of age, mean weight velocity z scores were

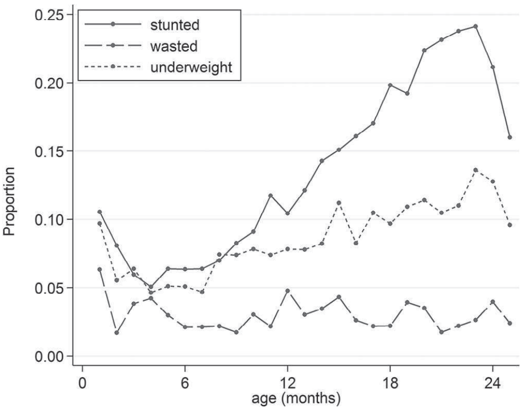

Figure 1. Proportion of 240 children enrolled in the MAL-ED study, Nepal, being stunted, wasted, or underweight according to age. Stunting is defined as LAZ < −2, wasting as WLZ < −2, and underweight as WAZ < −2, according to the WHO Child Growth Standards.

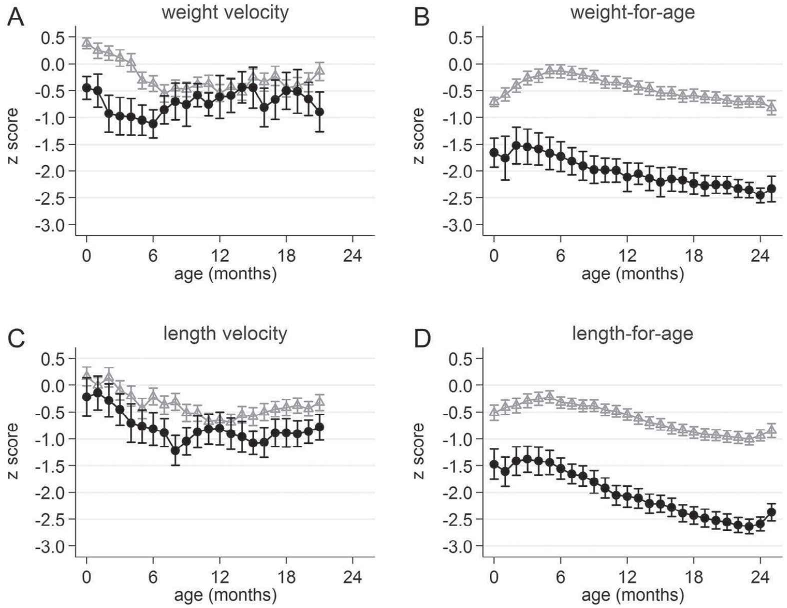

Figure 3. Mean z scores for different anthropometric indices with 95% CI over time from age 0 to 24 months according to **A** and **B,** underweight at 24 months or **C** and **D,** stunting at 24 months (yes = *black circles*; no = *gray triangles*) of 240 children enrolled in the MAL-ED study, Nepal. Underweight and stunting is defined as WAZ and LAZ < –2, respectively. All velocity z scores use a 3-month increment and are plotted at the beginning of the growth period, eg, a velocity z score plotted at 3 months is the velocity for the period from 3 to 6 months.

lower for the periods starting during the first 6 months of life (**Figure 3**, A). For those stunted at 2 years of age, length velocity z scores were lower throughout the first 2 years of life. However, there were some periods where there was a substantial overlap of the 95% CIs of the growth velocity estimates (**Figure 2**, C).

Linear and logistic regression models showed that most periods of the different anthropometric indicators were significant predictors for growth at the age of 2 years. A general trend could be observed, ie, indicators of attained growth during the first year predicted attained growth at 2 years of age better than velocity z scores, **Tables II-IV** (**Tables III** and **IV** available at www.jpeds.com). LAZ at 12 months could explain 75% of the variation in LAZ at 24 months, whereas LVZ from 6 to 12 months only explained 24%. For WLZ at 2 years, the R^2 of WLZ at 6 months was 0.50 and for WVZ between 0 and 6 months 0.28. Also, more variation of WAZ at 2 years was explained by an indicator of attained growth (WAZ at 12 months, $R^2 = 0.66$), than by a velocity z score (WVZ 0-6 months, $R^2 = 0.44$). The value for AUROC ranged between 91 and 95 for WAZ, LAZ, and WLZ at 12 months and was somewhat lower for weight and length velocity at different time periods (70-84). No difference between girls and boys could be observed. The trend that the older the children, the better the ability to predict nutritional status at 2 years of age, as seen in indicators of attained growth, did not appear in indicators for growth velocity.

Discussion

In this study, indicators of attained growth during the first year of life predicted stunting, wasting, and underweight at age 2 years better than velocity z scores. WAZ, LAZ, and WLZ at age 12 months had excellent AUROC (91-95) to predict the value of the same indicator at age 24 months. Maximum AUROC values for weight and length velocity in different growth periods were somewhat lower (70-84).

In agreement with our study results, Simondon et al[12] found weight measured at one time point (12 months) to be most predictive of stunting at age 1-5 years. Nevertheless, in their study, weight velocity from 3 to 6 months had equally high sensitivity and specificity values. They used predicted quarterly weight gains as velocity measure, which does not take measurement error and transient weight losses into account. Temporary weight loss, eg, weight loss caused by disease with catch-up growth during recovery, is well described in literature. Advantages of predictions by modeled growth velocity become clear, although the disadvantage for practical settings, where only raw measurement values are used, needs to be emphasized.

Table II. Early attained growth and growth velocity z scores on LAZ or stunting (LAZ < −2) at 24 months

		Linear regression		Logistic regression	
	n	Coefficient (95% CI)	R^2	OR (95% CI)	AUROC
WVZ, mo					
0-3	227	0.33 (0.23, 0.44)	0.14	0.46 (0.32, 0.65)	0.71
0-6	221	0.42 (0.32, 0.52)	0.23	0.37 (0.25, 0.54)	0.75
3-6	160	0.28 (0.17, 0.39)	0.13	0.58 (0.39, 0.85)	0.72
6-9	183	0.26 (0.13, 0.39)	0.08	0.56 (0.39, 0.82)	0.68
6-12	181	0.41 (0.28, 0.55)	0.17	0.43 (0.27, 0.68)	0.73
9-12	218	0.20 (0.06, 0.33)	0.04	0.84 (0.59, 1.18)	0.55
LVZ, mo					
0-3	186	0.16 (0.05, 0.27)	0.04	0.74 (0.53, 1.02)	0.61
0-6	182	0.22 (0.10, 0.35)	0.07	0.65 (0.43, 0.91)	0.65
3-6	160	0.13 (0.01, 0.24)	0.03	0.80 (0.58, 1.10)	0.59
6-9	183	0.28 (0.16, 0.40)	0.11	0.47 (0.32, 0.70)	0.70
6-12	181	0.44 (0.33, 0.56)	0.24	0.29 (0.18, 0.47)	0.79
9-12	218	0.24 (0.13, 0.36)	0.07	0.54 (0.37, 0.77)	0.67
WAZ, mo					
0	227	0.27 (0.14, 0.41)	0.07	0.47 (0.32, 0.69)	0.68
3	188	0.39 (0.26, 0.51)	0.17	0.37 (0.24, 0.56)	0.74
6	188	0.48 (0.37, 0.59)	0.27	0.27 (0.16, 0.45)	0.78
12	223	0.56 (0.47, 0.66)	0.37	0.25 (0.16, 0.40)	0.81
LAZ, mo					
0	227	0.40 (0.29, 0.51)	0.20	0.37 (0.26, 0.54)	0.76
3	188	0.54 (0.43, 0.65)	0.32	0.22 (0.13, 0.39)	0.82
6	188	0.82 (0.72, 0.92)	0.57	0.08 (0.04, 0.18)	0.90
12	223	0.87 (0.80, 0.93)	0.75	0.02 (0.01, 0.07)	0.95
WLZ, mo					
0	224	−0.13 (−0.24, −0.01)	0.02	1.16 (0.84, 1.60)	0.57
3	188	−0.02 (−0.14, 0.10)	0.00	0.92 (0.67, 1.27)	0.50
6	188	0.13 (0.01, 0.26)	0.02	0.73 (0.51, 1.04)	0.58
12	223	0.23 (0.11, 0.34)	0.07	0.67 (0.49, 0.92)	0.61

In children with cystic fibrosis in the US, attained growth measures (WAZ and LAZ) at age 4 months predicted low WAZ and LAZ (<10th percentile) at 24 months better than WVZ and LVZ at different age periods[17] when the WHO Child Growth Standards were used. The authors argue that one reason why attained growth indictors performed better might have been that growth velocity z scores were more sensitive to the therapy of cystic fibrosis. Although velocity z scores increased after the introduction of therapeutic measures, they were still insufficient for most children. They would have needed to be positive for a sufficient amount of time to counterbalance completely the growth deficit seen in attained growth measures. Similar reasons could have interfered with the predicting ability of weight and length velocity z scores in our study, because children found sick were referred to health services and treated. This explanation is strengthened by the findings of a study with children from all 8 sites of the MAL-ED study, in which rates of growth defined by a linear piecewise model were found to be greater after periods with high enteropathogen detections. Still, values for indicators of attained growth were decreasing with age.[22]

In the study of Ruel et al,[14] anthropometric indicators were ranked in the same order for their ability to predict stunting at age 3 years as they were in our study, ie, LAZ performed best followed by WAZ, WVZ, LVZ, and WLZ. Attained growth indicators performed better in children aged 6 months compared with 3 months. For children with cystic fibrosis in the US, early attained weight and length (at 4 months) was more predictive than at later ages (6, 12, 18 months), but in their study sample, more children were classified as undernourished in early ages, because the underlying cause (cystic fibrosis) was treated. In our study, the proportion of malnourished children increased with increasing age. This continuous deterioration in nutritional status typically is seen in low-income countries,[2] leading to better predictions of future nutritional status with increasing age as seen in our analysis.

Our hypothesis, that velocity z scores would perform better to predict future growth, was based on the theoretical idea that low growth rates would accumulate and in the end lead to a detectable low nutritional status. This was described in a study in Guatemala,[11] where mean weight-for-age of the study sample was not below standard mean before 5 months, although weight gains already were lower much earlier. Even though growth velocity z scores during several time periods significantly predicted growth at age 2 years in our study, they performed worse than attained growth measures. In earlier analyses, however, we have shown that growth velocities were better than attained growth to predict child death within 3 months,[23] supported by other studies where growth velocity was lower in the time period just before death whereas no association was shown with attained indices.[24,25] We also found that velocity z scores could depict changes in growth according to the well-known seasonal cycle of food availability in an area heavily depending on subsistence farming, which was not apparent in attained growth.[26] This might point to the important advantage of growth velocities over attained growth measures of being able to capture current risk factors, thus representing the current risk profile and better predict short term health consequences.

Differences in mean z scores for weight-for-age and length-for-age already were apparent at birth, emphasizing the importance of intrauterine life and other prenatal factors for optimal growth development. Differences remained throughout the study period, with persistently lower weight and length velocity z scores in those children that were malnourished at age 2 years further augmenting the difference in attained growth. This gives an indication that infancy is still an important period to avoid or hamper critical growth deficits at later ages.

The study has several strengths, including being community-based, with random selection of the children, and only a few children lost to follow-up (5% at the end of the study), reducing the possibility of selection bias. Most children were measured within accurate 1-month intervals with a thorough validation procedure, allowing for a very strict definition of target ages (±3 days) for this analysis. Compared with this, the study by Heltshe et al[17] allowed for ±9 days' deviation; however, length was not measured at birth, and length measurements within the first 17 days were used as proxy for birth length. Therefore, length velocity z scores in the periods 0-3 and 0-6 months are artificially low as the result of less time to grow in these 3- and 6-months periods, which could have influenced the predictive abilities in these age periods. Nevertheless, additional analyses, in which we estimated birth length from regression lines based on the 2 subsequent length values, did not change the results substantially (data not shown). Low goodness of fit of the models of LVZ also in later age periods (assessed by R^2 and AUROC values) supports the robustness of our findings.

Our results show that measuring growth at one time point in infancy seems to be sufficient to distinguish between those at high risk of becoming malnourished and those at lower risk. For low-income settings with high prevalence of malnutrition, where resources are often scarce, simplicity of growth monitoring is likely to encourage health personnel to actually do it. The same conclusion is given by Piwoz et al,[11] where weight gain was the best predictor for weight-for-age at 12 months, but because of the favored simplicity, the authors advised using attained weight for monitoring programs. Malnutrition, however, remains an enormous problem in low-income countries with serious consequences and efforts need to be put into optimizing detection and treatment of it. We would like to point out the value of assessing growth cross-sectionally and longitudinally, both reflecting different aspects of growth. The decision on which of the methods to use needs to be evaluated carefully, taking into account the purpose and the resources available. Despite the possible drawbacks of growth velocities concerning their practicality at present,[23,27] because their greater sensitivity to capture influencing factors,[26] their potential to predict short-term consequences,[23] and their strength to reflect the dynamics of growth rather than status, we think that they could be a valuable tool for research in the field of malnutrition that merits further study. ■

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Table III. Early attained growth and growth velocity z scores on WLZ or wasting (WLZ < −2) at age 24 months

		Linear regression		Logistic regression	
	n	Coefficient (95% CI)	R^2	OR (95% CI)	AUROC
WVZ, mo					
0-3	227	0.40 (0.30, 0.50)	0.22	0.51 (0.28, 0.93)	0.70
0-6	221	0.45 (0.36, 0.55)	0.28	0.50 (0.26, 0.94)	0.69
3-6	160	0.32 (0.21, 0.43)	0.17	0.84 (0.40, 1.76)	0.59
6-9	183	0.19 (0.06, 0.32)	0.05	0.91 (0.41, 2.02)	0.57
6-12	181	0.21 (0.07, 0.35)	0.05	0.96 (0.40, 2.34)	0.52
9-12	218	0.10 (−0.03, 0.23)	0.01	0.61 (0.32, 1.15)	0.60
LVZ, mo					
0-3	186	−0.08 (−0.19, 0.03)	0.01	1.18 (0.66, 2.13)	0.57
0-6	182	−0.01 (−0.13, 0.11)	0.00	0.89 (0.41, 1.94)	0.53
3-6	160	0.07 (−0.04, 0.19)	0.01	1.15 (0.56, 2.37)	0.51
6-9	183	0.04 (−0.08, 0.17)	0.00	1.33 (0.63, 2.81)	0.59
6-12	181	0.05 (−0.08, 0.18)	0.00	2.03 (0.83, 4.95)	0.66
9-12	218	0.03 (−0.09, 0.14)	0.00	1.44 (0.77, 2.70)	0.65
WAZ, mo					
0	227	0.36 (0.23, 0.48)	0.12	0.36 (0.18, 0.73)	0.71
3	188	0.54 (0.43, 0.65)	0.34	0.38 (0.20, 0.73)	0.78
6	188	0.64 (0.54, 0.73)	0.49	0.28 (0.12, 0.66)	0.77
12	223	0.58 (0.49, 0.67)	0.42	0.33 (0.18, 0.62)	0.82
LAZ, mo					
0	227	0.17 (0.06, 0.29)	0.04	0.57 (0.31, 1.04)	0.65
3	188	0.16 (0.03, 0.30)	0.03	0.54 (0.26, 1.12)	0.63
6	188	0.26 (0.11, 0.41)	0.06	0.61 (0.26, 1.44)	0.60
12	223	0.18 (0.06, 0.31)	0.04	0.77 (0.38, 1.54)	0.53
WLZ, mo					
0	224	0.25 (0.14, 0.35)	0.08	0.68 (0.37, 1.24)	0.63
3	188	0.46 (0.36, 0.56)	0.31	0.47 (0.25, 0.89)	0.74
6	188	0.60 (0.52, 0.69)	0.50	0.22 (0.08, 0.58)	0.84
12	223	0.60 (0.52, 0.68)	0.49	0.26 (0.12, 0.55)	0.91

Table IV. Early attained growth and growth velocity z scores on WAZ or underweight (WAZ < −2) at age 24 months

		Linear regression		Logistic regression	
	n	Coefficient (95% CI)	R^2	OR (95% CI)	AUROC
WVZ, mo					
0-3	227	0.47 (0.38, 0.56)	0.30	0.37 (0.24, 0.57)	0.78
0-6	221	0.55 (0.47, 0.64)	0.44	0.22 (0.13, 0.38)	0.84
3-6	160	0.38 (0.28, 0.49)	0.25	0.38 (0.22, 0.66)	0.81
6-9	183	0.28 (0.15, 0.40)	0.09	0.52 (0.34, 0.81)	0.73
6-12	181	0.38 (0.24, 0.51)	0.15	0.41 (0.24, 0.68)	0.75
9-12	218	0.18 (0.05, 0.31)	0.03	0.68 (0.45, 1.02)	0.59
LVZ, mo					
0-3	186	0.03 (−0.08, 0.14)	0.00	0.81 (0.56, 1.19)	0.57
0-6	182	0.12 (−0.00, 0.23)	0.02	0.52 (0.32, 0.84)	0.68
3-6	160	0.12 (0.01, 0.23)	0.03	0.75 (0.51, 1.11)	0.62
6-9	183	0.18 (0.06, 0.31)	0.05	0.64 (0.41, 0.98)	0.62
6-12	181	0.27 (0.15, 0.40)	0.10	0.63 (0.40, 0.98)	0.63
9-12	218	0.15 (0.03, 0.27)	0.03	0.85 (0.57, 1.26)	0.54
WAZ, mo					
0	227	0.40 (0.28, 0.52)	0.16	0.32 (0.20, 0.53)	0.76
3	188	0.59 (0.49, 0.69)	0.42	0.23 (0.13, 0.40)	0.87
6	188	0.72 (0.64, 0.80)	0.63	0.07 (0.03, 0.18)	0.93
12	223	0.72 (0.65, 0.79)	0.66	0.06 (0.02, 0.15)	0.95
LAZ, mo					
0	227	0.34 (0.23, 0.44)	0.15	0.39 (0.26, 0.59)	0.77
3	188	0.41 (0.28, 0.53)	0.19	0.20 (0.10, 0.38)	0.84
6	188	0.63 (0.51, 0.76)	0.35	0.06 (0.02, 0.17)	0.91
12	223	0.60 (0.50, 0.70)	0.39	0.15 (0.08, 0.28)	0.86
WLZ, mo					
0	224	0.11 (−0.00, 0.22)	0.02	0.68 (0.47, 0.98)	0.59
3	188	0.31 (0.21, 0.42)	0.15	0.65 (0.44, 0.98)	0.63
6	188	0.51 (0.41, 0.61)	0.35	0.37 (0.22, 0.62)	0.76
12	223	0.56 (0.47, 0.64)	0.44	0.21 (0.12, 0.37)	0.86

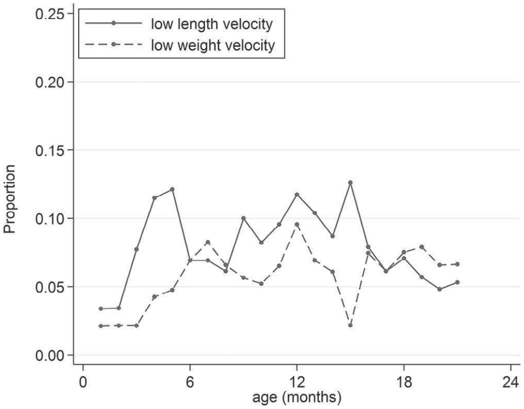

Figure 2. Proportion of 240 children enrolled in the MAL-ED study, Nepal, having a low weight or length velocity z score (<–2) according to age. All velocity z scores use a 3-month increment and are plotted at the beginning of the growth period, eg, a velocity z score plotted at 3 months is the velocity for the period from 3 to 6 months.

Errata for Growth velocity of young children in two low-resource settings

Patterns and abilities to predict negative health outcomes

Catherine Schwinger

Thesis for the degree philosophiae doctor (PhD)
at the University of Bergen

C Schwinger
(signature of candidate)

(signature of faculty)

24.11.17

Errata

Page 6	Title of Figure 1 should read: "Conceptual framework for optimal fetal and child growth and development."
Page 25	"Stunting, wasting and underweight were defined as Z-score for $\leq$-2 for length-for-age, weight-for-age and weight-for-length, respectively", should read "[...] for length-for-age, weight-for-length and weight-for-age"
Page 26	The following reference should be added to the first formula on this page: "WHO 2009. WHO Child Growth Standards- Growth velocity based on weight, length and head circumference: methods and development. Geneva: World Health Organization."
Page 33	Figure 7: The legend in locant A should read "WVZ 0.67"
Page 33	Figure 7: ROC curve for absMUAC appears higher than it should be. The AUC estimate is correct.
Page 36	"It is also referred to as accuracy in this thesis" should read "It is also referred to as inaccuracy in this thesis".
Page 39	"The inter-observer technical error of measurement (TEM) was 0.343 for weight and 0.070 for height, [...]", should read "[...] was 0.343 cm for length and 0.070 kg for weight".