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Stunted growth in children from fetal life to adolescence

Risk factors, consequences and entry points for prevention - Cohort studies in rural Bangladesh

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Abstract

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Stunted growth affects one in four children under the age of five years and comes with great costs for the child and society. With an increased understanding of the long-term consequences of chronic undernutrition the reduction of stunted growth has become an important priority on the global health agenda. WHO has adopted a resolution to reduce stunting by 40% by the year 2025 and to reduce stunting is one of the targets under the Sustainable Development Goals.

The aim of this thesis was to study linear growth trajectories, risk factors and consequences of stunting and recovery of stunting from fetal life to adolescence in a rural Bangladeshi setting and to assess the cost-effectiveness of a prenatal nutrition intervention for under-five survival and stunting.

A birth cohort of children of women participating in the Maternal and Infant Nutrition Interventions trial (MINIMat), a randomized prenatal food and multiple micronutrient (MMS) trial, was followed from birth to adolescence. Information about socioeconomic and nutritional characteristics of the mother and father was collected, and frequent anthropometry assessments of the child were done at birth, in infancy, and during childhood and adolescence. At puberty, pubertal stages according to Tanner, age at menarche and start of the pubertal growth spurt in boys were assessed. Calculations were made regarding the cost-effectiveness of prenatal food and micronutrient intervention related to the disability adjusted life years (DALYs) lost by death and stunting.

At birth, the children were on average short compared the WHO growth reference and more than half of the children were Small-for-Gestational-Age. Linear growth faltered dramatically up to 2 years, after which height-for-age Z-score increased up to adolescence. The prevalence of stunting was highest at 2 years (50%) and thereafter decreasing to 25% in adolescence. Birth size, maternal anthropometry and parental education were the most influential factors for linear growth up to and stunting at 2 years. Conditions after birth, such as feeding practices and morbidity, were less important. At 10 years, children born to short mothers (<147.5 cm), mothers with no education, or those conceived in the pre-monsoon season had an increased probability to be stunted. The median age at menarche was 13.0 years. Children that were stunted in infancy and childhood had later pubertal development as compared to non-stunted children. Children that recovered from stunting had a similar timing of puberty as their peers who had never been stunted. Supplementation with combined early prenatal food and multiple micronutrients was highly cost-effective in averting DALYs from under-five deaths and stunting.

The results from this thesis support the conclusion that a lifecycle approach is needed for the prevention of stunting. The gaps between current knowledge, policy and practice needs to be closed, with more emphasis given to prenatal interventions.

Keywords: stunting, linear growth, child health, undernutrition, Bangladesh, cost-effectiveness, data mining, puberty, prenatal interventions, global health

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For the present and future generations of girls, women, mothers and children facing undernutrition

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Svefors, P., Rahman, A., Ekström, EC., Khan, AI., Lindström, E., Persson, LÅ., Ekholm Selling, K. (2016) Stunted at 10 Years. Linear Growth Trajectories and Stunting from Birth to Pre-Adolescence in a Rural Bangladeshi Cohort. *PLOS ONE*, 11(3)

II Svefors, P., Sysoev, O., Persson, LÅ., Ekström, EC., El Arifeen, S., Naved, R., Rahman, A., Khan, AI., Ekholm Selling, K. Relative importance of pre- and postnatal determinants of stunting. Data mining approaches to the Maternal and Infant Nutrition Interventions in Matlab (MINIMat) cohort, Bangladesh. *Submitted manuscript*

III Svefors, P., Pervin, J., Khan, AI., Rahman, A., Ekström, EC., El Arifeen, Ekholm Selling, K., Persson, LÅ., S. Stunting, recovery from stunting and puberty timing in the MINIMat cohort, Bangladesh. *Manuscript*

IV Svefors, P., Ekholm Selling, K., Shaheen, R., Khan, AI., Persson, LÅ., Lindholm, L. (2018) Cost-effectiveness of prenatal food and micronutrient interventions on under-five mortality and stunting: Analysis of data from the MINIMat randomized trial, Bangladesh. *PLOS ONE*, 13 (2)

Contents

Abbreviations

SDG	Sustainable Development Goals
WAZ	Weight-for-Age Z-score
WHZ	Weight-for-Height Z-score
HAZ	Height-for-Age Z-score
BMI	Body Mass Index
DOHaD	Developmental Origins of Health and Disease
LMIC	Low- and Middle-Income Countries
HAD	Difference in Height in Centimeters from Reference Median
YLL	Years of Life Lost
YLD	Years Lost due to Disability
DALY	Disability Adjusted Life Years
MMS	Multiple Micronutrient Supplementation
E	Early (invitation)
U	Usual (timing)
Fe	Iron
LE	Life Expectancy
RLE	Remaining Life Expectancy
OR	Odds Ratio
DM	Data Mining
HR	Hazards Ratio
CEA	Cost Effectiveness Analysis
ICER	Incremental Cost-Effectiveness Ratio

Definitions

Undernutrition — The outcome of inadequate food intake and recurrent infections.

Stunting — A deficit in length (for children aged under 2 years) or in height (for children aged 2 years or more) relative to the child's age, according to a standard that reflects optimal growth. Defined as 2 standard deviations or more below the median value of the WHO Growth Standards. Reflects long-term exposure to inadequate diets, infectious diseases or inappropriate child care.

Wasting — A deficit in weight relative to a child's length or height. Defined as 2 standard deviations or more below the WHO standards for weight for length or height. An indicator of acute food shortage or severe infectious disease.

Underweight — A deficit in weight relative to a child's age. Defined as 2 standard deviations or more below the WHO standards for weight for age. Underweight can be a result of stunting, wasting or a combination of both.

Perinatal deaths — Deaths around the time of birth. Includes stillbirths and first week deaths.

Neonatal deaths — Deaths of infants occurring during the first 28 days of life.

Infant mortality — Deaths in children less than one year old.

Low birth weight	A birth weight below 2500g
Small for gestational age	A birth weight below the 10th percentile for gestational age and sex
Data mining	Methods that represent a synergy of ideas from statistics, artificial intelligence and database methods
Cost effectiveness analysis	A type of economic evaluation that summarizes the health benefits and resources used by health interventions. Answers the question “How much health benefit do we get for our money?”
YLL	Years of life lost due to premature mortality. Calculated as the number of deaths multiplied by the standard life expectancy at the age at which death occurs
YLD	Years of life spent in an impaired health state. Calculated as the duration of the disease multiplied by a weight factor that reflects the severity of the disease on a scale from 0 (perfect health) to 1 (dead).
DALY	A measure of overall disease burden from mortality and morbidity. Calculated as the sum of YLL and YLD. One DALY lost is to be interpreted as one lost year of healthy life.
Discounting	A technique commonly used in cost-effectiveness analysis to 'make fair' comparisons of costs and outcomes of interventions or programs that occur at different times.

Introduction

Maternal and child undernutrition

Despite recent global health achievements, maternal and child undernutrition remain significant public health challenges and are identified as global health priorities (1, 2). According to global estimates maternal and child undernutrition causes 3.1 million child deaths annually (3) and contributes to 35% of the disability-adjusted life years (DALYs) lost in children younger than 5 years (4). Impaired antenatal and early life nutrition increases the risk of neonatal deaths and has important consequences for the healthy development and economic productivity of individuals and society (4).

Undernutrition is defined as the outcome of inadequate food intake and recurrent infections (5). Child undernutrition encompasses micronutrient malnutrition (deficiencies in vitamins and minerals), underweight (low weight-for-age), wasting (low weight-for-height) indicating acute weight loss, and stunting (low height-for-age), indicating chronic exposure to undernutrition and other restrictions of a child's linear growth. Figure 1 illustrates the number of children affected and definitions of different manifestations of undernutrition.

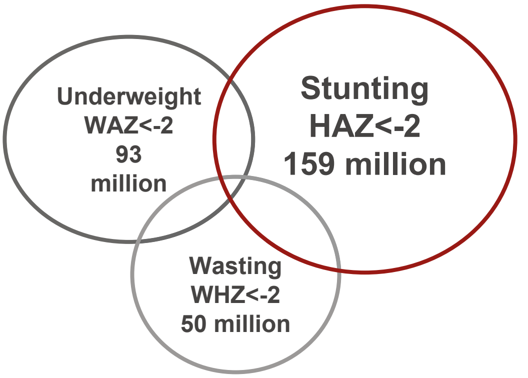


Figure 1. Number of children affected and definitions of different manifestations of undernutrition. WAZ (Weight-for Age Z-scores), WHZ (Weight-for-Height Z-scores), HAZ (Height-for-Age Z-scores)

Stunted linear growth

Stunting, defined as a length or a height less than -2 standard deviations below the WHO height reference median (6), is the most prevalent manifestation of child undernutrition affecting one in four children under five years of age globally (Figure 1). With an increased understanding of the long-term consequences of chronic undernutrition, international actors have shifted their focus from efforts to reduce the prevalence of underweight children to the prevention of stunting (7,8). The World Health Assembly (WHA) and the Sustainable Development Goals (SDG) agenda have endorsed stunting as a key indicator for monitoring child health and nutrition. In 2012 the WHA adopted a resolution to reduce stunting by 40% by the year 2025 (7) and to reduce stunting is one of the targets under the second SDG to end hunger and improve nutrition (2).

About half of all stunted children live in Asia in spite of an impressive reduction of stunting in the region from 60% in 1990 to 34% in 2015 (8). Bangladesh remains among the countries with the highest prevalence in the world: 36% of the children under five years of age are stunted (9). Figure 2 illustrates recent global estimates of stunting prevalence.

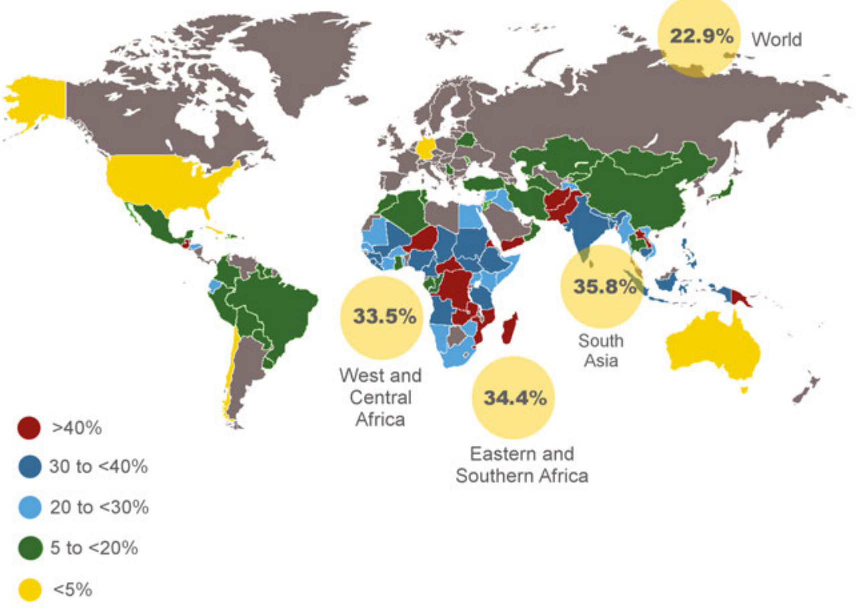


Figure 2. Percentage of children under 5 years who are stunted. Data are the most recent available between 2010-2017. Source: UNICEF, WHO, World Bank Joint Child Malnutrition dataset. World map designed by freepik.com

Linear growth and height potential

Growth failure in the form of stunting indicates a failure to reach one's potential for height. Attained height is the result of complex interactions of environmental influences and an individual's genetic potential, illustrated in Figure 3. The genetic growth potential is determined by DNA sequence polymorphism (10,11) and the epigenetic heredity (12). Epigenetic modifications result from changes to gene expression in response to the environment. This can occur during fetal life, or be inherited from the mother and father. That is, one inherits a set of genes (DNA sequence polymorphism) but the *degree* of expression of the genes is determined by epigenetic modification by the exposure to the environment in early life. The strong influence of the environment on linear growth and height through epigenetic modulation is illustrated by height changes over generations, and the height differences between current populations in different countries (12,13). During the last century height has increased in populations where health and adequate nutrition have been or become satisfactory and relatively equally distributed. This trend has mainly been attributed to general improvements in nutrition and health that have been associated with economic development and is consistent with animal models where several generations are necessary to 'wash out' effects of undernutrition (14). The mean adult height among men in Sweden increased from 167 cm in the mid-19th century to 178 cm in 1996 (15). In low-income country populations the mean adult height is significantly lower: in Bangladesh the mean male adult height was 162 cm in 1996 (15).

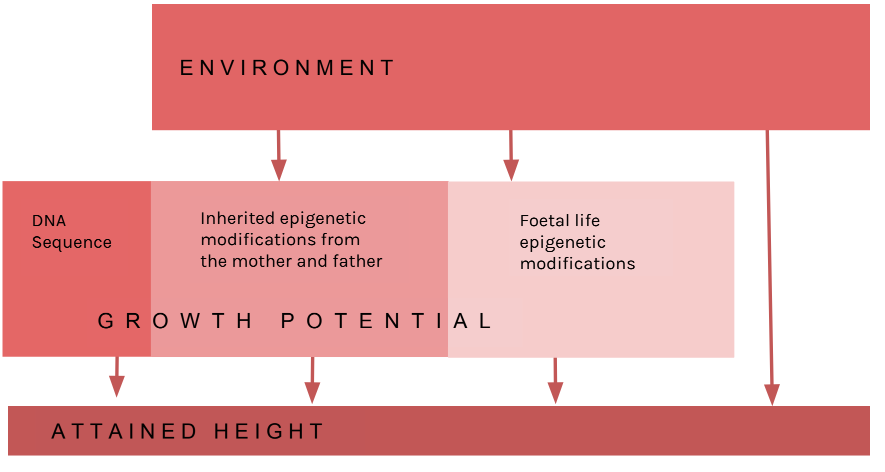


Figure 3. Linear growth and attained height is the result of complex interactions of environmental influences and one's genetic growth potential

Growth reference and characterization of growth

As children of all ethnic backgrounds have similar linear growth potential when their nutrition, health, and care needs are met (16) WHO has developed two international references that represent the best description of physiological growth for all children: One reference is from birth to five years of age and the second is from five to 19 years of age. The reference for children 0-59 months is based on a study undertaken between 1997-2003 and includes growth data from 8500 breastfed children from Brazil, Ghana, India, Norway, Oman and the USA who were living in environments that support optimal growth. The growth reference for children 5 to 19 years is based on a reconstruction of data from healthy children and adolescents with expected heights collected for the construction of the 1977 National Center for Health Statistics (NCHS)/WHO reference.

To characterize growth compared to the reference population, standard deviation scores are calculated. Height-for-Age Z-scores (HAZ) are calculated by taking the difference in height from the measured child and the median height of the reference for the same sex and age. The difference is then divided by the standard deviation for the same sex and age. Children who have a HAZ below minus two are defined as stunted.

The standard deviations for height-for-age increase with age, reflecting the increasing variation in normal growth with age. Thus, increases in HAZ with age can be the result of both decreasing deficit in height or the increasing standard deviations. Due to this, height-for-age difference (HAD), the actual height difference from reference median in centimeters, without dividing by the standard deviation, can be used as an additional way of depicting growth in populations of children over time.

Timing of growth and growth failure

Child growth has three distinct phases; infancy, childhood and puberty. From fetal life the growth rate is high with a deceleration up to about three years of age. This is followed by a period with lower, slowly decelerating growth velocity until puberty. Puberty starts with an increased rate of growth. After the peak height velocity has been reached during puberty the growth rate decelerates until growth ceases and adult height is reached (17). In stunted children, puberty usually take place at an older age (18). A later puberty onset prolongs the childhood growth phase and results in a taller height at the start of puberty and in a taller adult height, as the puberty growth component is similar in stunted and non-stunted children (19).

As the growth rate is highest during fetal life and infancy this is when linear growth is most susceptible to environmentally modifiable factors. This period is also when most of the growth failure takes place (20,21). In a pooled analysis of 19 birth cohorts with longitudinal follow-up, 20% of stunting was attributable to being born small-for-gestational-age (20).The typical growth and growth faltering patterns among children in poor populations are illustrated in a comparison of childhood growth patterns in 54 low-to-middle-income countries (LMICs) (21). In South Asia children are typically born with a size below the WHO growth reference, which indicates that the growth faltering frequently starts already in fetal life. After birth average HAZ scores among infants in low-income populations continue to decline in all regions until about 24 months of age after which the deficit in HAZ scores becomes more or less constant (21). The actual height difference from reference median in cm (HAD), however, continues to increase after 24 months (22).

The evidence that most growth faltering takes place up to two years has influenced the concept of the first 1000 days as a critical period for interventions to support linear growth.

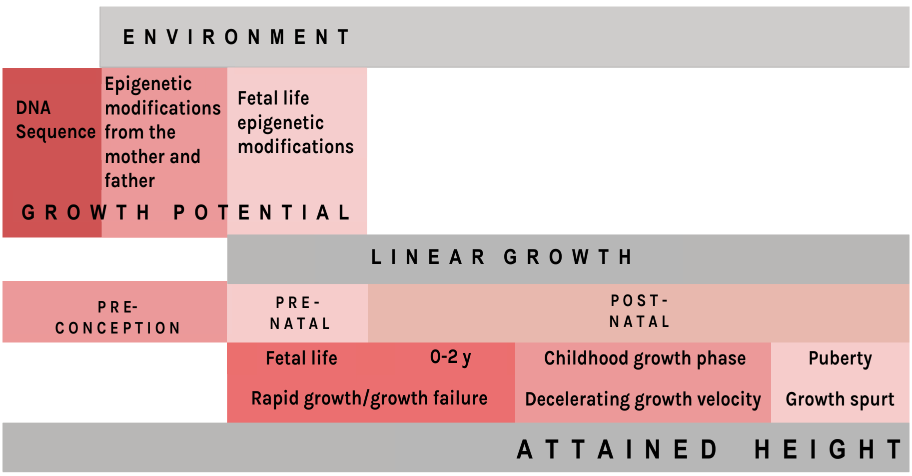


Figure 4. Timing of environmental influences on the genetic growth potential and the different growth phases from conception to puberty.

Causes and consequences of stunted growth

Linear growth is the most frequently used indicator of children's health and well-being. Stunted growth (23,24) reflects a variety of environmental determinants influencing child growth including poor maternal and child nutrition throughout the life cycle; intrauterine growth restriction (25-28) inadequate breast-feeding and inappropriate complementary feeding together with frequent infections (29) and inflammation.

Stunted growth is a logical response to poor nutrient availability, where linear growth is stopped to preserve energy for the brain and vital functions. Still, although poor growth might be a survival strategy, growth failure comes with huge costs for the child and society. Stunting in early life is linked to increased risk of morbidity and mortality, impaired cognitive development, lower future productivity, and adverse maternal reproductive outcomes (30). Stunted girls often become malnourished mothers who give birth to stunted children, thereby creating a vicious intergenerational cycle maintaining poverty, poor health and reduced human capital (30). Moreover, the "Developmental Origins of Health and Disease" (DOHaD) hypothesis states that undernutrition during critical periods of early development influences changes in metabolism, growth and body composition and can be associated with an increased risk of adult cardiovascular disease, type 2 diabetes and metabolic syndrome (31,32). Recovery from stunting may prevent several of these negative consequences for short and long-term health and is hence desirable (33). Paradoxically, there is also evidence that catch-up growth, following early life undernutrition, might increase the risk of adult chronic diseases (34-36).

The context, causes, and short- and long-term consequences, including the complex interaction between household, environmental, socioeconomic and cultural influences that cause stunting, are displayed in the World Health Organization (WHO) Conceptual Framework on Childhood Stunting (Figure 5).

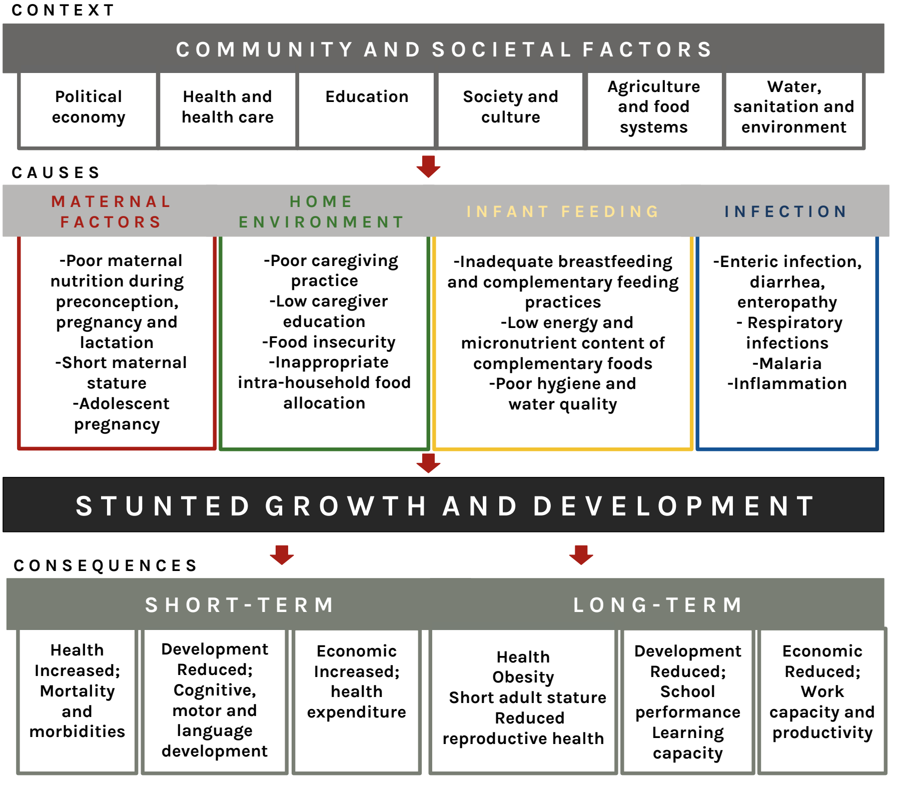


Figure 5. Causes and consequences of stunting based on the WHO conceptual framework on Childhood Stunting: adapted from Stewart, C.P. et al., 2013 (37).

Puberty

The timing of puberty is an intermediate factor associated with early life nutrition as well as future health outcomes. Puberty start and linear growth restriction can be understood as two outcomes of nutritional cues. An older age at puberty onset prolongs the childhood growth phase and is an opportunity for the stunted child to gain in adult height compared to their non-stunted peers with a normal puberty start (19). Epidemiological and adoption studies have indicated that early life undernutrition, which is followed by rapid post-natal growth, may result in early puberty and younger age at menarche (38-40). Earlier puberty onset shortens the childhood growth face, resulting in shorter adult heights. In addition, an younger menarche has been associated with an increased risk of adult chronic diseases in low-, middle- and high-income countries (41-43), including Bangladesh (44). In light of the evidence of adverse outcomes of so-called catch-up growth, concerns have been raised regarding the potential long-term negative effects of recovery from stunting.

Interventions targeting child and maternal undernutrition

If implemented at a sufficient scale, child and maternal nutritional interventions are judged to have the potential to reduce stunting by 20 % (33) and DALYs due to child death by 25% in the short term (45) and in the long term these interventions are expected to be both cost effective and provide a high economic return to society (33) . The period from conception throughout pregnancy and the post-natal period from birth up to 2 years, i.e., the first 1000 days of life, is when growth is most susceptible to environmentally modifiable factors. Nutrition programs increasingly target women and children during this critical period (21, 4). Child health nutritional interventions include promotion of breastfeeding, complementary feeding, and micronutrient supplementation (46). Post-natal nutrition specific interventions are important to improve child development and reduce micronutrient deficiencies and prevent child deaths (33). These interventions, however, have reportedly modest effects on linear growth (47, 48). Interventions focused on water, sanitation and hygiene (WASH) improvements have the potential to affect health and nutrition outcomes through the reduction of infectious diseases and environmental enteric dysfunction. However, reviews of WASH interventions, as well as two recent studies in Bangladesh and Kenya, report small to none improvements in linear growth (49,50).

The established prenatal nutrition interventions include balanced energy-protein supplementation, multiple micronutrient supplements, and nutritional counseling and education for pregnant women. Randomized trials and systematic reviews evaluating these interventions in low- and middle-income countries report positive effects on birth weight and a reduced risk of low birth weight (LBW) (51-58). In addition, prenatal balanced protein-energy supplements have resulted in reduced perinatal mortality (51,59,60).

The MINIMat trial in Bangladesh

Micronutrient supplementation with iron and folate is routinely recommended to all pregnant women worldwide to prevent maternal anemia, low birth weight, and preterm birth (61).The fact that women in resource-poor settings frequently enter pregnancy deficient in several micronutrients made UNICEF/WHO/ United Nations University to develop a multiple micronutrient supplement (MMS) for research purposes. The results from studies of the MMS efficacy and safety compared to routine supplementation with iron and folate have varied from reduced prevalence of low birth weight (52,62) to suggested increased risks of perinatal and neonatal mortality (63). These studies were all carried out in resource poor settings where the population often face both macro- and micronutrient deficiencies and MMS were in most cases not given in combination with any food supplementation.

The Maternal and Infant Nutrition Interventions (MINIMat) trial was a randomized prenatal nutrition supplementation trial, carried out in rural Bangladesh. Multiple micronutrient supplementation (MMS) was provided from 14 weeks of gestation and combined with an early invitation (E –around pregnancy week 9 pregnancy) or usual timing (U-around pregnancy week 20) of food supplementation. There was a substantial reduction in infant mortality with MMS combined with early (E) invitation to prenatal food supplementation (EMMS) as compared with 60 mg iron 400 gm folic acid and start of food supplementation at the usual time in pregnancy (U60Fe) (64). Conversely, infant mortality risks did not differ across the three micronutrient treatment groups. In addition, MMS supplementation resulted in more stunting when compared with Fe60F, while the early invitation to food supplementation as compared with usual timing of start led to a reduced frequency of stunting before the age of five years (65). This combination of favorable and unfavorable effects illustrates that nutrition interventions may influence multiple outcomes that may be positive as well as negative from a public health perspective.

Rationale

It is imperative to understand the dynamics and determinants of stunted growth to develop and deliver appropriate interventions. Although many aspects of stunting are well documented, most of the information is based on cross-sectional studies and focuses on children up to five years of age. Relatively few longitudinal studies in LMICs address linear growth from birth and beyond the age of five. This lack of studies limits the current knowledge of children's growth trajectories in these contexts and the early environmental influences. Few studies have employed a holistic approach, concurrently accounting for household, environmental, nutritional, biological, and socioeconomic influences. The MINIMat trial have generated a rich, unique database, which provides an excellent opportunity to investigate different longitudinal aspects of child growth from fetal life to adolescence. The application of data mining techniques allows further understanding of intricate patterns in the data related to the risk of stunting and the relative importance of pre- and post-natal factors.

Furthermore, in light of recent evidence of adverse outcomes of so-called catch-up growth, concerns have been raised over the potential long-term effects of recovery from stunting. The timing of puberty is an intermediate factor that is associated with early life nutrition as well as future health outcomes. The association between recovery from early growth restriction in children who remain in a low-resource setting and their pubertal development is poorly understood.

Lastly, few studies have analyzed the cost-effectiveness of nutrition interventions in low-income countries, a fact that can possibly deter large-scale implementation. Nutrition interventions may influence multiple outcomes that may be positive as well as negative. The MINIMat interventions were very cost-effective in regards to reduced infant mortality (66). However, the reduced stunting by the early prenatal food supplementation, on the one hand, and the increased stunting by the multiple micronutrients, on the other hand, were not included in the previous cost-effectiveness analysis. Cost-effectiveness analyses often forms part of the basis for decisions about large-scale implementation, and it is therefore vital to include the potential long-term effects of nutrition intervention as well as its primary outcomes.

Aims

The overall aim of this thesis is to analyze the linear growth trajectories and stunting from fetal life to adolescence, and to study the relative importance of pre- and postnatal risk factors, the consequences of stunting for pubertal development, and the cost-effectiveness of a prenatal nutrition intervention in a cohort of children in rural Bangladesh.

The specific objectives of the papers that are included in the thesis are to:

- describe linear growth trajectories and stunting from birth to 10 years in rural Bangladesh and to analyze the association with maternal nutrition, household wealth, season of conception and gender.

- identify the most critical determinants of linear growth from 0–24 months and the risk factors for stunting at 2 years, and to identify subgroups with different growth trajectories and levels of stunting at 2 years.

- analyze the association between intrauterine growth restriction, infancy and childhood stunting, recovery from stunting, and the outcome timing of puberty.

- evaluate the cost-effectiveness of the MINIMat interventions taking into account both premature death (under five-year mortality) and long-term disability (stunting) in terms of cost per disability adjusted life years (DALY) averted.

Methods

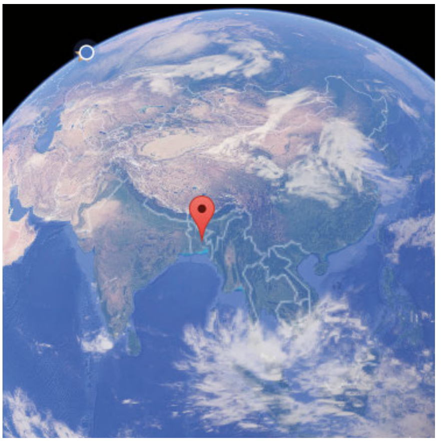
This thesis is based on information collected from a cohort of children and their mothers participating in the MINIMat trial, carried out in rural Bangladesh. So far, these children have been followed from early pregnancy to adolescence. The participants, outcomes, exposures and types of analysis of the different papers are presented in Table 1. Both epidemiological and health economic methods were used. Classical descriptive and inferential statistical methods were employed in Papers I and III. These two papers focused on linear growth trajectories and stunting at 10 years of age and to what extent earlier stunting influenced the timing of puberty. In Paper II, data mining techniques were applied to the extensive MINIMat database to further explore the intricate patterns of risk factors of stunting at two years. A cost-effectiveness analysis was carried out in Paper IV. The costs and the effects of the MINIMat interventions were analyzed, taking into account both premature death and long-term disability (stunting). All statistical analyses were performed using the programming language R(67).

Table 1. Participants, outcomes, exposures and analysis methods of paper I-IV

Paper	Participants	Outcomes	Exposures	Analysis
I	Children followed from birth to 10 years	HAZ[1] 0-10 y Stunting[2] at 10 y	Maternal height Maternal education Season of conception	Descriptive statistics Generalized linear mixed model Logistic regression
II	Children followed from birth to 24 months	HAZ change 0-24 m Stunting at 24 m	309 maternal, household, infant feeding and morbidity variables	Conditional inference trees Conditional random forest
III	Children followed from birth to adolescence	Tanner stage Age at menarche Start of puberty growth spurt	SGA[4] Stunting 0,12,24,54m Recovery from stunting	Descriptive statistics Logistic regression Cox' proportional hazards regression
IV	Children from birth to 5 years	ICER[3]		Cost-effectiveness analysis

[1]Height-for-age z-score [2] <-2 standard deviations below WHO growth reference
[3]Incremental cost-effectiveness ratio [4] Small-for-gestational age

Study setting



Bangladesh is located in South Asia where the Ganges River flows into the Bay of Bengal. With a population of 164 million, Bangladesh is the world's eighth-most populous country and the third most populous Muslim-majority country after Indonesia and Pakistan. Over the last 3,000 years the Bengal area has experienced many different foreign rules. With the partition of the British India in 1947, the area was divided between India and Pakistan. After the bloody Bangladesh War of Liberation in 1971, Bangladesh gained independence. After the war, the country was desperately poor. During recent decades it has undergone an exceptional economic growth rate coupled with impressive improvements in health and human development (68). National poverty has declined from 56.6% in 1991 to 24.3% in 2016 (69). The neonatal mortality rate has decreased from 64.2 in 1990 to 20.1 per 1000 live births and is today half of the world average (70). This success has been attributed to the collaboration between governmental and non-governmental organizations that have pursued women-focused, equity-oriented, national programs targeted at family planning, reduction of home births, optimization of immunization coverage, provision of food supplementation and achievement of the world's highest coverage of oral rehydration therapy (68). Despite substantial reductions in child mortality and poverty, however, the prevalence of maternal and child malnutrition remain among the highest in the world. Thirty-six per cent of children under five are stunted, 14 % wasted and 22 % are born with a low birth weight (9). Women of reproductive age are typically short and slender (9) and have a low weight gain in pregnancy (71). Anemia (9), zinc, vitamin B12 (72), and vitamin A (73) deficiencies are also prevalent.

The Maternal and Infant Nutrition Interventions in Matlab trial

The Maternal and Infant Nutrition Interventions in the Matlab (MINIMat) trial (isrctn.org identifier: ISRCTN16581394) was a factorial randomized trial carried out in rural Bangladesh focused on an early prenatal food and micronutrient supplementation for pregnant women and the effect on short and long-term health of their offspring. Primarily, the effects of the interventions on maternal hemoglobin, birth weight, gestational age at birth, and infant mortality were evaluated (64). The children of mothers who received prenatal interventions were followed monthly from birth to one year, then every three months up to 24 months, and then again at 4.5, 10 years and twice during the age span of 12-14 years. Currently, a 15-year follow-up is taking place.

Study area

The trial was carried out in Matlab, a rural sub-district 57 km south-east of the capital Dhaka. The population in Matlab is mainly poor rice farmers frequently exposed to food insecurity and widespread child and maternal undernutrition still prevails in this region. The International Center for Diarrheal Disease Research, Bangladesh (icddr,b) provides health services in the area and runs a Health and Demographic Surveillance System that has been in place since the mid-1960s. Every month community health workers collect and update data on demographic and selected health information, covering a population of about 220,000 in more than 140 villages. A unique identification system allows tracking over time and across studies and databases.

Prenatal food and micronutrient supplementation

The MINIMat trial recruited pregnant women from November 2001 to October 2003. When a woman reported to a community health worker that her menstruation was delayed by more than 14 days, she was offered a pregnancy test and her date for the last menstrual period (LMP) was recorded. If LMP date was missing, the gestational age assessment was based on ultrasound examination. A total of 4,436 pregnant women within the icddr,b service area were recruited to participate in the MINIMat trial. The pregnant women were enrolled at around gestational week eight and randomized to receive one of six combinations of food and micronutrient supplements. There were two daily food supplementation groups with 600 kcal six days per week; the early invitation (E, at about 9 weeks of pregnancy), or the usual timing (U, at about 20 weeks of pregnancy). There were also three micronutrient groups; 60 mg iron and 400 µg folic acid (routine), multiple micronutrients (MMS) with 15 micronutrients, including 30 mg iron and 400 µg folic acid or 30 mg iron and 400 µg folic acid (to control for the lower amount of iron in the MMS supplement). The two (food timing) by three (micronutrient supplementation) factorial design resulted in the six intervention groups: E30Fe (n = 739), E60Fe (n = 738), EMMS (n = 740), U30Fe (n = 741), U60Fe (n = 738), and UMMS (n = 740). The 4,436 pregnant women that participated gave birth to 3,625 live born children from April 2002 to June 2004.

Data collection; socioeconomic, anthropometric and puberty assessments

During enrollment, community health research workers interviewed the mothers in their homes. They used structured questionnaires that included socioeconomic characteristics (SES), parental education, food security, maternal morbidity and pregnancy history. In the third trimester, paramedics interviewed the women in private about their experiences of domestic violence.

Maternal weight and height were measured at around 8 weeks of gestation and at follow-ups. During the first two years, the mother-and-child pairs were visited monthly in their homes during the first year and every three months during the second year. On these occasions, data on infant feeding practices, child morbidity and anthropometry were collected. The children's weight and height were then again measured at 4.5, 10 years, and twice at puberty follow-up in the age interval 12 to 14 years. The anthropometric assessments were performed during clinical visits at the local sub-centers run by the icddr,b in the Matlab area.

For the 10-year follow-up, only children born from April 2002 to June 2003 were invited to participate, representing a one calendar year birth cohort. A team consisting of nurses, a medical doctor and a laboratory technician, when needed, assisted by trained field staff, conducted all measurements. Refresher training on data collection methods, including standardization of anthropometric measurements, was conducted periodically during all follow-ups. The recumbent length at birth and during infancy (until 1.5 years) was measured with a locally manufactured, collapsible length board with a precision of 0.1 cm. A SECA electronic or beam scales (UNICEF Uniscale; SECA Gmbh & Co, Hamburg, Germany), with a precision of 0.01 kg was used when measuring birth weight. To measure maternal anthropometry and height and weight in the children during follow-up assessments, an electronic scale (Uniscale; SECA) and a freestanding stadiometer to the nearest 0.1 cm were used.

During the puberty follow-up anthropometry and pubertal development were assessed twice with a six-month interval. Data collection was done at sub-centers separately for girls and boys and conducted by teams of female and male nurses and doctors, respectively. Guided by pictures, participants self-assessed pubertal development: breasts or testicles, as appropriate, and pubertal hair development according to Tanner (74). The female staff interviewed the girls whether they had had their first menstruation and the date of menarche was noted. Information collected within the MINIMat trial from enrollment up to adolescence is presented in Figure 6.

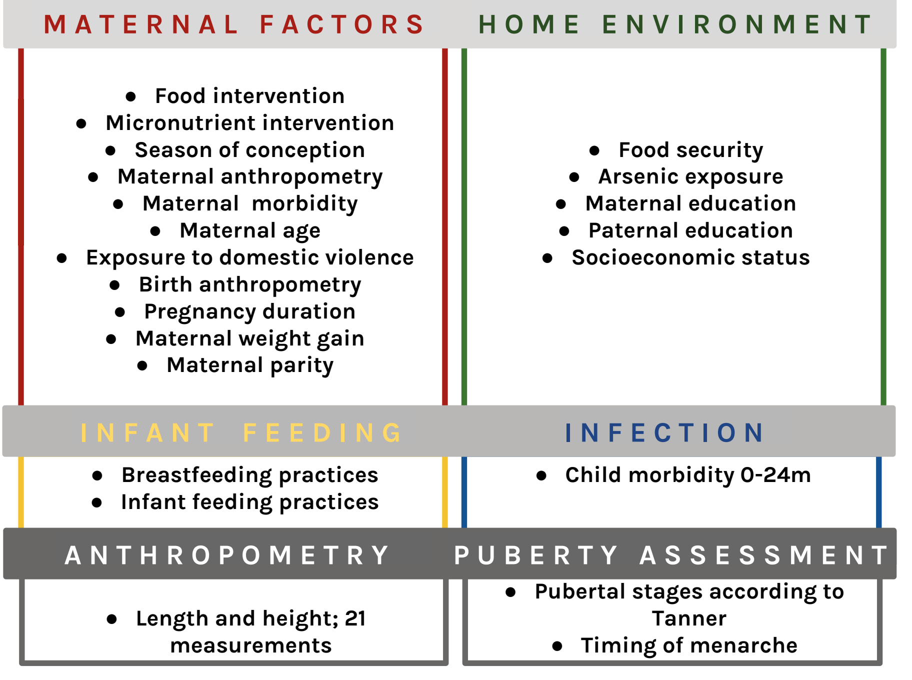


Figure 6. Information collected within the MINIMat trial from enrolment to adolescence. Grouping and color coding according to the WHO conceptual framework on Childhood Stunting: (37)

Characterization of growth

To characterize growth, *height for age z-scores* (HAZ) and the *difference in height in cm* (HAD) from reference median were calculated. For simplicity, the terms height, HAZ and HAD are used throughout this thesis, irrespective of the child's age, despite that supine length, rather than standing height, was measured in children less than 1,5 years of age.

Stunting categories were created (stunted or not) based on the HAZ of the child. Children with HAZ below -2 was defined as stunted. HAZ was calculated using the program WHOAnthro from birth to 4,5 years and AnthroPlus at ten and 12-14 years of age based on WHO growth references for birth to five years and five to nineteen years of age, respectively (6,75). Using the same references HAD was calculated as the difference between the measured height and the median sex- and age-specific height obtained from the reference data.

Ethical considerations

Written and oral informed consent was obtained from all participating women in the MINIMat trial and from the parents of the participating children. The Ethical Review Committee at icddr,b in Bangladesh, and the Regional Ethical Review Board at Uppsala University, Sweden, approved the original trial and each follow-up.

Analysis

Samples

The selection criteria for the analyzed samples in Paper I-III are presented in Table 2.

Table 2. Selection criteria and sample sizes of subjects in paper I-III

Paper	Selection criteria	n
I	Height measurements at birth, 24, 54 months and 10 years	n=1054
II	Height measurements at birth and 24 months	n=2723
III	Height measurements at birth 12, 24, 54 months and at puberty follow up	n=1930
	Sub-samples boys: height measurements at birth 12, 24, 54 months, 10 years and at the two puberty follow ups	n=420

Linear interpolation

If a height measurements were missing in the age interval between birth and two years of age, the data were linearly interpolated (Paper I and IV). For example, if the 3-month height measurement was missing, it was imputed by linear interpolation of the 2- and 4-month heights. If two consecutive values were missing, the values were imputed from the weighted average of the previous and subsequent measurements. In paper IV the HAZ were linearly interpolated from two to 4.5 years, for every 3-month period to attain a more accurate estimation of number of months lived with stunting.

Classical statistical analysis

Paper I

The outcomes of interest in the first paper were repeated measurements of HAZ from birth up to 10 years of age and stunting at 10 years. The exposure variables were maternal height in tertiles, maternal educational level and season of conception. To model the repeated measurements of the continuous outcome HAZ over the 19 different time points from birth to pre-adolescence generalized linear mixed models (GLMM) were used. Binary logistic regression analysis was used to quantify the relationship between the exposures and the child's probability of being stunted at 10 years of age. Both crude and adjusted analyses were performed. In the crude analyses the fixed factors maternal height in tertiles, maternal educational level and season of conception were included one by one. In the adjusted model adjustments were made for maternal parity, maternal socioeconomic status and maternal age at enrolment. The longitudinal GLMM was performed using the nlme package (76).

Paper III

The stages of pubertal development according to Tanner (74), the age at menarche in girls and the start of pubertal growth spurt in boys were the outcomes of interest in the third paper. When the year but not the month of menarche was known, the month of June was imputed (n=3). In the cases (n=362) when the month but not the date was known, the value 15 was imputed. For the girls who did not participate in the second pubertal data collection (n=43), the information about menarche from the first round was used. Stage of pubertal development from the second data collection was used for girls and boys. Median age at menarche was calculated by time-to-event analysis according to Kaplan Meier. Boys with height assessments at 4.5 and 10 years, and the two puberty follow-ups were included in an assessment where the height velocities between 4.5 and 10 years and between the two pubertal measurements were compared. Boys with a height velocity between the two puberty follow-ups that were higher than the velocity at 4.5 to 10 years were classified as having started the growth spurt. Those whose height velocity was not different from the pre-pubertal velocity and who had reached less than stage 4 in genital development were classified as pre-pubertal. Boys with no height increase or a height velocity below the pre-pubertal speed and who had reached genital development stage 4-5 were considered to already have passed the growth spurt. Lastly, these three groups were re-classified into two groups: Those not having started the growth spurt and those having started or already passed the growth spurt.

The exposure variables were intrauterine growth, stunting, and recovery from stunting at and between the following ages: birth, 12, 24, and 54 months. Intrauterine growth was represented by small or appropriate for gestational age (77) and stunting at birth. Children who had been stunted at birth, 12, 24 and 54 months but were not stunted at the following age were categorized as having recovered from stunting.

Cox's proportional hazards and Logistic regression analyses were used to examine the relationship between the exposures and the outcome age at menarche and the outcome of whether the boy was pre-pubertal or pubertal (had started or already completed the growth spurt). Both crude and adjusted hazards ratios and odds ratios were calculated. In the adjusted model the variables maternal education, maternal body mass index (BMI) at recruitment (around gestational week 8), socioeconomic status of the household (represented by tertiles of asset scores (78)), parity and preterm birth were included. All analyses were performed using the packages "Epi" (79) and "survival" (80).

Data mining (Paper II)

The number of risk factors for stunted growth and the complexity of the associations between these risk factors and linear growth restriction make traditional statistical models ineffective from a predictive perspective. Furthermore, classical statistical methods do not have the capacity to identify groups with different risks based on combinations of predictors.

Data Mining (DM) includes a set of methods that represent a synergy of ideas from statistics, artificial intelligence and database methods (81). These methods are able to fit intricate dependencies between the outcome and predictor variables in a non-parametric way, i.e. without the need for the user to specify the functional form of the dependence. Decision trees (82) are well-used data mining methods that allows for specifying a high number of predictor variables, handling variables of different types and discovering complex interactions between predictor variables automatically and include them into the model. In this thesis decision trees methods were applied to assess the relative importance of risk factors for stunting at two years, and to identify risk groups with a high prevalence of stunting at two years.

Because traditional decision trees, such as the Classification and Regression Trees (CART), have been shown to be biased (83), conditional inference trees were used. Conditional inference trees (CIT) is a decision-tree method that embeds a statistical hypothesis-testing framework into a recursive partitioning algorithm used for model building. This method was used to identify subgroups with different risk patterns of stunting. For the validation of the models, cross-validation, a well-established model selection method that selects a tree with an optimal predictive performance for new unseen data was applied. To rank the importance of predictors for the presence of stunting at 24 months of age conditional random forest (CRF) analyses were performed. In CRF the importance of a variable is computed by comparing the predictive mean squared error (MSE) from the original data and a dataset where the corresponding variable values are specified incorrectly, which makes the variable irrelevant for the prediction. The random forests analyses were created based on 3000 trees, and the 30 variables with the highest importance measure are presented.

Cost-effectiveness analysis (Paper IV)

Cost-effectiveness analysis (CEA) is a type of economic evaluation where one summarizes the health benefits and resources used by health interventions so that policy makers can choose among them. It essentially provides the answer to the question "How much health benefit do we get for our money?". The basic calculation involves dividing the cost of an intervention in monetary units by the health gain. Health gains can be measured in several ways including lives saved, cases of illness prevented or disability adjusted life years averted. No attempt is made to value the health gain, so implicitly it is assumed that the outcome of interest is desirable. Normally, the aim with a CEA is to estimate the difference between a current situation and a situation with a potential improvement. The result is typically expressed as a ratio of change in cost to the change in health gain, called incremental cost effectiveness ratio (ICER) (84).

Cost data

For the cost-effectiveness study, cost data were retrieved from a recent study by Shaheen *et al.* (66), which evaluated the cost-effectiveness of the MINIMat interventions in regards to reduced infant mortality. Direct costs for the intervention included staff, administration and training, community volunteer time and the cost for the micronutrient and food supplements. The indirect costs included the cost of the participants' time. All the cost items except the micronutrient capsules were summarized, representing the cost of food per pregnant woman. Lastly, the total cost for supplementing one woman was calculated by taking the cost of food per pregnant woman multiplied by the adherence to food, plus the cost for micronutrients capsules, also multiplied by the adherence to micronutrients (85).

Health gains

The effect measure was presented as disability adjusted life years (DALYs) averted, a measure of overall disease burden from mortality and morbidity. DALYs combine years of life lost due to premature mortality (YLLs) and the time spent in an impaired health state, measured as years lived with disability (YLDs). One DALY lost is to be interpreted as one lost year of healthy life, and one DALY averted is thus equivalent to the gain of one year of healthy life. The term disability in this thesis refers to loss of health due to stunting. As the MINIMat interventions had an effect on both under-five deaths and stunting, DALYs were equal to YLL due to all-cause premature mortality plus YLD due to stunting. The key assumptions behind the calculation of DALYs are presented in Figure 7.

KEY ASSUMPTIONS TO CALCULATE DALYs

Duration of disability: Duration of stunting, for up to 5 years, was obtained from observed data. From 5 to 10 years, the average proportion of recovery and incidence of stunting in each intervention group between 4.5 and 10 were used. Children who were stunted at 4.5 years were assumed to be stunted at 5 years, and children who were stunted at 10 years were assumed to continue being stunted throughout life.

Disability weights used: 0.002 (stunting) and 0.024 (developmental delay). Stunted children were assumed to be equally affected by the disability caused by stunting throughout infancy, childhood and adulthood.

Discount rate: 3%

Life expectancy: LE at birth for YLL, and RLE at 5 years for YLD. Discounted LE and RLE for girls; 28.66 and 29.03 years. Discounted LE and RLE for boys; 28.16 and 28.84

Figure 7. Key assumption behind the calculation of DALYs

YLLs were calculated by subtracting the age at death from the life expectancy at birth in the Matlab area. YLDs were calculated as the sum of months the children had been stunted times a disability weight. Two different disability weights were used. The disability weight attributed to stunting by the global burden of disease study was 0.002 (86). In addition, to avoid underestimating the potential long-term consequences of cognitive impairment, we chose also to include the higher disability weight of 0.024 that is attributed for development disability due to malnutrition (86).

Analyses

To obtain the incremental cost effectiveness ratios (ICERs) for DALYs averted, we calculated the DALYs and the costs for supplementing one pregnant woman following the regimes in each of the MINIMat intervention alternatives. The six intervention groups were then sorted according to ascending costs and alternatives with both a higher cost and a higher DALY estimate were excluded (i.e., dominating alternatives). This procedure resulted in three remaining intervention alternatives. Lastly, we calculated the increment in costs and DALYs across these three alternatives and divided the cost differences by the differences between DALYs, which resulted in the ICERs.

Results

From 2001 to 2003 4,436 women were enrolled in the MINIMat trial. After enrolment 845 women were lost to follow-up before delivery, mainly due to fetal loss, outmigration or withdrawal of consent. Out of the 3,625 live born children 3256 had length data from birth. The reasons for losses from follow-up after birth up to puberty included factors such as outmigration, refusal to participate, and death (Figure 8). A reason for exclusion from analysis was a missing anthropometry assessment from an age included in the analysis.

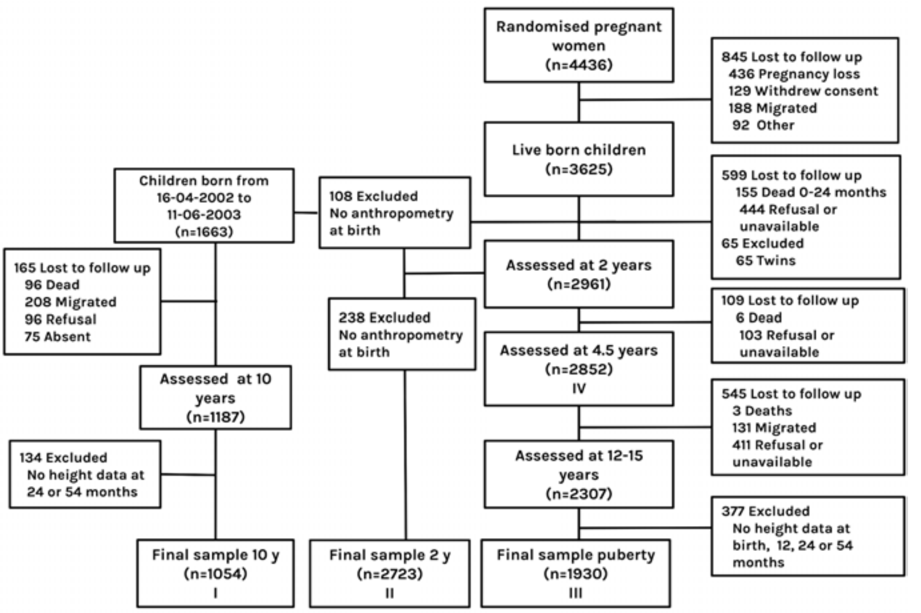


Figure 8. Flow chart of children participating in the MINIMat trial from birth to adolescence

The women participating in the MINIMat study had an average age of 26 years (SD 5.6) at recruitment and were short and slender with a mean height of 148.9 cm (5.3 SD) and weight of 45.3 kg (6.8 SD), respectively. The average years of education were equivalent to the completion of primary school and similar for women and men (5.0 versus 5.6 years). The characteristics of the mothers, fathers and households are presented in Table 3 and for children in Table 4.

Table 3. Baseline characteristics of women participating in the MINIMat trial

	n/n	%
Perceived income expenditure status		
Surplus	881/3254	27.1
Equal	1731/3254	53.2
Occasional deficit	535/3254	16.4
Constant deficit	99/3254	3.0
Don't know	8/3254	0.2
Maternal age		
<20 years	521/3256	16.0
20-29 years	1856/3256	57.0
≥30 years	879/3256	27.0
Maternal height		
<145 cm	517/3256	15.9
≥145 cm	2735/3252	84.1
Maternal BMI		
<18.5	913/3256	28.1
≥18.5	2331/3256	71.9
Parity		
First child	1039/3256	31.9
Second child	914/3256	28.1
Three or more	1303/3256	40.0
Maternal education		
No education	1052/3256	32.3
Enrolled in primary school (1-5y)	730/3256	22.4
Completed primary school (> 5 y)	1473/3256	45.2
Paternal education		
No education	972/3242	30.0
Enrolled in primary school (1-5y)	763/3242	23.5
Completed primary school (> 5 y)	1507/3242	46.5

The children were generally born small with low weights (2693g, SD 410) and short lengths (47.7 cm, SD 2.2) compared to reference children (WAZ -0.99, HAZ -0.97). Almost two thirds were born small for gestational age, but only 8% were born prematurely, which is almost half of the prevalence in other areas of Bangladesh (87).

Table 4. Baseline characteristics of children of mothers participating in the MINIMat trial

	n/n	%
Sex		
Girl	1655/3256	50.8
Boy	1601/3256	49.2
Gestational age		
Term (≥37 weeks)	3000/3256	92.1
Preterm (<37 weeks)	256/3256	7.9
Birth size for gestational age		
AGA[1]	1334/3256	41.0
SGA[2]	1922/3256	59.0
Stunting		
Not stunted	2698/3256	82.9
Stunted	558/3256	17.1
Season of conception		
Winter (Nov-Feb)	1161/3256	35.7
Pre-monsoon (Mars-May)	952/3256	29.2
Monsoon (June-Oct)	1143/3256	35.1

[1]Small for Gestational Age (77)
[2]Average for Gestational age

The randomized interventions were not associated with any of the baseline characteristics of the mother, household or children (data not shown). Mothers of the children not included in the analyses were somewhat more frequently young (<20 years), first-time mothers, having more than 6 years of education, and belonging to households in the lowest socioeconomic tertile (data not shown). Non-participating children in the puberty follow-up had more frequently been stunted at birth as compared to participating children (19.2 and 16.3%, respectively). Other background characteristics did not differ between participating and non-participating children.

Linear growth from birth to adolescence

The height-for-age Z-scores (HAZ) and the difference in height in cm from reference median (HAD) from birth up to 14 years are shown in Figure 9. The mean HAZ at birth was low and declined rapidly up to two years of age resulting in a mean HAZ at 2 years of -2.10. From two to 14 years of age, HAZ increased (mean HAZ at 14 years -1.38). The difference in height in cm from reference (HAD) showed a similar declining pattern up to two years of age but continued to decline beyond the age of two years. The prevalence of stunting at birth was 17% and increased to 54% at two years of age (Figure 10). Few children recovered from stunting during infancy and early childhood (0-2years) but by 4.5 years the stunting prevalence had decreased to 34% and by

14 years to 25%. In infancy and early childhood (0-2 years) and at puberty follow up (age 12-14 years) boys had a higher prevalence of stunting than girls (p-value <0.01) (Figure 10). In childhood the gender pattern was reversed; fewer girls recovered from stunting after two years and at 4.5 and 10 years girls had a higher prevalence of stunting than boys (Figure 10). The mean change in HAZ for children who recovered from stunting was 1.1 HAZ 0-12 months, 0.62 HAZ 12-24 months, 0.85 HAZ 24-54 months and 0.74 HAZ in the age interval 54 months to 10 years.

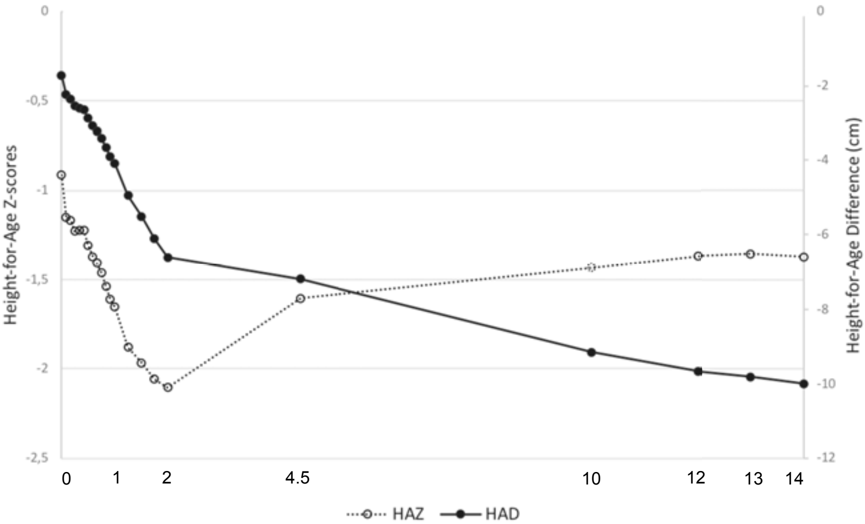


Figure 9. Height-for-age Z-scores and height-for-age difference from birth to 14 years of age

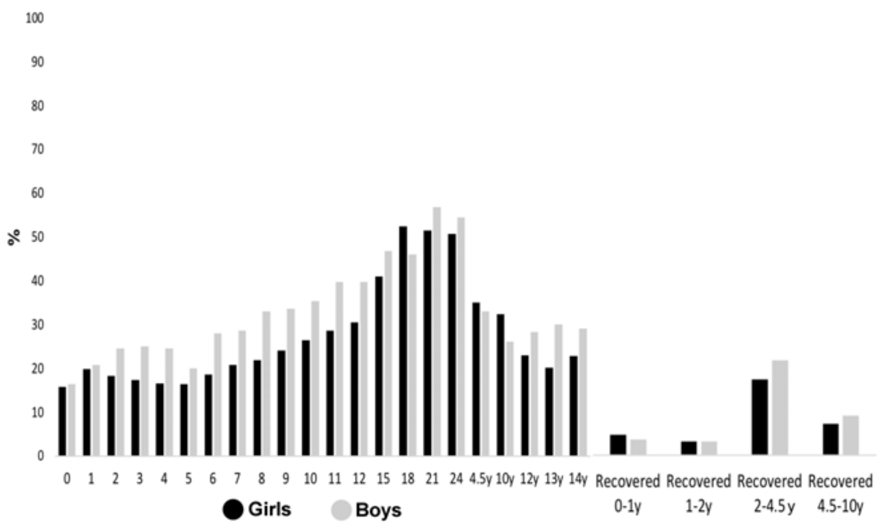


Figure 10. Stunting prevalence from birth to 14 years of age and recovery from stunting between the ages 0-1 y, 1-2y, 2-4.5 y and 4.5-10 y, stratified for sex

Risk factors for stunting at two years

HAZ and WAZ at birth were the most important predictors of stunting at two years, followed by maternal height, being born Small-for-Gestational-Age (SGA), maternal weight at 8 weeks of gestation, household asset score, and parental education. See Figure 11 .

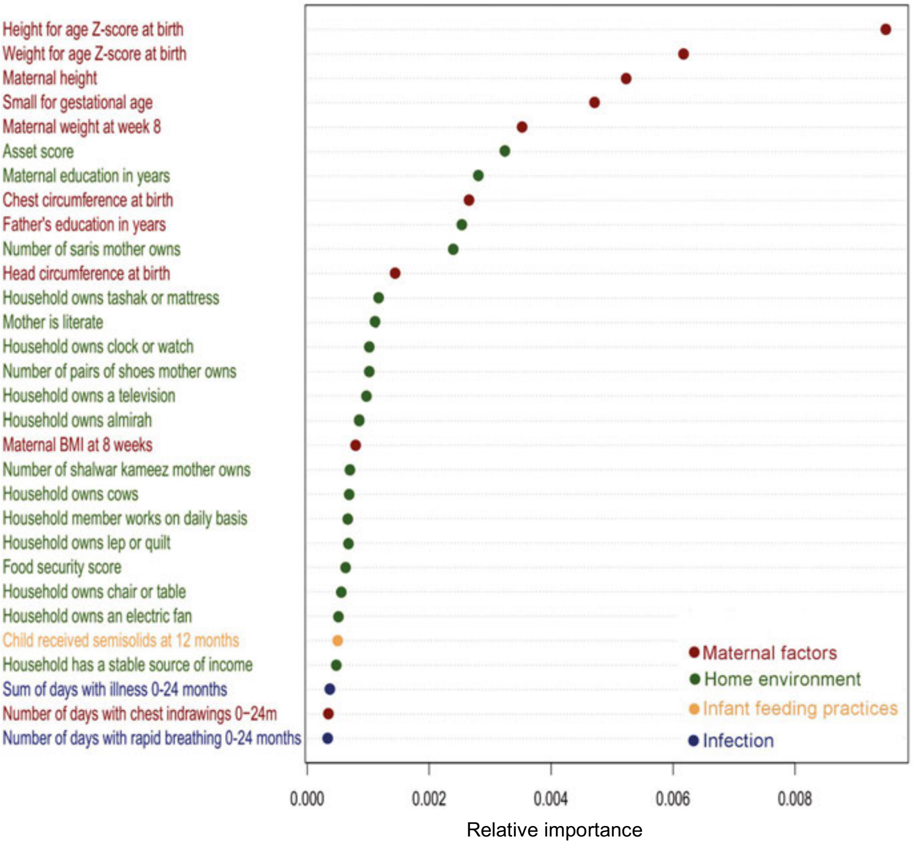


Figure 11. Conditional random forest plot ranking the relative importance of 30 predictors with regard to their ability to explain the presence of stunting at 24 months of age. The MINIMat cohort in rural Bangladesh. Color-coding according to the WHO conceptual framework on causes of stunting

The predictors that defined subgroups with different risks of stunting were HAZ at birth, maternal height, father's educational level, and the number of saris owned by the mother (Figure 12). The probability of stunting ranged from 14% to 84%. Children with the highest probability of stunting had a HAZ at birth below -1.19 and were born to mothers with a height below 151.4 cm who owned less than or equal to 5 saris. Children of a father with more than 7 years of education, who had a HAZ at birth above -0.2, had the lowest probability of stunting at 24 months.

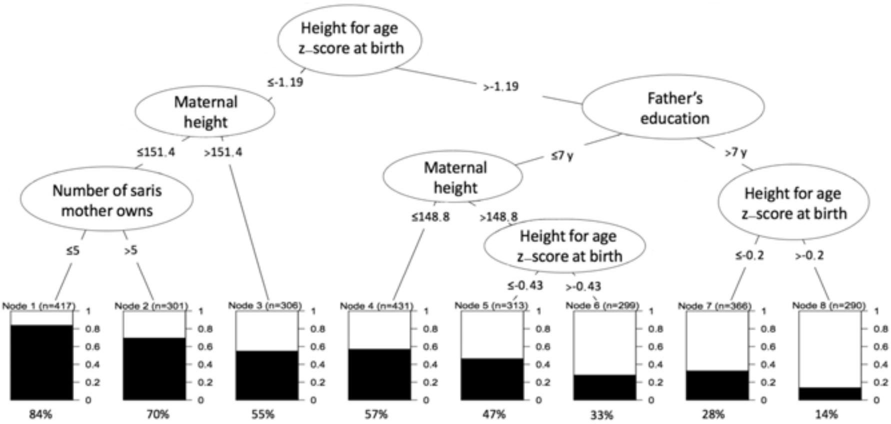


Figure 12. Conditional inference tree identifying sub-groups with different probabilities of stunting at 24 months

Linear growth by prenatal factors

The height-for-age z-scores stratified for the prenatal factors maternal height in tertiles, maternal education and season of conception are presented in Figure 13. For maternal height and education linear growth displayed a parallel pattern, with the lowest HAZ scores in children with the shortest mothers (i.e. those shorter than 147.5 cm) and mothers with no education. Children born to short or uneducated mothers also had a higher prevalence of stunting at all ages (Figure 4 and 5, Paper I) and a two-to-three times higher probability of being stunted at 10 years as compared to tall mothers (OR_{adj} 2.93, 95% CI: 2.06–4.20, Table 3, Paper I) or mothers with more than 5 years of education (OR_{adj} 1.74, 95% CI 1.17–2.81, Table 3, Paper I). Children conceived in the pre-monsoon season had lower HAZ scores and a higher probability of being stunted at 10 years of age (OR_{adj} 1.94, 95% CI 1.37–2.77, Table 3, Paper I) compared to children conceived in winter. However, there was no difference in HAZ or stunting prevalence in children who were conceived in the monsoon season as compared to winter.

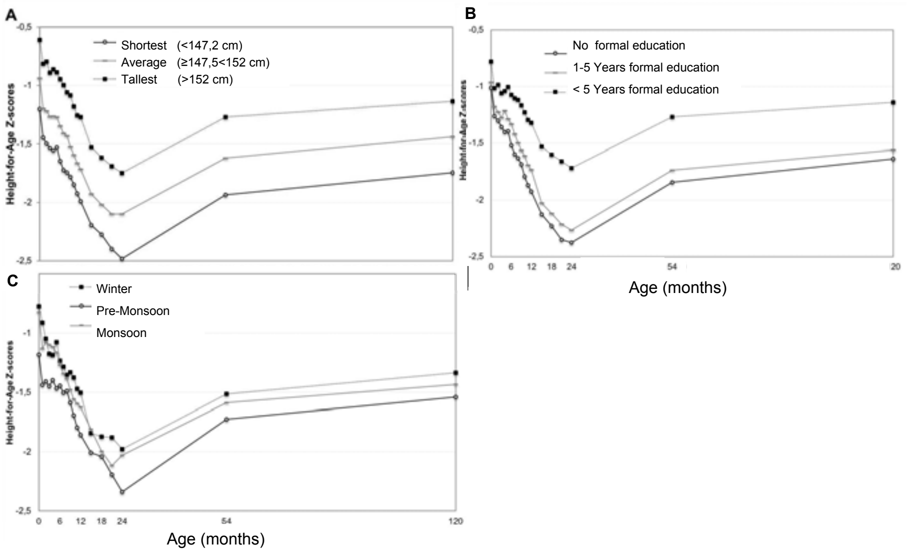


Figure 13. Height-for-age Z-score stratified for maternal height (A), maternal education (B) and season of conception (C)

Pubertal development

At the last round of puberty follow-up (age 12 to 14 years), all girls had reached Tanner stage 2 or higher in breast development, with a majority of girls having reached stage 3 (68.5%). See Figure 14. Most girls were at stage 2 of pubic hair development (42.5%) or 3 (49.8%). Three quarters (76.2 %) of the girls had reached menarche with a median age at menarche of 13.0 years. Most boys were at genital and pubic hair stage 3 (27.1%, 47.7%) or 4 (72.3%, 51.4%). See Figure 15.

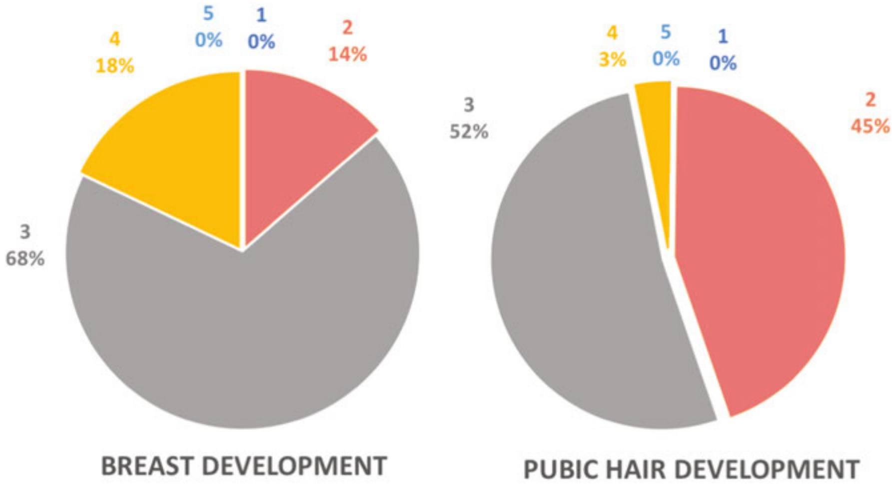


Figure 14. Breast and pubic hair development stages in girls according to Tanner

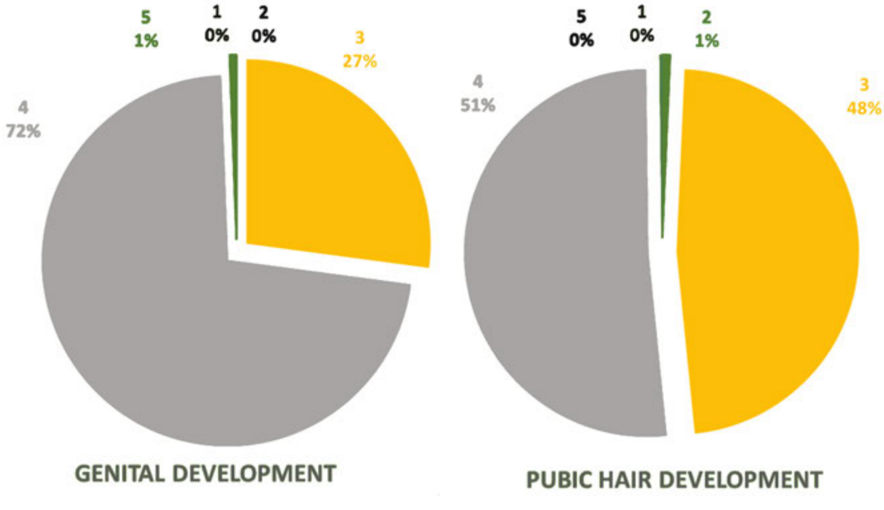


Figure 15. Genital and pubic hair development stages in boys according to Tanner

Girls and boys who were stunted at 12, 24 and 54 months were less likely to be in a higher Tanner stage (Table 3 and 4, Paper III) and having reached menarche or entered into the pubertal growth spurt. Adolescents who recovered from stunting, however, had similar pubertal development and age at menarche or timing of growth spurt as adolescents who had never been stunted (Figure 16, Table 5 and 6, Paper III).

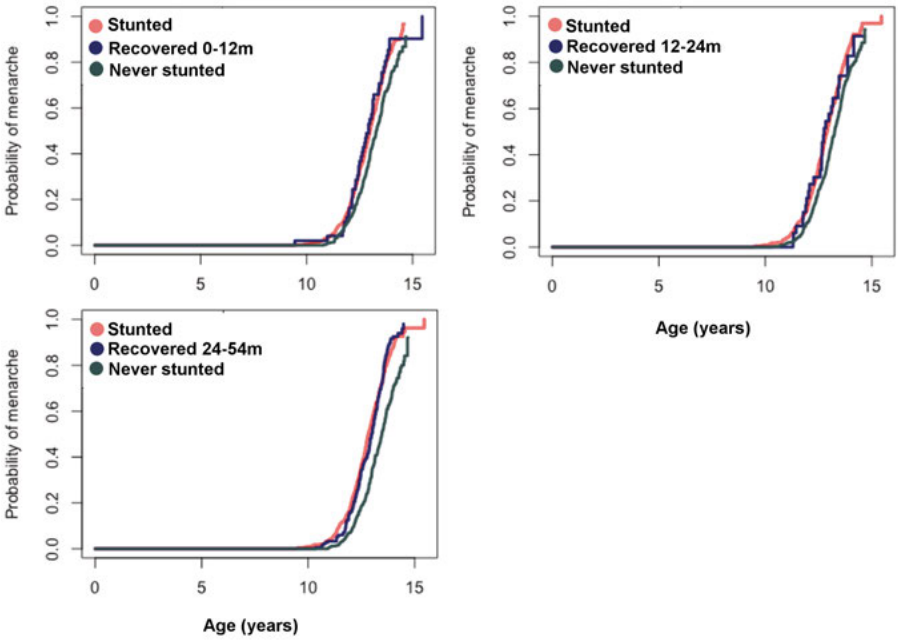


Figure 16. Kaplan Meier curves displaying the probability of having reached menarche stratified for stunting and recovery from stunting between the ages birth to 12 months,12 to 24 months and 24 to 54 months

Cost-effectiveness of the MINIMat interventions effects on infant mortality and stunting

By design, the cost of supplementing one woman was highest for the EMMS group (Table 5). The average number of years lost to premature mortality was lowest in the EMMS group and highest in the UMMS group (0.62, 2.09 YLLs, Table 4, Paper II). The UMMS group also had the highest estimated number of years lived with stunting (12.92 YLS). The least number of years lived with stunting was found in the U30Fe group (9.72 YLS). DALYs lost were lowest in the EMMS group (0.64 DALYs/child lost) and highest in the UMMS group (2.12 DALYs/child lost), irrespective of disability weight used (Table 4, Paper IV). After excluding the dominated alternatives (i.e., alternatives with both a higher cost and DALY estimate, see Figure 17) three remaining intervention arms were kept; EMMS, U30Fe and U60Fe.

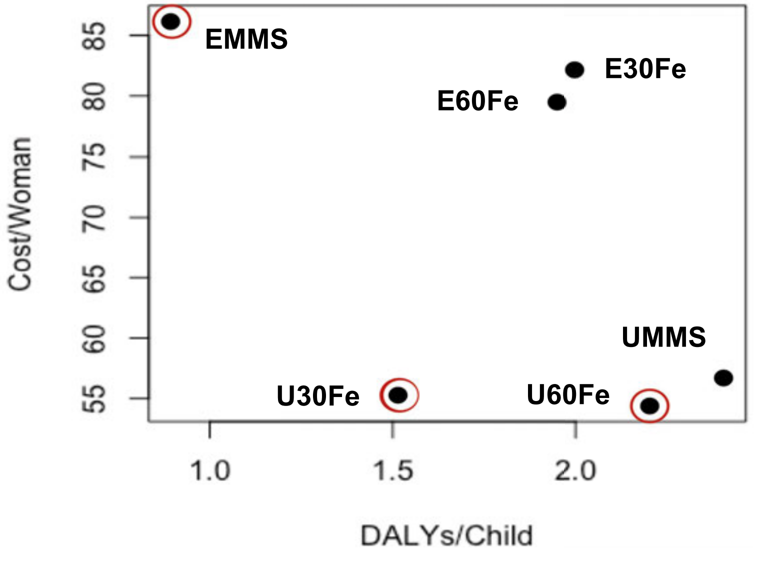


Figure 17. Cost per woman and DALY per child for the six intervention alternatives. Alternatives with both a higher cost and DALY estimate than any other alternative were excluded, i.e., E60Fe, E30Fe and UMMS. EMMS, U30Fe and U60Fe had either a lower cost or DALY estimate and were kept for further analysis. E=early invitation to food supplementation, U=usual invitation to food supplementation, 30Fe=30µ Iron and Folate, 60Fe=60µ Iron and Folate, MMS=Multiple Micronutrients

The incremental cost-effectiveness ratios (ICERs) were calculated for the three remaining intervention alternatives (Table 5). By switching from standard U60Fe to U30Fe, 0.64 DALYs per child were averted and by switching from standard U60Fe to EMMS, 1.21 DALYs per child were averted (Table 5). The ICER for one extra DALY averted by switching from U60Fe to U30Fe were US $1.34 and from U60Fe to EMMS US $24.4 (Table 5).

Table 5. Cost per woman, DALYs per child, incremental cost, incremental DALYs and incremental cost-effectiveness ratios for cost per DALY averted.

	Cost/woman	DALYs /child[1]				
U60Fe	54.42	2.20				
U30Fe	55.34	1.30				
UMMS	56.73	2.12				
E60Fe	79.46	1.73				
E30Fe	82.12	2.74				
EMMS	86.19	0.64				
Incremental cost-effectiveness ratios after excluding dominated alternatives						
			Comparison	**Incremental cost**	**Incremental DALYs**	**ICER[2]**
U60Fe	54.42	2.20	U60Fe-U30Fe	0.92	0.64	1.4
U30Fe	55.34	1.52	U30Fe-EMMS	30.86	0.66	46.8
EMMS	86.19	0.89	60Fe-EMMS	31.78	1.30	24.4

[1]Disability weight 0.002
[2] Incremental cost/Incremental DALYs
E=early invitation to food supplementation, U=usual invitation to food supplementation, 30Fe=30μ Iron and Folate, 60Fe=60μ Iron and Folate, MMS=Multiple Micronutrients

Discussion

In this thesis, linear growth trajectories and stunting from birth to adolescence were examined in a birth cohort from rural Bangladesh. The relative importance of pre- and postnatal risk factors for stunting was assessed and the consequences of stunting and recovery from stunting for pubertal development studied. Further, the cost-effectiveness of a prenatal nutrition intervention was analyzed. The findings bring attention to the importance of prenatal factors for the development of stunting. No adverse effects by recovery from stunting on timing of puberty were found, and the cost-effectiveness of the MINIMat food and micronutrient interventions on premature death and stunting were confirmed.

Growth trajectories, stunting and recovery from stunting

The children in the MINIMat cohort exhibited substantial growth restriction and high rates of stunting in infancy, childhood and adolescence. The children were born short compared to the WHO growth reference and almost 60% were born small-for-gestational-age. HAZ and HAD dramatically decreased from birth to two years of age. After two years of age HAZ increased, while growth faltering expressed as the absolute deficit in cm to reference median (HAD) continued to decline up to 14 years. The prevalence of stunting increased up to two years of age when 50% of the children were stunted. About half of the children recovered from stunting after two years, but at 14 years one quarter of the children were still stunted. This growth pattern is consistent with established growth trajectories in South Asia (21,22) and reported patterns of stunting and recovery from stunting in both Africa and Asia (26,88).

Increases in height-for-age scores coexisting with further increase in absolute height deficits may seem contradictory. These results, also reported in other recent studies (22,89), are due to the increasing standard deviations with increasing child age. This, is turn, reflects the increasing variation in normal growth over age. Accordingly, the increases in HAZ by age might be the result of both a decreasing magnitude of the deficit as well as the increasing standard deviations with age. Increases in height-for-age Z-scores, and the recovery from stunting, are thus not synonymous with catch-up growth. Catch-up implies that children grow faster than expected to regain lost height. In a population perspective, the increases in HAZ after 24 months may reflect the decreasing vulnerability to exposure to risk factors after the age of two years, and the increasing standard deviations with age. The increases in absolute height deficit in turn, reflect the absence of population catch-up. By reporting both HAZ and HAD it is possible to provide a comprehensive perspective of the growth patterns of a population.

Substantial research evidence links stunting to future adverse outcomes and a decrease in stunting prevalence is hence desirable. Stunting is defined by height-for-age scores (23) and to date, no alternative definition or threshold based on absolute height deficits exists.

The prevalence of stunting differed between girls and boys. Boys had a higher prevalence during infancy and at puberty, whereas girls had a higher prevalence of stunting in childhood. This may be explained by differences in fetal growth (90,91), variation in susceptibility to exposures during early development (92), and gender inequalities at home and in society that begin already in childhood (91,92). A relatively later timing of pubertal growth spurt in boys compared to girls in our study sample, as compared to the WHO reference population, may also be a factor to consider.

Pre and post-natal risk factors of stunting

The most important factors for stunting at 24 months were prenatal factors including birth size, the mother's anthropometry, and parental education level. Conditions after birth, such as feeding practices and child morbidity, were less important. These findings support the results from multi-country longitudinal and cross-sectional studies that have found birth weight, maternal height, household wealth, maternal education, and dietary diversity to be the most important determinants for stunting among children up to 24 months of age (28,93).These results add to the growing evidence that a large part of linear growth faltering has its origins already in fetal life(20,29,93). Especially in South Asia where children display growth deficits compared to reference children already at birth (30).

The importance of pre-natal factors for subsequent linear growth were further supported by the analysis in Paper I, where we observed associations between the mother's height, educational level, and environmental influence from early life exposure (season of conception), and infancy and childhood growth and stunting at 10 years of age.

These pre-pregnancy factors generate a vicious intergenerational cycle, where small mothers give birth to small children of whom a high proportion become, and remain, stunted (Paper I). The proposed mechanisms that could explain these intergenerational effects on linear growth are shared genetic characteristics, epigenetic effects, a small uterine volume with a reduced space for fetal growth (94, 95) and for the next generation, sociocultural factors, such as the transmission of poverty (96). In the conditional inference trees analysis, the sub-group of children that were born with a higher HAZ to shorter mothers were as likely to be stunted as the children with a lower HAZ at birth born to taller mothers. This suggests that intergenerational improvements in height are possible and that interventions with a special focus on adolescents and women of reproductive health are required to break the vicious intergenerational cycle. This is discussed further in the next section.

Although levels of stunting still prevail as one of the highest in the world, Bangladesh has made exceptional health achievements including reduced total fertility rate, child mortality and stunting during the last few decades. These health achievements can partly be attributed to the progress in access to education, especially for girls (97). The net enrolment rate at the primary school level increased from 80 % in 2000 to 98 % in 2015. In addition, the gender gap has been reduced. In the DHS data from 2011 mothers had almost one full year of education more than the fathers among parents below the age of 25.

The woman's position in the household and society is another important factor influencing the mother's ability as the primary caregiver to provide adequate care for her children (98). The number of saris the mother owned was ranked high in the random forest analysis and categorized subgroups with a higher probability of stunting. This ranking reflects the resources the mother has access to in the household but may also be a marker of the woman's status in the household.

Children conceived in the pre-monsoon period had lower HAZ scores and an increased risk of stunting at 10 years in comparison with children conceived during the winter season. The periods of relative food insecurity frequently occur in Bangladesh during May to June and October to November, prior to the two major rice harvests (99). Children conceived during the pre-monsoon season (Mars-May), which is characterized by relative food insecurity, also enter into the third trimester during the second food insecurity period. The peak of diarrheal diseases and increased workload taking place during the pre-monsoon season (100) may additionally influence the health of mothers and the growth of their fetuses (101).

Post-natal factors, such as child morbidity and suboptimal infant and early childhood feeding practices, have repeatedly been reported as significant risk factors for stunting (102-104). Infant feeding at 12 months and the sum of days with illness were among the 30 most important variables for stunting but were ranked relatively low and did not show up in any of the conditional inference trees. One explanation to the low ranking could be Bangladesh's remarkable success in achieving the world's highest coverage of oral rehydration therapy for children with diarrhea (105) and the almost universal immunization coverage (106,107). This accomplishment has reduced or partly eliminated immunization-preventable morbidity, which may have consequences for linear growth. Complementary feeding trials have generally shown a modest effect on linear growth (48). In spite of the few documented effects of complementary feeding programs on stunting, these interventions have often been given priority in national or global efforts to combat stunting. Complementary feeding programs and efforts to improve water quality and sanitation have, however, had more success in improving child development (49,108).

Entry points and possibilities of prevention

What can be done to improve linear growth pre- and postnatally? The period from conception to two years of age is identified as the window of opportunity for the prevention of undernutrition. Evidence from adoption studies demonstrate that partial to complete catch-up of linear growth failure is possible, if it occurs before the age of two years (19). As mentioned earlier, however, varied types of post-natal child health interventions have had limited success in achieving linear growth improvements in children in low resource settings. Intergenerational influences could be one reason for the lack of impact. Yet, results from the WHO Multicentre Growth Reference Study and migration studies suggest that substantial improvements in birth weight and linear growth of children can be achieved in only one generation, if the formerly undernourished mother gain access to adequate nutrition and health prior to conception and in the first 1000 days of the child's life (109). Although it is unrealistic to expect similar results from intervention programs in low-resource settings, there is probably still much that can be done by implementing interventions prior to and during pregnancy.

Established prenatal nutritional interventions include nutritional counseling and education, balanced energy-protein supplementation, and multiple micronutrient supplements. Unfortunately, most studies evaluating these interventions only report birth weight, not length, a reason why evidence to directly assess the effect on fetal linear growth is limited. Meta-analyses and randomized trials evaluating these interventions report increased birth weight and a reduced risk of LBW (51-58). In the MINIMat trial, children of mothers who participated in food supplementation from early pregnancy (versus the usual start) had a 13% reduction in stunting up to five years (65).

Preconception interventions may be even more appropriate (110) as pregnancy might be too late to correct nutritional deficiencies, although preconception programs are complex to implement. A small number of trials examining the effect of interventions initiated before pregnancy are underway, but few results have been published so far (111,112) .

Adolescence is another appropriate period for interventions, especially in South Asia, where marriage at a young age and first pregnancy is common (113). Adolescence is the period of the second growth spurt. Conception during that period, as well as inadequate nutrition and health, results in short stature in adulthood for the mother plus fetal growth restriction and stunting in their children (114).

Knowledge, policy and practice

As highlighted above, the first 1000 days of life are universally recognized as the optimal period for the prevention of undernutrition. Policy documents emphasize the importance of interventions targeting women of reproductive age and children during this time span (7,45). With the exception of prenatal iron-folic acid supplementation, all nutrition interventions currently recommended by the WHO focus on the postnatal period (46). A knowledge, policy, and practice gap prevails, despite the consensus on the importance of the first 1000 days.

The results from this thesis strengthen the evidence that the process of stunting starts already before birth, as well as the importance of intergenerational effects. Postnatal interventions can influence factors in the environment that constrain the ability to increase linear growth. Prenatal interventions, on the other hand, have the potential to modulate the actual growth potential in present and future generations through changes in gene expression in response to the fetal environment. Although worthwhile, the focus on postnatal interventions results in missed opportunities to intervene when the process of stunting is being established.

DALYs and cost-effectiveness of the MINIMat trial interventions

In the MINIMat food and micronutrient interventions, children whose mothers participated in food supplementation from early pregnancy (versus the usual start) combined with multiple micronutrients (MMS) had a substantial reduction in under-five year mortality. In addition, early invitation to food supplementation compared with the usual timing of the start of supplementation was associated with a 13% *reduction* in stunting before the age of five years (65), while MMS supplementation was related to a 15% *increase* in stunting in comparison with standard 60 mg iron, 400 µg folic acid. This combination of favorable and unfavorable effects illustrates that nutrition interventions may influence multiple outcomes that may be positive as well as negative from a public health perspective.

The main aim of the cost-effectiveness study was to evaluate the cost of switching from the routine prenatal supplementation of 60 mg iron and folate plus the usual timing of daily food supplements (U60Fe) to the potentially superior multiple micronutrients plus an early invitation to food supplementation (EMMS), when both favorable and unfavorable outcomes were included. The children whose mothers received the MMS in combination with an early food supplementation had the lowest DALY estimate while children whose mothers received the MMS in combination with usual timing of food supplementation had the highest DALY estimate. This was because the UMMS group had the highest number of years lost to premature death (YLLs) and the highest number of years lost to stunting (YLDs). Meta-analyses of trials evaluating prenatal multiple micronutrient vs. iron and folate supplementation have reported limited increases in birth weight (52,62), and some reduction in the prevalence of small-for-gestational-age births (133).They do not report, however, any reduction in the risk of child mortality or subsequent linear growth failure (115). The newly updated WHO guidelines on antenatal care do not routinely recommend multiple micronutrients for pregnant women (116). What makes the MINIMat interventions different from the trials included in the above-mentioned studies is that the multiple micronutrient supplementation was combined with *food* supplementation *early* in pregnancy. The reduction in mortality was only seen as a combined effect of early food supplementation and MMS. MMS given *without* food supplementation in early pregnancy (UMMS) had the highest DALY estimates. These results indicate positive outcomes of providing MMS, in a population like this, only when it is combined with increased macronutrient intake that is initiated in early pregnancy.

Including the effects on stunting in the cost-effectiveness analysis did not alter the conclusion that the MINIMat interventions of early prenatal food and MMS supplementation were highly cost-effective in a population with prevalent maternal undernutrition. The ICER of US$ 24 for switching from an invitation to food supplementation at the usual time in pregnancy and iron-folic acid supplementation to an early initiation of food supplementation combined with MMS, compares favorably to corresponding interventions in South Asia (117-119). The cost per DALY averted can be considered affordable in a low-resource setting and viable from both a public health and economic perspective in a setting with prevalent maternal undernutrition and relatively frequent food insecurity.

Consequences of stunting and recovery from stunting for pubertal development

The research question “Does recovery from stunting come with any adverse future effects?” guided the analysis in Paper III. Epidemiological and adoption studies have reported associations between greater post-natal growth and an early puberty (37, 39, 120, 122). In an adoption study from Sweden, girls with the most pronounced stunting and fastest catch-up growth had the lowest age at menarche (19). Early puberty onset has, in turn, frequently been associated with adult chronic disease (40-43).These reported associations between timing of puberty and adult chronic diseases do not necessarily reflect causal pathways (41). Timing of puberty and adult chronic disease risks may, however, share common developmental origins. Age at puberty may therefore be seen as an early indicator for the interactions between genetics and environmental conditions, which possibly affect future adult health.

As expected, children in our study that were stunted in infancy and childhood had later pubertal development. Girls had a later menarche and boys started their growth spurt later, as compared to non-stunted children. Children who recovered from stunting, however, had a similar timing of puberty as children who were not stunted, irrespective of when the recovery occurred. That is, there was no evidence of adverse effects of recovery from stunting in infancy or childhood in terms of very early pubertal development. It should be noted that the adolescents in the MINIMat cohort were born into and remained in an underprivileged setting, which is a significant difference from the adoption studies. In addition, although children that recovered from stunting displayed increases in HAZ scores they did not have the substantial rapid catch-up growth as in the children adopted into affluent environments.

Methodological considerations

Generalizability

The MINIMat study was carried out in rural Bangladesh, where maternal and child undernutrition still prevail. Bangladesh is situated in South Asia that accounts for the largest burden of stunted children. Children are typically born below the WHO growth reference, reflecting that the growth faltering frequently starts already in fetal life. Sub-Saharan Africa has the second highest rate of stunting. Although these sub-continents share similar proportions of stunted children and growth patterns from 3 to 24 months, the Sub-Saharan African children usually have a size at birth similar to that of the WHO growth reference, i.e., are born slightly bigger than children in South Asia (21).

In addition, the nutrition transition, characterized by less physical activity and increased access to highly processed foods and sugar-sweetened beverages, which is ongoing in many low- to middle-income settings, is not yet fully present in the rural study area of Matlab. Thus, the results of our study are mainly representative for other rural areas in Bangladesh and perhaps also to neighboring countries in South Asia where children are born small and remain short and light.

Some potential determinants of stunting were not present in the MINIMat database. The cohort did not include the collection of stools for the study of enteropathogens in the child (29), paternal height, which may be related to fetal growth, or the mothers' smoking habits. Smoking was, however, extremely rare among women in the study area. Furthermore, household water, sanitation, and hygiene (WASH) characteristics that have been shown to be associated with the risk of stunting by increasing primarily diarrheal diseases

(121) were limited to information on arsenic contamination of the drinking water. Still, diarrhea and other morbidity information was included in our analyses.

Potential biases

The MINIMat study was implemented in an area with a well-developed research infrastructure ideal for obtaining high-quality longitudinal data. To ensure that the sample was representative of the population, all pregnant women within the study area were invited to participate in the MINIMat trial and the refusal rate was low. Around 400 children did not have anthropometry from birth and were excluded from all the analyses. These children were characterized by having younger, more educated mothers from a lower socioeconomic group. This may be explained by the fact that younger women gave birth outside the study area more frequently, for example when staying in their maternal home. Children whose mothers were more educated and from a lower socio-economic group continued to be less likely to participate in the subsequent follow-ups. More educated women and women from a lower socioeconomic group may be more likely to migrate from the study area or spend more time outside the home. These differences, however, were small and it is unlikely that they influenced the main findings of this thesis.

Experienced field workers, study nurses and medical doctors collected data during pregnancy, at birth, and in the follow-up during infancy, childhood and adolescence. To minimize measurement errors the data collectors participated in frequent refresher training, including anthropometry standardization exercises.

Self-assessment of puberty development can be appropriate in larger epidemiological studies to examine the relative distribution of being in an earlier or later pubertal development stage, but is not well suited to determine the precise staging of development or onset of puberty for the individual (122-125). Studies on the reliability of self-assessment have also reported that girls tend to underestimate their development stage, whereas boys tend to overestimate (125). These biases were probably also present in our study, where boys generally reported being in a later puberty stage than girls, despite the fact that girls generally enter puberty at a younger age than boys (74).

For the assessment of puberty timing, information on age at menarche for girls was collected and onset of pubertal growth spurt for boys was calculated and analyzed. The date of menarche was collected by a self-reported date of onset at two time points, increasing the probability of collecting the data close to the event and minimizing recall errors (126). The analysis of start of growth spurt was done in a sub-set of boys who had anthropometric measurement at 10 years of age. The 10-year follow-up was done in one of the two-calendar-year birth cohort. Hence, the selection should not suffer from any selection bias related to the exposures.

The different growth references used in this thesis were developed based on height data from different children; the WHO Child Growth Standards from birth to 5 years of age and the 1977 NCHS/WHO reference from 5 to 19 years. The 1977 NCHS/WHO reference has been reconstructed and merged with the WHO growth curves to provide a smooth transition (127). The disparities between the growth curves in the junction at 5 years were small (0.1-0.4 cm for boys and girls over the range of Z-scores) and it is unlikely that this has influenced the results of this thesis.

Most nutrition interventions have multiple objectives and outcomes. In the cost-effectiveness analysis there were two outcomes, i.e., premature mortality and disability caused by stunting. It should be noted that these outcomes do not represent all potential benefits or harmful effects caused by the MINIMat intervention (128). An example is the unfavorable metabolic profiles in children allocated to the multiple micronutrient supplementation, with lower levels of IGF and HDL at 4,5 years (129).

DALYs were used to summarize the health gains (and losses) of the interventions. No attempt is made to value the health gain in cost-effectiveness analysis. The disability weights used to calculate DALYs should, however, reflect the severity of the disease or the health state. The weight attributed to stunting by the global burden of disease study, 0.002, is small. The weight, and thus the cost-effectiveness analysis, does not consider stunting's additional health and economic consequences for the individual and society, such as lower school performance (130) and future earnings, higher risk of adult chronic disease (131), and impaired pregnancy outcomes for women (132). The conclusion that switching from UFe60 to EMMS is highly cost-effective would, however, not change if the impact of stunting increased, as U60Fe had higher years lost to stunting (YLS) than EMMS.

Confounding

The multiple modeling accounted for potential confounders in Paper I and III. The potential confounders were included based on whether they were associated with both the exposures and outcomes. The differences between the crude and adjusted analyses were small. Residual confounding, however, cannot be completely ruled out.

Strengths and limitations of applying Data Mining methods

With decision-tree-based methods a large number of predictor variables of different types can be modeled and interactions are automatically identified and included without the need to specify the form of dependence or to deal with issues regarding multi-collinearity. In classical regression models, the inclusion of such a large number of predictor variables and their interactions is not computationally possible. Unlike conventional statistical models that compute relative risks or odds ratios, random forest modeling ranks the predictors according to how important these are for explaining the variation in the outcome. The random forest analysis does not, however, provide information about whether the predictors have a negative or positive association with the outcome. The conditional inference trees, on the other hand, display precise information about the direction, size and priority of the association of the predictors with the outcome. The identification of risk groups, including the prioritization and relevant cut-offs of risk factors, can be of considerable public health relevance for the design and targeting of appropriate interventions with the most significant benefits.

Furthermore, if the data contain two essential and highly correlated predictors, the conditional inference tree method may select only one of them in the analysis, although the other predictor might be as important. Lastly, decision-tree-methods do not deliver p-values or confidence intervals. The cross-validation method, however, ensured that the selected tree models were optimal in terms of predictive performance.

Conclusions and recommendations

The findings presented in this thesis are related to the extent, risk factors and consequences of maternal and child undernutrition in general, and stunting in particular, in the context of rural Bangladesh. It also discusses entry points for prevention and the cost-effectiveness of a prenatal food and micronutrient intervention. The key findings and conclusions were:

1. The children in the MINIMat cohort exhibited substantial growth restriction and high rates of stunting in infancy, childhood and adolescence. Despite individual recovery from stunting, no true population catch-up occurred after infancy.

2. Prenatal factors were the most influential risk factors of stunting at two years and continued to be associated with childhood growth and the risk of being stunted at the age of ten.

3. In contrast to earlier studies in high-income settings or in children adopted by families in high-income countries, no unfavorable association between recovery from stunting in infancy or childhood and early timing of puberty was found.

4. The inclusion of stunting as an outcome did not alter the conclusion that the MINIMat interventions of early prenatal food and MMS supplementation were highly cost-effective in a population where maternal undernutrition is still common.

5. To prevent stunting, interventions should increasingly focus on adolescent girls and women of reproductive age in the period prior to and during pregnancy in addition to the postnatal period up to two years.

Considering the short and long-term consequences of stunting for the individual and society, the prevention and treatment of stunting should be highly prioritized in national and global public health agendas. The findings from this thesis highlight the importance of prenatal factors as well as the biological and social intergenerational effects on linear growth. The lifecycle approach to prevent stunting needs to be reinforced. The gaps between current knowledge, policy and practice should be closed, with more emphasis given to prenatal interventions. A lifecycle approach might involve the launch and evaluation of interventions that focus on adequate health, education and nutrition in the preconception period and during pregnancy. This is especially important in South Asia with its high burden of maternal undernutrition and young age at first pregnancy. Bangladesh has already made impressive progress by launching women-oriented efforts such as securing female literacy, empowerment and family planning. Gender inequality still prevails though, and it has been suggested that it contributes to the prevailing poor nutritional status of women and young children despite the greater improvements in other health metrics. The combination of nutrition-specific interventions with further empowerment of women should be continued. These efforts may include improved dietary intake and health services to women, prevention of early-age marriage and conception, the completion of secondary education, increased purchasing and decision power to women, and the elimination of domestic violence.

Despite the challenges of implementing and evaluating multi-sectorial interventions targeting women prior to conception, this should be a priority for future research. Furthermore, evaluating the cost-effectiveness of nutrition interventions is important to support decision-makers in their prioritizing and financing of nutrition interventions targeting maternal and child undernutrition.

Targeting and reaching adolescences and women of reproductive age at sufficient numbers will be challenging. Identifying and targeting high risk sub-groups, in this setting characterized by short, poor women with low education, and their children, might be one strategy to implement and evaluate. In our study (as is the case in the rest of Bangladesh), the entire HAZ distribution is shifted to the left, indicating that all children, not only those below the stunting cut-off, are affected by growth faltering to some degree. Thus, in addition to nutrition-specific interventions targeting vulnerable populations, continued efforts to reduce poverty are needed.

I hope the findings provided by this thesis encourages decision-makers to prioritize and finance nutrition specific and nutrition-sensitive interventions for adolescent girls and women of reproductive age, and that this will, in turn, benefit the present and future generations of women, mothers, and children in rural areas of Bangladesh and other low-income countries.

Summary in English

Stunting, defined as a deficit in height relative to the child's age according to a standard that reflects optimal growth, is the most prevalent manifestation of child undernutrition and reflects long-term exposure to undernutrition, infectious diseases or inappropriate child care. With an increased understanding of the long-term consequences of chronic undernutrition, international actors have shifted their focus from efforts to reduce the prevalence of underweight children to the prevention of stunting. In 2012 the World Health Assembly (WHA) adopted a resolution to reduce stunting by 40% by the year 2025 and to reduce stunting is one of the targets under the second Sustainable Development Goal (SDG) to end hunger and improve nutrition.

To reach these goals, and to develop and deliver appropriate interventions, it is imperative to understand the dynamics and determinants of stunted growth. The findings presented in this thesis are related to the extent, risk factors and consequences of maternal and child undernutrition in general, and stunting in particular, in the context of rural Bangladesh. It also discusses entry points for prevention and the cost-effectiveness of a prenatal food and micronutrient intervention.

The participants were mothers and children participating in the Maternal and Infant Nutrition Interventions (MINIMat) trial, a prenatal nutrition supplementation trial, carried out in rural Bangladesh. From November 2001 to October 2003 4,436.pregnant women were randomized into receiving either early, or usual timing (routine) of invitation to food supplementation. There were also different micronutrient groups, multiple micronutrients supplementation (MMS) with 15 micronutrients or iron and folic acid supplementation (routine).

The frequent follow-ups of the mothers and the cohort of children participating in the MINIMat trial from birth to puberty have generated a rich, unique database, which provides an excellent opportunity to investigate different longitudinal aspects of child growth from fetal life to adolescence. The aims of this thesis were to examine: the linear growth trajectories and stunting from birth to adolescence, the relative importance of pre- and postnatal risk factors for stunting and the consequences of stunting and recovery from stunting for pubertal development in children in rural Bangladesh. Further, the cost-effectiveness of the prenatal nutrition intervention was analyzed, including both favorable (reduced infant mortality and stunting) and unfavorable (increased stunting) outcomes.

The children in the MINIMat cohort exhibited substantial growth restriction and high rates of stunting in infancy, childhood and adolescence. The children were born short compared to the WHO growth reference and almost 60% were born Small-for-Gestational-Age. Height-for-age Z-scores (HAZ) dramatically decreased from birth to two years of age. After two years of age HAZ increased, while growth faltering expressed as the absolute deficit in cm to reference median (HAD) continued to decline up to 14 years of age. The prevalence of stunting increased up to two years of age when 50% of the children were stunted. About half of the children recovered from stunting after two years, but at 14 years of age one quarter of the children were still stunted. This growth pattern is consistent with established growth trajectories in South Asia and reported patterns of stunting and recovery from stunting in both Africa and Asia.

The most important risk factors for stunting at 24 months were prenatal factors including birth size, the mother's anthropometry and parental education level. Conditions after birth, such as feeding practices and child morbidity, were less important. The importance of pre-natal factors for subsequent linear growth were further supported by associations between the mother's height, educational level, and environmental influence from early life exposure (season of conception), and stunting at 10 years of age.

Children that were stunted in infancy and childhood had a later pubertal development. Girls had a later menarche and boys started their growth spurt later, as compared to non-stunted children. In contrast to earlier studies in high-income settings or in children adopted by families in high-income countries, no unfavorable association between recovery from stunting in infancy or childhood and early timing of puberty was found.

When favorable (decreased under-five year mortality) and unfavorable (increased stunting), outcomes of the MINIMat trial were included in a cost-effectiveness analysis, the MINIMat interventions were highly cost-effective in a setting with prevalent maternal undernutrition and relatively frequent food insecurity. The cost for switching from a late start of invitation to food supplementation in pregnancy and iron-folic acid supplementation to an early initiation of food supplementation combined with MMS, can be considered affordable in a low-resource setting and viable from both a public health and economic perspective.

Considering the short and long-term consequences for the individual and society, the prevention and treatment of stunting should be highly prioritized in national and global public health agendas. The first 1000 days of life are universally recognized as the optimal period for the prevention of undernutrition and policy documents emphasize the importance of interventions during this time span. However, with the exception of prenatal iron-folic acid supplementation, all nutrition interventions currently recommended by the WHO focus on the postnatal period. The findings from this thesis highlight the importance of prenatal factors as well as the biological and social intergenerational effects on linear growth. The lifecycle approach to prevent stunting needs to be reinforced and the gaps between current knowledge, policy and practice should be closed, with more emphasis given to prenatal interventions. Hopefully, the findings provided by this thesis can encourage decision-makers to prioritize and finance nutrition interventions for adolescent girls and women of reproductive age.

Sammanfattning på svenska

Långsam tillväxt hos barn och att därmed bli för kort för sin ålder (stunting) är den mest utbredda manifestationen av undernäring hos barn och återspeglar långvarig exponering för undernäring och upprepade infektioner. Med en ökad förståelse för de långsiktiga konsekvenserna av kronisk undernäring har internationella aktörer skiftat fokus från att minska förekomsten av undervikt till att förebygga tillväxthämning hos barn. WHO har som mål att minska tillväxthämning hos barn med 40% till och med 2025, och att minska andelen barn som är för korta för sin ålder är ett av delmålen under det andra hålbarhetsmålet att utrota hunger.

För att nå dessa mål, och att utveckla lämpliga interventioner, är det viktigt att förstå dynamiken och riskfaktorerna för hämmad längdtillväxt hos barn. De resultat som presenteras i denna avhandling är relaterade till omfattning, riskfaktorer och konsekvenser av undernäring hos barn och mammor i allmänhet, och hämmad längdtillväxt hos barn i synnerhet, på landsbygden i Bangladesh. Tidpunkter och åtgärder för prevention och kostnadseffektivitet av en nutritionsintervention till gravida mammor diskuteras också.

Deltagarna i studierna som ligger till grund för denna avhandling var mammor och barn som medverkade i MINIMat studien (Maternal och Infant Nutrition Interventions in Matlab) som genomförs på landsbygden Bangladesh. Från november 2001 till oktober 2003 blev 4 436 gravida kvinnor randomiserade till en tidig (graviditetsvecka 9) eller sen inbjudan (graviditetsvecka 20, rutin) till ett program med kostsupplementering. Kvinnorna randomiserades även till supplementering med multipla mikronäringsämnen (MMS) eller järnfolsyra-supplement (rutin).

De upprepade uppföljningarna av mammorna och barnen som deltar i MINIMat-studien har gett upphov till en unik, omfattande databas som möjliggör studier av olika longitudinella aspekter av barns tillväxt från fosterlivet upp till pubertet. Syftet med den här avhandlingen var att undersöka: längdtillväxt från födsel till pubertet, den relativa betydelsen av pre- och postnatala riskfaktorer för tillväxthämning samt konsekvenserna av tillväxthämning och återhämtning från tillväxthämning för pubertetsutveckling hos barn på landsbygden i Bangladesh. Dessutom utvärderades kostnadseffektiviteten av MINIMat interventionerna, med hänsyn både till studiens gynnsamma (minskad spädbarnsdödlighet och tillväxthämning) och ogynnsamma (ökad tillväxthämning) utfall.

Barnen i MINIMat-kohorten hade utbredd förekomst av tillväxthämning som spädbarn, barn och ungdomar. Barnen föddes korta jämfört med WHO: s tillväxtreferens och nästan 60% föddes små för sin gestationsålder (Small-for Gestational-Age, SGA). Barnen tappade dramatiskt i längd från födsel upp till två års ålder då förekomsten av tillväxthämning var som högst, 50%. Ungefär hälften av barnen återhämtade sig efter två år, men vid 14 år var en fjärdedel av barnen fortfarande för korta för sin ålder. Detta tillväxtmönster överensstämmer med etablerade tillväxtkurvor i Sydasien.

De viktigaste riskfaktorerna för att vara kort för sin ålder vid 24 månader var prenatala faktorer, mer specifikt: storlek vid födelsen, mammans längd och vikt samt föräldrarnas utbildning. Förhållanden efter födseln, såsom amning och förekomst av sjukdom hos barnet, var mindre viktiga. Betydelsen av prenatala faktorer för senare linjär tillväxt hos barnet stöddes ytterligare av associationer mellan moderns längd, utbildningsnivå samt yttre förhållanden vid tidig graviditet (säsong på året vid konception) och förekomsten av tillväxthämning vid 10 års ålder.

De barn som var för korta för sin ålder hade en senare pubertetsutveckling. Flickor hade en senare menarche och pojkar startade sin tillväxtspurt senare, jämfört med icke-tillväxthämmande barn. Till skillnad från tidigare studier i höginkomstländer eller av barn som adopterats av familjer i höginkomstländer, såg vi inget ogynnsamt samband mellan återhämtning från tillväxthämning och tidig debut av pubertet.

MINIMat-interventionerna med tidig start av kostsupplementering och MMS-tillskott visade sig vara mycket kostnadseffektiva i en kontext där undernäring hos mammor och barn är utbrett. Kostnaden för att övergå från sen start av kostsupplementering samt järn och folsyratillskott till en tidig start av kostsupplementering kombinerat med MMS kan betraktas som skälig både ur ett folkhälso- och ekonomiskt perspektiv.

Med tanke på de korta och långsiktiga konsekvenserna för både individ och samhälle bör åtgärder som förebygger och behandlar tillväxthämning hos barn vara högt prioriterade både nationellt och globalt. De första 1000 dagarna av livet är allmänt erkänd som den optimala perioden för att förebygga tillväxthämning och policydokument betonar ofta vikten av insatser under denna tidsperiod. Med undantag för järn och folsyratillskott under graviditeten fokuserar dock alla nutritionsinterventioner som för närvarande rekommenderas av WHO på den postnatala perioden. Resultaten från denna avhandling, och från tidigare studier, belyser vikten av prenatala faktorer. Gapet mellan existerande kunskap, policy och praxis bör slutas, och en större vikt läggas vid prenatala interventioner. Förhoppningsvis kan resultaten från denna avhandling uppmuntra beslutsfattare att prioritera och finansiera interventioner som riktar sig mot tonårsflickor och kvinnor i reproduktiv ålder.

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