Undernutrition in early life: using windows of opportunity to break the vicious cycle

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CHAPTER 01

General introduction

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The current state of undernutrition

Undernutrition is still prevalent worldwide, predominantly in low-and middle-income countries. Today, approximately 690 million people are undernourished.[1] Of all population groups, women and children are the most vulnerable to undernutrition because of their increased physiological demand for nutrients. Recent estimates show that nearly 153 million women are undernourished as measured by body mass index which is a manifestation of current nutritional status. The prevalence of undernutrition among women of reproductive age is over 20% in most South Asia and sub-Saharan Africa countries.[2] Also, 450 million women are of short stature, which indicates intergenerational and chronic undernutrition.[3] Among under five children, 149.2 million which approximates 22.0% are stunted, a reflection of chronic undernutrition in early years of life.[4] By region, South Asia and sub-Saharan Africa countries are most affected by undernutrition and stunted growth among children (Figure 1). In most of these countries the prevalence of stunting among under five children surpassed 20.0% showing that chronic undernutrition in early years of life is a significant public health problem.[5] On the other side of the spectrum, overweight and obesity are increasing in low-and middle-income countries,[4] especially among those chronically undernourished in early years of life related to the gradual change in economic circumstances and living conditions. Hence, the increasing overnutrition, on top of the already high prevalence of chronic undernutrition, imposes a double burden of disease in low-and middle-income countries.

Tackling the ongoing challenge of undernutrition has been a global priority, especially since 2000. Failing to achieve the Millennium Development Goals in 2015, the Sustainable Development Goals agenda was established, with a 2030 horizon. One of the targets of the Sustainable Development Goals is eliminating all forms of undernutrition. Specific to stunting, the target is a 50% reduction. Despite the impressive gains, still the global progress is not on course to meet the nutritional targets like that of stunting by 2030. Also, the success so far is uneven across the regions (Figure 1). If current trends continue, nearly 129 million under five children will be stunted by that date mostly in low-income countries. The absolute number of stunted children is currently increasing in Africa.[6] For instance, it increased from 54.4 million in 2000 to 61.4 million in 2020. The consequences of the current coronavirus pandemic may increase the number further.[4]

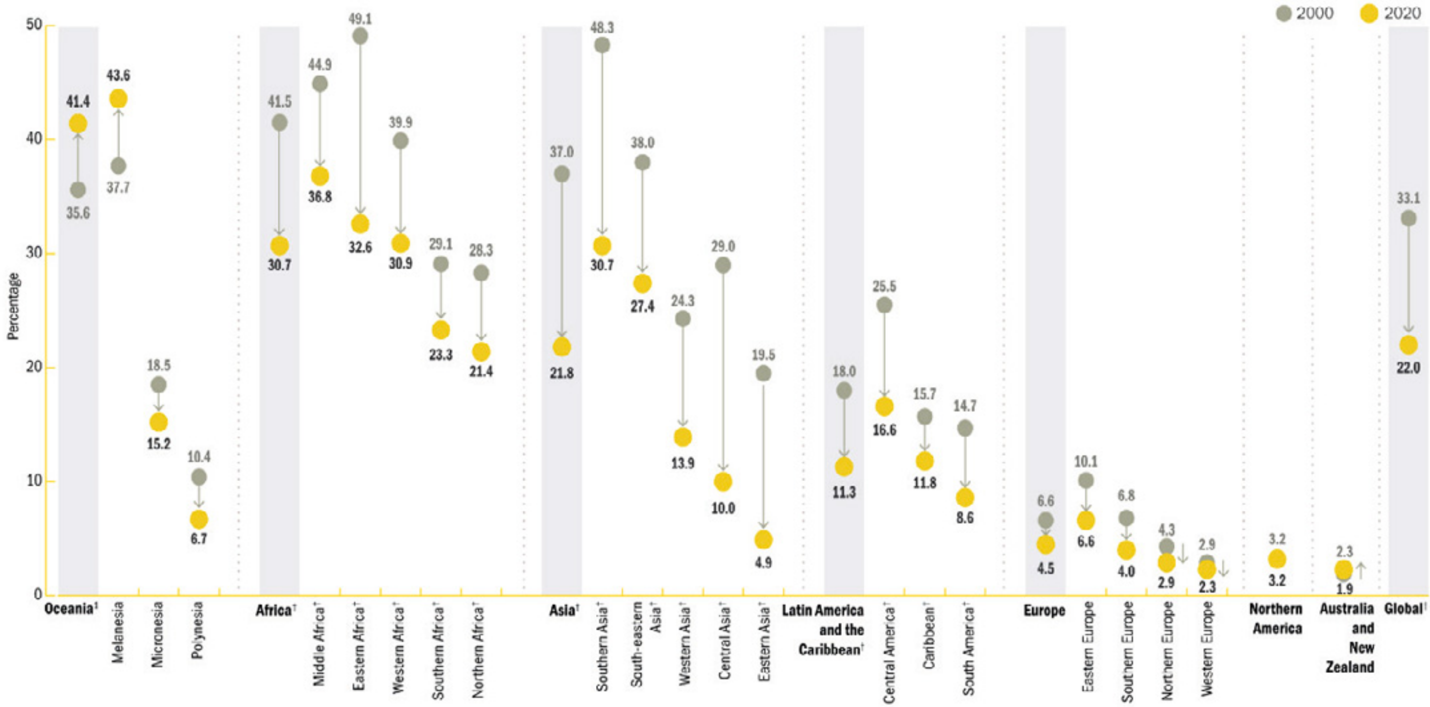

Figure 1. Trends in the percentage of children under 5 affected by stunting, by United Nations region/sub-region, 2000 and 2020 (Source: UNICEF, WHO, World Bank. Levels and trends in child malnutrition: key findings of the 2021 edition of the joint child malnutrition estimates. Geneva: World Health Organization; 2021.)

Undernutrition in early life and its consequences

As noted earlier, stunting reflects chronic undernutrition early in life. In this case, early life refers to life in utero and early childhood, usually the first 1,000 days, i.e., from the moment of conception up to two years after birth. In areas where maternal undernutrition is rampant, chronic undernutrition often starts in utero and continues after birth or may even worsen because of recurrent infectious diseases and/or inadequate care. Small for gestational age at birth, and low birth weight are the surrogates for intrauterine growth retardation, which may be partly attributed to chronic undernutrition in utero. For instance, some studies in low-income countries reported that about one-third of children are stunted at birth, reflecting growth failure in utero.[7–9] In the absence of adequate dietary intake and healthcare, chronic undernutrition can also begin after birth during postnatal development. In low-income countries, chronic undernutrition in early life is one of the leading underlying causes of childhood death. For surviving children, chronic undernutrition in early life has negative consequences far beyond early childhood.[10] It extends across the life course and even to subsequent generations.[11]

One consequence of prolonged deprivation of adequate nutrition in early life as briefly introduced earlier is stunted growth, i.e., linear growth retardation. Achieved growth for age, determined as a child's height-for-age z-score, is used as a measure of linear growth. Accordingly, stunting is defined as height-for-age z-score more than 2 standard deviations below the median height-for-age z-score of the WHO reference population.[12] The first two years are a time of fast linear growth when children grow about 24 cm annually, decreasing to less than 10 cm thereafter. Most linear growth failure occurs during the first 1,000 days post conception. Height at the end of the first 1,000 days is linked to final height, and thus stunting at 2 year likely predicts lower adult height.[13] Apart from linear growth, the first 1,000 days is a period of fast organ development and maturation, requiring relatively high nutrient intakes. If undernutrition present over longer periods, even small deficits may have substantial impact on brain and neurodevelopment, and therefore, chronic undernutrition in early life also diminishes cognitive growth and development.[14,15] Furthermore, the problem of chronic undernutrition is intergenerational (Figure 2), since a stunted child is likely to remain stunted throughout life.[16] Regardless of the start and duration of undernutrition, when undernourished girls become prospective mothers, they are more likely to give birth preterm and/or to infants with low birth weight and/or small for gestational age.[3,17–20] Thereby, chronic undernutrition and its consequences continue across generations.[21,22]

Besides its impact on physical and cognitive growth and development, the first 1,000 days of life is a critical time for the foundation of health across the lifespan. For instance, in response to chronic undernutrition in early life, genome expression may be modified, leading to alterations in metabolic, cardiovascular, and endocrine functions. Such alterations cause adverse health effects, such as chronic non-communicable diseases later in life.[23–32] Chronic non-communicable diseases, in turn, increase the risk of both pregnancy complications and adverse perinatal outcomes.[33–35] For example, hypertensive disorders of pregnancy increase the risk of intrauterine growth retardation,[35] which can perpetuate a cycle of chronic undernutrition. Chronic diseases incur enormous human and economic costs, falling hardest on the poor income countries and the most vulnerable population groups, especially women and children.

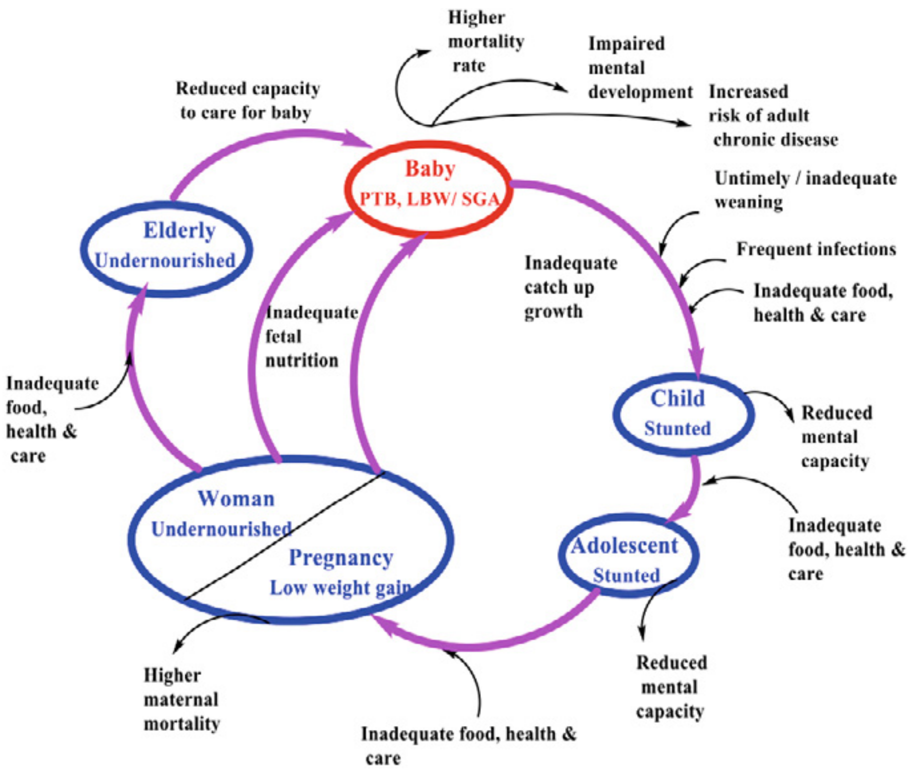

Figure 2. Nutrition through the life course (Source: ACC/SCN. Fourth report on the world nutrition situation. Geneva: ACC/SCN in collaboration with IFPRI;2000.). PTB; preterm birth, LBW; low birth weight, and SGA; small for gestational age birth.

Chronic undernutrition in early life casts a shadow over a child's future productivity and has far-reaching economic consequences. As a rough estimation, an undernourished child may lose 10% or more of his/her lifetime earnings.[36,37] In areas where undernutrition in early life is abundant, this will grossly impact the national economic productivity due to its effect on human capital, which adds fuel to the existing poverty and amplifies the risk of, and risks from, undernutrition. Globally, the impact of chronic undernutrition in early life is estimated to reach 3.5 trillion US dollars on the global economy per year, equivalent to 500 US dollars per individual. South Asia and African countries in general incur larger penalties, approximately 9 to 10% of gross domestic product per capita and Ethiopia is one of the poorest and most affected countries. Undernutrition costs Ethiopia about 4.7 billion US dollars yearly, accounting for over 15% of its annual gross domestic product.[38] Of note, the cost of treating undernutrition and its consequences later in life are also considerable. The economic impact of undernutrition may, therefore, be a significant impediment to efforts to reduce poverty and achieve the nutritional targets of the Sustainable Development Goals.

In view of all the aforementioned consequences of chronic undernutrition in early years of life, there is a need to better identify and understand determinants of stunted growth, addressing the possible contributions across the preconception, prenatal and postnatal period. Such understanding may help to design appropriate interventions that help achieve the 50% reduction in stunted growth by 2030. However, there are limited studies in this regard in areas with the highest burden of chronic undernutrition in early years of life.

Windows of opportunity to break the vicious cycle

The current thinking favours optimizing maternal and child nutrition to break the intergenerational cycle of chronic undernutrition and its consequences. The pregnancy and the first 2 years afterwards, roughly the first 1,000 days of life, are considered a critical intervention period to optimize maternal and child nutrition.[39–41] In addition, the pre-pregnancy period is also increasingly recognized as a relevant window prior to the first 1,000 days of life as maternal nutrition before conception is considered vital for the healthy development of her embryo, fetus, infant, and child.[42] Although body weight may not adequately reflect nutritional status, healthy pre-pregnancy weight, gestational weight gain and postnatal weight are proxies for improved nutritional status before, during and after pregnancy, respectively. Improved maternal nutritional status during these critical periods has been linked to optimal birth outcomes like birth weight for gestational age and sex, birth weight, and length of gestation within the normal range, as well as child growth and development.[43–45]

Maternal undernutrition before, during and after pregnancy, however, remains unacceptably high in low-and middle-income countries, mainly in Asia and Africa. For example, over 30.0% of pregnant women in Africa are undernourished, as measured by mid-upper arm circumference (MUAC <21 cm) and/or body mass index (BMI <18.5 kg/m^2).[46] As MUAC is less sensitive to weight change over a short time period, the number of undernourished pregnant women reflects how prevalent pre-pregnancy undernutrition still is today. Moreover, short stature, a reflection of chronic undernutrition early in life, is also common in low-income countries where the rate of childhood stunting is very high.[47] Unfortunately, most women in low-and middle-income countries do not gain adequate weight during pregnancy. For instance, a recent review noted that >58% of pregnant women in sub-Saharan Africa do not achieve sufficient gestational weight gain.[48] Not only before and during pregnancy, but also after pregnancy maternal undernutrition is very high. Consequently, poor maternal and child health outcomes are a major public health problem. Given the insufficient evidence from low-income countries and the fact that maternal undernutrition before, during and after pregnancy are common, results of studies focusing on these topics can have implications for local healthcare practices as well as further afield.

In low-income countries where maternal undernutrition is high, adverse birth outcomes like preterm birth (defined as birth before 37 weeks of gestation), low birth weight (weight <2.5 kg), and small for gestational age birth (birth weight <10th centile for a specific completed gestational age and sex, using InterGrowth Standard) continue to be high. For example, it is estimated that 20.5 million (14.6%) babies are born defined as low birth weight and/or small for gestational age annually, with 95% of those in low-income countries.[49] Also, nearly 15 million babies are born preterm annually.[50] Unfortunately, approximately 6.5 million small for gestational age or preterm births are linked with short maternal stature in low- and middle-income countries alone annually.[3] The impact of the high prevalence of pre-pregnancy underweight and inadequate gestational weight gain, the current manifestations of maternal undernutrition on birth outcomes, child growth and health may be even higher compounded with the existing chronic undernutrition. Even if adequate pre-pregnancy weight and gestational weight gain are achieved, it is still unclear if they can compensate the influence of short maternal stature on adverse birth outcomes.

Besides maternal nutrition, other factors like distress may negative impact maternal health and pregnancy outcomes. Perinatal distress, for instance, refers to high symptoms of anxiety, depression, and/or stress during the perinatal period, i.e., the period between 22 weeks of gestation and the end of the first week postpartum. Perinatal distress affects about 25% of pregnant women in low-income countries.[51–54] The high prevalence of perinatal distress may, then, predispose women to low gestational weight gain.[55] It may also be linked with adverse birth outcomes such as preterm birth, low birth weight, and small for gestational age birth.[51,56,57] After birth, perinatal distress may affect early childhood growth and development,[58–63] and health later in life and the health of future generations.[60–62] However, the association of perinatal distress with adverse birth outcomes has been reported inconsistently, especially in low-income countries.[51,64,65] Additionally, it is unclear if perinatal distress independently increases the risk of adverse birth outcomes or is a mediator in the pathway between socioeconomic adversity to fetal growth, pregnancy loss, adverse birth outcomes, child growth, and perinatal death, especially in the context of prevalent undernutrition, effects of distress may adversely contribute to pregnancy outcomes.

Causes of undernutrition and missing the windows of opportunity

Multifaceted nutrition-sensitive and nutrition-specific factors may be related with undernutrition in early years of life and its consequences.[66] According to the UNICEF framework (Figure 3), the causes of undernutrition are divided into immediate, underlying, and basic causes. The immediate causes are the direct determinants of undernutrition and are amenable to nutrition-specific interventions and program. Pre-pregnancy illnesses, illnesses during pregnancy, distress, fasting, and dietary diversity can exemplify the variables representing immediate causes. The basic and underlying causes are the indirect determinants of undernutrition and are amenable to nutrition-sensitive interventions and program. Education, employment, wealth index, access to food, access to health service, health extension package implementation, access to an improved drinking water source, access to an improved sanitation facility, women empowerment, intimate partner violence, social support and inadequate care can be considered to reflect the basic and underlying causes. Of note, as the basic causes include a multitude of factors reflecting the social, economic and political context concerned poor availability and control of resources that often operate at societal level, they are not adequately addressed in this thesis.

To date, most of the scientific evidence is generated in developed countries. There is a paucity of evidence to understand the burden of undernutrition in early life and how the preconception period and the first 1,000 days of life can be used as opportunities to break the vicious cycle of chronic undernutrition and its consequences in low-and middle-income countries. Therefore, data on which nutrition-sensitive and-specific factors matter most is required to identify possible targets and develop context-specific interventions to improve maternal and child health outcomes. Similarly, evidence is needed to map out how adequate nutrition before, during and after pregnancy can be used as a window of opportunity to improve maternal and child health at population level. Such improvements could also benefit the next generation in preventing the cross-generational perpetuation of chronic undernutrition and its consequences.

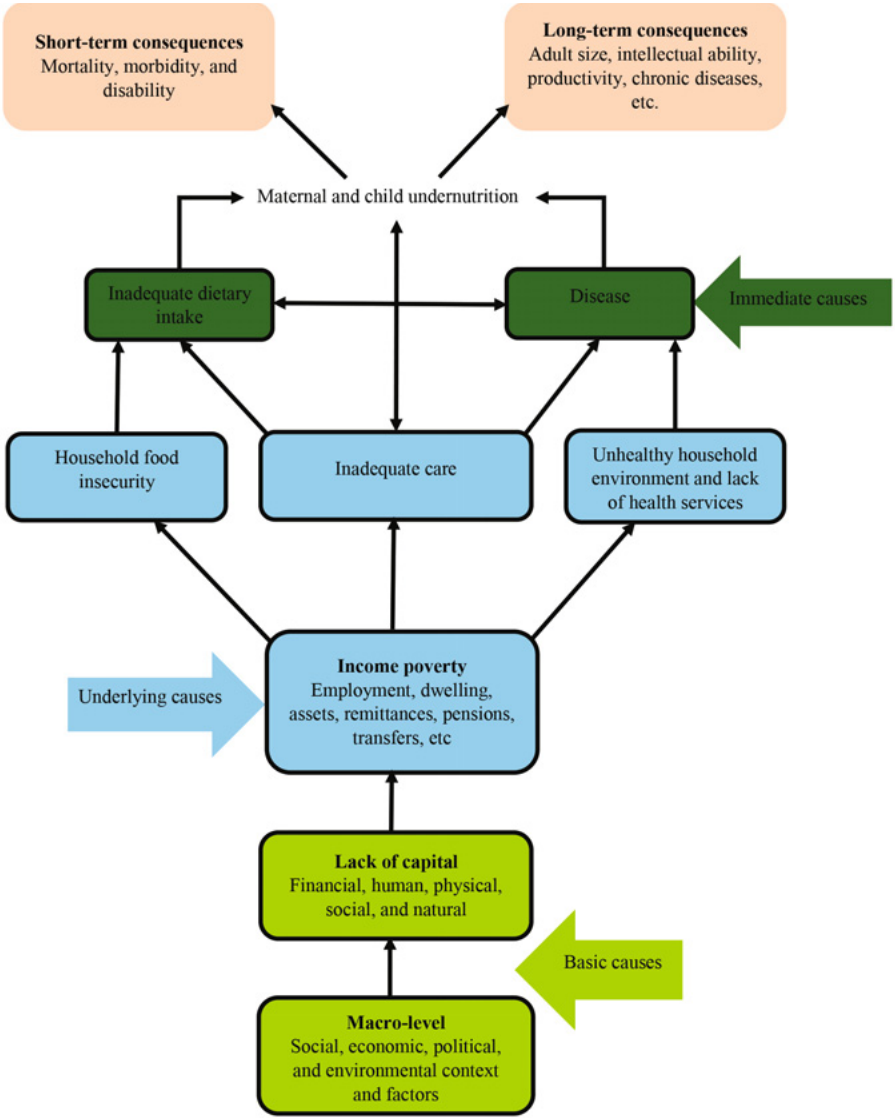

Figure 3. Framework showing the possible causes of maternal and child undernutrition (Source: Black *et al*. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet*. 2008;371(9608):243-60).

Aims of the thesis

In Ethiopia, like other low-income countries, maternal undernutrition before, during, and after pregnancy is widespread. Overall, more than 30% of women are undernourished before pregnancy, and nearly two-thirds do not gain adequate weight during pregnancy.

[67–69] Unfortunately, women's poor nutritional status also remains after pregnancy during the lactation period.[70,71] Indeed, adverse birth outcomes are prevalent in Ethiopia—for instance, one-fifth of infants are born with low birth weight,[72] and over 40% under five children are stunted.[73] Furthermore, there is a sparsity of data generated from birth cohorts that helps identify possible targets for intervention and support to improve maternal and child health outcomes. This could be because it requires enrolling women before pregnancy. In addition, the follow-up time extends until birth and beyond, at least until early childhood, which is somehow difficult in low-income settings where preconception care is rudimentary, and childbirth is most likely to happen at home.

Therefore, this thesis aims to provide better insights into the links between undernutrition in early life and health outcomes by assessing maternal and child nutritional situation during the critical time points. Investigating the associations between maternal nutrition status, various health, and socio-economic indicators, and pregnancy outcomes could help identify windows of opportunity for intervention and guidance on the most impactful factors to address. To this end, the data analyzed in this thesis may help understand what can be done to break the vicious circle of malnutrition in low-and middle-income countries.

Outline and data source of the thesis

Data source of the thesis

The **KI**lite-Awlaelo **T**igray **E**thiopia (KITE) cohort is the data source for this thesis work. The KITE was a birth cohort established in Kilite-Awilaelo Health and Demographic Surveillance Site (KA-HDSS) in the Tigray region of northern Ethiopia for the purpose of this thesis work. Before starting recruitment, the weight of about 17,500 non-pregnant women living in the study was measured. Subsequently, 991 eligible pregnant women identified between February and September 2018 were included consecutively and followed until delivery and beyond extending to 18 to 24 months postpartum. The criteria for inclusion were being married, being aged 18 or over, having weight measured before pregnancy, and having completed ≤20 weeks of gestation. A general overview of the timing and content of data collection is provided below.

At inclusion (≤20 weeks of gestation): a wide range of socioeconomic characteristics, reproductive and obstetric conditions, psychosocial factors, food and dietary habits, and anthropometric measures were collected at inclusion. Some of the socioeconomic and reproductive characteristics were extracted from the database of the surveillance site. Additionally, some baseline data were extracted from the prenatal records. Specifically, data on hemoglobin tests, urine analyses, stool examination, Venereal Disease Research Laboratory (VDRL) test, Rh factor blood test, and human immunodeficiency virus (HIV) test were extracted when available from the prenatal records of the women.

At 32 to 36 weeks, at birth and/or immediately after birth: prenatal care attendance, illness during pregnancy, pregnancy complications, and anthropometric measures were obtained. Additionally, birth weight, gestational age, complications at birth or in the immediate postnatal period were collected. Some of the data collected at this stage were extracted from the prenatal records of the women.

At 18 to 24 months postpartum: data on child age, feeding practices, history of diarrheal, febrile and respiratory illnesses, vaccination status and length/height were collected. Additionally, mother-child bonding and maternal weight were measured.

Outline of the thesis

In this thesis, we addressed maternal nutrition before, during and after pregnancy, pregnancy outcomes, and child growth at the end of the first 1,000 days of life. The overall outline of the thesis is provided below.

In chapter 1, we provided an introduction to maternal and child nutrition with special emphasis to the notion of early life, i.e., the first 1,000 days of life. Concepts and presently used models to understand and study this period are introduced in this chapter. Additionally, the aims of the thesis and a brief overview of the **KI**lite-Awlaelo **T**igray **E**thiopia (KITE) cohort, the specific research questions, and the outline of the thesis are provided.

In chapter 2, we assessed the distribution of pre-pregnancy nutritional status and specific socioeconomic characteristics, reproductive and obstetric conditions, food and dietary habits, and psychosocial characteristics associated with pre-pregnancy nutritional status, in rural and urban areas of northern Ethiopia. Pre-pregnancy undernutrition, was defined as body mass index (BMI) <18.5 kg/m^2 and/or mid-upper arm circumference (MUAC) <21 cm.

In chapter 3, we evaluated adequacy of gestational weight gain in Ethiopia. Next, we investigated the impact of preconception and prenatal factors influencing gestational weight gain. Moreover, the probability of achieving adequate gestational weight gain by optimizing the foremost factors was estimated. Adequacy of gestational weight gain, the difference between weight at 32 to 36 weeks of gestation and weight before pregnancy, was classified based on the Institute of Medicine guideline.

In chapter 4, we investigated the influence of maternal nutritional status before and during pregnancy on adverse birth outcomes. Additionally, we have evaluated the direct and indirect effects of maternal stature and pre-pregnancy weight on adverse birth outcomes. More specifically, we examined whether normal pre-pregnancy weight and adequate gestational weight gain can compensate for the influence of short maternal stature on adverse birth outcomes. Specific adverse birth outcomes concerned preterm birth (PTB, before 37 completed weeks of gestation), low birth weight (LBW, <2,500 g at birth), and small for gestational age birth (SGA, birth weight <10th percentile for gestational age and sex).

In chapter 5, we assessed the influence of perinatal maternal distress on adverse birth outcomes. Furthermore, we examined if perinatal maternal distress is an independent risk factor or a mediator in the pathway of socioeconomic adversities to birth outcomes. Perinatal maternal distress refers to high symptoms of anxiety, depression, and/or stress during the perinatal period, i.e., the period between 22 weeks of gestation and the end of the first week postpartum. Socioeconomic adversity is defined as poor economic status, food insecurity, women's disempowerment, intimate partner violence, lack of social support, and stressful life events.

In chapter 6, we investigated postpartum weight change in relation to pre-pregnancy weight and gestational weight gain. To this end, weight change was calculated by subtracting pre-pregnancy weight from postpartum weight. Additionally, we assessed a wide range of prenatal factors with respect to their association with postpartum weight change in kg. Similarly, we identified factors associated with a shift in weight after pregnancy compared to pre-pregnancy, i.e., from normal to underweight or from underweight to normal weight category.

In chapter 7, we evaluated growth outcomes of the children born in the study and identified the preconception, prenatal and postnatal characteristics associated with stunted growth at the end of the first 1,000 days, i.e., at 18 to 24 months of life. Stunted growth was defined as height-for-age more than two standard deviations below the median of the WHO reference population.

In chapter 8, we summarized and discussed the main findings reported in this thesis. In addition, methodological considerations important for the interpretation of the findings as well as perspectives for future research are shared.

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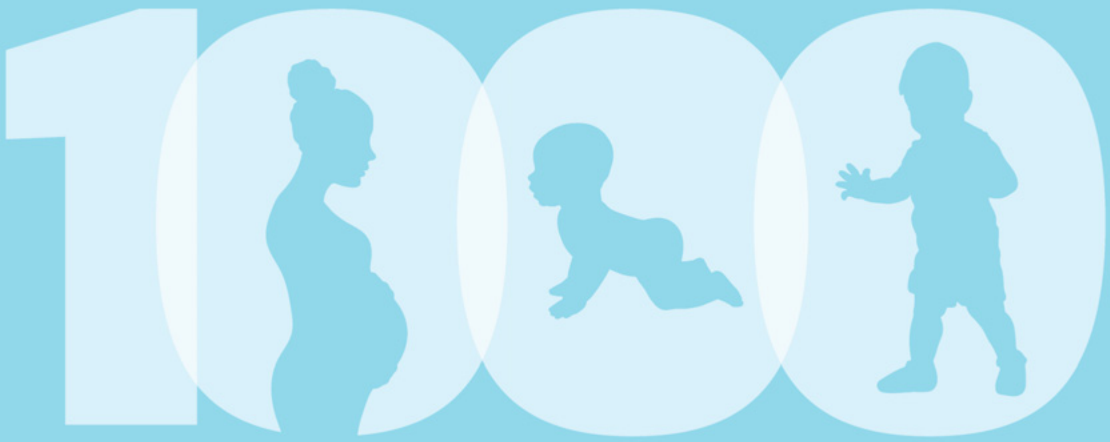
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