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Prenatal food and micronutrient supplementation to malnourished women in Bangladesh

Effects, Equity, and Cost-effectiveness

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Abstract
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Maternal nutrition is closely linked to child health and survival. In Bangladesh there is a high prevalence of undernutrition in the form of chronic energy deficiency [CED, Body Mass Index <18.5 (kg/m2)] in women and low birth weight. The aims of this thesis are to explore women's perceptions of maternal undernutrition, to analyse the association between prenatal food supplementation and birth weight (BW), to analyse whether food- and multiple micronutrient interventions generate pro-disadvantaged equity in child survival, and to examine whether an early prenatal invitation to food supplementation and multiple micronutrient supplements (MMS) represents value for money in infant survival compared to invitation to food supplementation at usual time combined with 60 mg iron and 400 µg folic acid (standard practice).

The study on women's perceptions (n=236) was nested into the MINIMat randomized trial where women (n=4436) were allocated to early (E), or usual (U) time of invitation to prenatal food supplementation and 30 mg iron with 400 µg folic acid, or 60 mg iron with 400 µg folic acid, or MMS. Live births (n=3625) were followed-up. The analyses of equity and cost-effectiveness were based on this trial. A cohort design (n=619) was employed for the analysis of food supplements and BW.

Women perceived maternal undernutrition as a serious health problem and attached very low scores to CED in pregnancy. An average of four months of prenatal food supplementation increased BW by 118 g. An early invitation to prenatal food supplementation and MMS lowered mortality in children before the age of five years and reduced social disparity in child survival chances. An increment from standard practice to E-MMS averted one extra infant death at a cost of US$797 to US$907, and saved one extra life year at a cost of US$27 to US$30.

High priority should be given to the nutritional status of pregnant women in societies where undernutrition and food insecurity occurs. Prenatal food supplementation has the potential to significantly increase BW, and an early initiation of prenatal food supplementation combined with MMS was considered cost-effective in lowering infant mortality and increase social equity in child survival chances.

Keywords: malnutrition, pregnancy, food supplement, micronutrient supplement, birth weight, infant mortality, effectiveness, economic evaluation, equity, Bangladesh

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To my parents,
Mohammad Abdul Ghani
and Tanjina Khatun

List of Papers

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

I. Rubina Shaheen and Lars Lindholm. Quality of life among pregnant women with chronic energy deficiency in rural Bangladesh. *Health Policy 2006*;78(2-3):128-34.

II. Rubina Shaheen, Andres de Francisco, Shams El Arifeen, Eva Charlotte Ekström, Lars Åke Persson. Effect of prenatal food supplementation on birth weight: an observational study from Bangladesh. *Am J Clin Nutr* 2006;83(6):1355-61.

III. Rubina Shaheen, Peter Kim Streatfield, Ruchira Tabassum Naved, Lars Lindholm and Lars Åke Persson. Equity in adherence to and effect of prenatal food and micronutrient supplementation on child mortality: results from the MINIMat randomized trial, Bangladesh. *BMC Public Health* 2014;14:5. doi: 10.1186/1471-2458/14/5.

IV. Rubina Shaheen, Lars Åke Persson, Shakil Ahmed, Peter Kim Streatfield, Lars Lindholm. Cost-effectiveness of invitation to food supplementation early in pregnancy combined with multiple micronutrients on infant survival: Analysis of data from MINIMat randomized trial, Bangladesh. *BMC Pregnancy Childbirth* 2015;15:125. doi: 10.1186/s12884-015-0551-y.

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Abbreviations

BINP	Bangladesh Integrated Nutrition Project
BMI	Body Mass Index (kg/m^2)
BRAC	Bangladesh Rural Advancement Committee
BW	Birth weight
CE	Cost-effectiveness
CED	Chronic Energy Deficiency
CNC	Community Nutrition Centre
HDSS	Health and Demographic Surveillance System
ICDDR,B	International Centre for Diarrheal Disease Research, Bangladesh
LBW	Low Birth Weight
LY	Life Years
MINIMat	Maternal and Infant Nutrition Interventions, Matlab
MMS	Multiple Micronutrient Supplements
NNP	National Nutrition Project
SES	Socio-economic status
UNICEF	United Nation's Children's Fund
WHO	World Health Organization

Introduction

Sub-optimal nutrition is common among women in low-income countries such as Bangladesh (1, 2, 3, 4). When manifested among pregnant women, the immediate effect of sub-optimal nutrition is foetal undernutrition that entails increased foetal, neonatal, infant and child mortality (1). This also contributes to the cycle of malnutrition over generations (5), especially when energy intake in pregnancy is low (6) and insufficient to compensate for the increased demand during pregnancy. Further, mounting evidence suggests that foetal undernutrition increases the risk for type 2 diabetes mellitus and cardiovascular diseases in adulthood (7-14).

In Bangladesh, interventions have been implemented to combat maternal undernutrition. These include prenatal iron and folic acid supplementations from around 1986 (15) and food supplementation through the Bangladesh Integrated Nutrition Project (BINP) in 1996 (16) followed by its successor the National Nutrition Program (NNP) . Based on the positive effects of prenatal food supplementation on birth weight (BW) in other low-income countries (1), it was assumed that this also should be true for Bangladesh. There was also an increasing felt need to move from iron-folic acid to multiple micronutrient supplements (MMS) under the assumption that populations in low-income countries are deficient in several micronutrients (17). Over time, it has become almost a prerequisite that comprehensive evaluations of interventions should also include cost-effectiveness and equity analyses. As reflected in Figure 1 in this thesis these issues related to prenatal food and micronutrient supplementations are addressed. The effects on BW and offspring mortality are presented as well as analyses of social equity in compliance to the interventions and effects on mortality. We present an analysis whether the interventions are worthwhile from a cost-effectiveness perspective. We also explored women's perceptions of maternal undernutrition. We used the terms undernutrition and sub-optimal nutrition interchangeably.

Maternal undernutrition

Maternal undernutrition is common in rural areas of South Asia including Bangladesh (1). About 19% of women in Cambodia have been found to be undernourished (18), and 40% in a study from rural Vietnam (19). In another study from central India (Nagpore and Indor), the proportion of underweight women was high (20). Maternal undernutrition in the form of low height is also common. In a study in Nepal, the mean height was 150.5 cm and 14% were below 145 cm (21).

Previous studies and recent data show that 30 to 50% of rural Bangladeshi women of childbearing age suffered from undernutrition characterized by chronic energy deficiency (CED): i.e., having a Body Mass Index (BMI) <18.5 kg/m^2 (2, 3, 4, 22). The burden of CED may vary depending upon the food security situation and its seasonal variation (2, 3). While intergenerational effects, in the form of undernourished women giving birth to undernourished babies, maintain the cycle of malnutrition (5), sub-optimal food intake during pregnancy is another major cause of low birth weight (LBW). Depending on the season, the daily energy intake among rural adults in Bangladesh reportedly varied from 1767 to 2055 kcal (3), while that in late gestation was estimated at 1464 kcal (6).

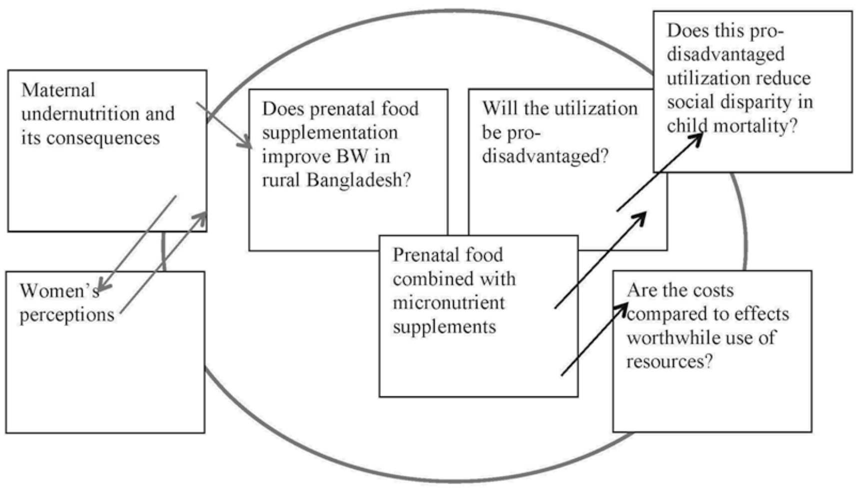

Figure 1. Maternal undernutrition, women's perceptions, interventions and relevant related questions addressed in the thesis.

There are seasonal fluctuations in calorie intake in Bangladesh, and individuals have to adjust to that. Research has shown that adults cope badly with seasonal fluctuations of total energy intake as reflected in body weight and BMI, and this is also true for women of reproductive age (2). The prevalence of CED was found to be as high as 67% during the peak season, February-March, as compared to 61% during the lean season, October-November (2). In Bangladesh the marked seasonal variations in food availability may be reflected not only in the calorie (macronutrient) intake but also in the consumption of micronutrients as also has been found in rural Nepal (21). In general, a very low adequacy of micronutrient intake was found in women in rural Bangladesh (23).

The choice of cut-off levels to classify undernutrition may be an issue. While <50 kg pre-pregnancy weight is considered as underweight in some areas of the world it may be “normal” in other areas; a body weight <45 kg may be considered as low weight in the latter area. Short stature and low pre-pregnancy weight, and maternal undernutrition is a reflection of the low status of women over generations that also may include less access to quality and quantity of food from early childhood (24, 25).

Maternal sub-optimal nutrition has severe consequences, including long-term effects on the offspring’s health and mortality (1). The world has experienced prolonged and acute food shortages in the form of famines, and findings from these famines may indicate the effects of maternal food deprivation on the offspring’s nutritional status and later outcomes. Research on the Dutch famine has examined the long-term sequel of the famine on offspring health (7, 8). Exposure to famine during early gestation has long-term effects on health (7) including increased risk of diabetes mellitus type 2 (8, 9, 10, 11, 12) and early development of coronary artery disease (13), indicating early programming effects by the intrauterine exposure to nutritional deprivation.

The last two major famines in the Bengal area were the Great Bengal famine in 1943 (26, 27) and the post-liberation famine in Bangladesh in 1974 (28, 29, 30). In these famines, effects on foetuses through pregnant mothers have so far remained undocumented, because the immediate mortality was so overwhelming that other less immediate outcomes were ignored. Although famines affecting mass population have not been reported from this area in recent years, chronic food insecurity is still prevalent (2, 3) and may affect foetal growth and survival, and indicate a social disparity in the availability of food.

Consequences of maternal undernutrition

Maternal undernutrition is closely related to the outcome of the offspring (1). Foetal undernutrition is associated with foetal, neonatal, infant and child mortality. The suboptimal foetal nutrition, later expressed in a LBW, may lead to increased susceptibility to infections, a poor general health of the infant (1) and in the longer perspective a propensity to develop metabolic syndrome and chronic diseases in adulthood (7, 8, 13). The immediate consequence of maternal undernutrition is possibly offspring mortality. Data from India have shown that short maternal height was associated with growth failure in childhood and increased child mortality (31). In the Gambia, perinatal mortality was reduced by food supplementation to pregnant women (32) indicating improvement of maternal nutritional status influences offspring mortality. In that geographical area, there was a marked seasonal variation in neonatal (32) and adult mortality (33) that partly may be due to altered immune function (32, 33). The different seasons may affect foetal viability via variation in total calorie intake as well as in availability of micronutrients in food that could lead to variation in immune function. This implies that consequences of maternal undernutrition on foetal outcome may depend on season of exposure during gestational life.

Infant and child mortality in Bangladesh

In Bangladesh, child mortality has been substantially and consistently reduced across the last two decades (34). From 1990 to 2000 and after that to 2012, infant mortality decreased from 100 to 64 to 33 per 1000 live births, i.e. a reduction by 66% from 1990 to 2012 (35). The corresponding figures for under-five mortality were 144 to 88, and after that to 41 per 1000 live births, implying 72% reduction from 1990 to 2012 (35). During the same period, Japan achieved 60% reduction of infant mortality, from 5 to 3 to 2 per 1000 live births, and 50% reduction in under-five mortality from 6 to 5 to 3 per 1000 live births, while Sweden achieved 57% reduction in infant mortality, from a rate of 6 to 3 to 2 per 1000 live birth of infant mortality and 7 to 4 to 3 per 1000 live birth in under-five mortality (35).

Despite the significant decline, neonatal deaths are still frequent in Bangladesh. This is reflected in the drastic differences in neonatal mortality between the high-income countries and Bangladesh. Data from 2012 show neonatal death rates on the level of one to two per 1000 live births in Japan and Sweden, and 24 per 1000 live births in Bangladesh (35) indicating that a significant proportion of neonatal deaths in Bangladesh is avoidable. While post-neonatal and child mortality has been significantly reduced, neonatal mortality comprises a major part of deaths in childhood (35). A study in South Asia and Sub-Saharan Africa presenting cause-specific mortality rates indicated persistently high neonatal mortality, which often is underestimated (36).

During the last ten years deaths due to neonatal tetanus, pneumonia, diarrhoea, measles, injury and malnutrition have decreased substantially (37, 38, 39). Consequently, two-thirds of infant deaths (40) and half of the under-five deaths (41) can be attributed to neonatal deaths. These deaths are mostly due to preterm births, intrapartum-related causes (birth asphyxia), infections and other neonatal causes (37, 42), indicating that suboptimal care during childbirth and postnatal period may be linked to this mortality. Most of these deaths are avoidable.

LBW is closely related to child mortality (1, 43, 44). There has been evidence on a significant reduction in the prevalence of LBW and also, in parallel, a reduction of the under-five mortality in Bangladesh. To achieve further reductions of under-five mortality, neonatal mortality needs to be lowered. That requires improved foetal health, especially among the poor and disadvantaged.

Birth weight and infant mortality

In 1976 WHO defined LBW as a birth weight (BW) <2500g, with the rationale that below this level the BW-specific infant mortality increased sharply (43, 44, 45, 46, 47, 48). However, the appropriateness of this cut-off level should be re-evaluated using more recent data since some LBW infants exhibit similar health as normal BW babies (49). There may be arguments regarding whether it is more important to focus on foetal health rather than on BW.

LBW is the result of either shorter duration of gestation, or intrauterine growth restriction (IUGR), or a combination of both (43). IUGR is often referred to as "small-for-gestational age" (SGA), or "small for dates". The most commonly used definitions of SGA are a BW less than 2500 g, and gestational age greater than or equal to 37 weeks and BW less than two standard deviations below the mean value for the gestational age (43). Preterm is defined as gestational age less than 37 weeks at birth. Some researchers, however, question the validity of the first definition for IUGR, small for date, since it is based on a biased sample of newborns while their counterparts are still inside the uterus (50). Another indicator of foetal growth restriction is the ponderal index, defined as BW in kilogram (kg) divided by birth length in meter cubed (BW in kg/Birth length m^3) (51, 52). The ponderal index is used to subdivide IUGR infants as proportionate or symmetric, or stunted, and disproportionate or asymmetric, or wasted (43, 53, 54). The lower tertile of the ponderal index is related to higher risk of death between eight and 365 days after birth (55).

There are associations between IUGR, maternal nutrition and food security. In societies where maternal undernutrition and chronic food insecurity are common food security and diet in pregnancy may influence maternal weight increase in pregnancy and BW. In this situation, LBW and suboptimal foetal health remain strong determinants of offspring mortality. Thus, the "birth weight paradox" indicates the distribution of causes of LBW differs between social groups, such as educational groups, and the causes are differently related to infant mortality (56). Foetal health is not only expressed in the BW but also in other aspects of health and wellbeing of the foetus. The causes of suboptimal foetal health range from genetics to socio-cultural factors but the foremost cause in low-resource countries is probably suboptimal maternal nutrition (57) and food insecurity over generations. In malnourished populations, foetal growth restriction is expressed during genetic imprinting (58). In high-income countries, where most LBWs result from pre-term delivery the causes of which are only partially known (1, 59), the main cause of LBW due to IUGR may be maternal smoking (60).

The non-nutritional causes of IUGR include haemorrhage, multiple births, uterine and placental abnormalities, parental size and genetics, and major congenital malformations (61). These causes explain about 50% of the variance in BW (62).

There may be a seasonal variation in BW due to differences in calorie intake. In the Gambia, the proportion of SGA infants was highest in August-December with a peak in November, 30.6%, and lowest in June, 12.9% (63). A recent study from rural India showed strong seasonality in calorie and protein intake and workload during pregnancy that could have effects on BW (64). In areas with a low prevalence of maternal undernutrition even among women with low BMI the prevalence of LBW was low, 7.3% (65). This figure should be compared to 30% in a mixed population of women in Bangladesh in 2000- 2002 (66). This underscores why maternal calorie and micronutrient deficiencies are associated with LBW (67).

In Bangladesh, the prevalence of LBW has decreased across the last two decades from 50% in rural Bangladesh (68), 40 to 46% in urban slums in Dhaka (69), 48% in rural Matlab in the years 1995-1997 (6) to 22% in rural Bangladesh in 2007 (70). But relatively recent data, 2001-2007, from rural northwest Bangladesh showed a very high prevalence, 55.3% (71). This indicates that there may be pockets in Bangladesh with persistent high to a very high prevalence of LBW. Prenatal food supplementation by the Bangladesh Integrated Nutrition Project (BINP) and the National Nutrition Project (NNP) may have contributed to the reductions of LBW that have been achieved in some areas. The reduction of adolescent fertility, from 22.6% in 2003 (72) to 12.7% in 2000 to 2007 (73), and an overall decline in fertility (74) may also have contributed in reducing LBW, since adolescent pregnancy is strongly associated with LBW and infant mortality (1).

A vast disparity remains in the burden of LBW, neonatal and infant death rates between Bangladesh and high-income countries as reflected in the proportions of LBW that was 4% in Finland and Sweden based on data for the years 2000 to 2002, and 8% in Japan compared to 30% in Bangladesh for the same years (66), and 22% for the year 2007 (70). Levels of more than 15% of LBW and more than 20% of IUGR indicate that LBW is a major public health problem in Bangladesh that needs population-wide interventions (1).

Another significant consequence of LBW is the intergenerational effects of undernutrition (5). A female LBW baby grows up as a malnourished woman, who gives birth to LBW babies including LBW girls, and the intergenerational cycle of malnutrition is maintained (5). In the present context with a growing burden of non-communicable diseases in low-income countries, an important consequence of suboptimal foetal nutrition is the increased susceptibility of these babies to develop metabolic syndrome (7-14, 75, 76, 77) in adulthood, type 2 diabetes mellitus and cardiovascular diseases. Other consequences of LBW include reduced working capacity (78), impaired cognitive function (79), higher susceptibility to morbidity (44), and impaired immune function (80).

Perceptions of maternal undernutrition

Research on perceptions of maternal undernutrition is limited. Studies addressing perceptions of malnutrition in general and of child undernutrition may provide clues to the perceptions of maternal undernutrition. In a study in Bihar, India, the researchers found that child undernutrition was not being viewed as a disease itself; different local disease concepts were identified describing the clinical symptoms of undernutrition (81). In another study in Madagascar major themes regarding barriers to proper nutrition were found to be inadequate purchasing power, limited access to health care, lack of health literacy and misconceptions about nutrition and malnutrition, and insufficient variation of crops produced (82). Malnutrition was viewed to be related to these indicators.

Using the SF 36 (short form 36), a study in Bangladesh compared the scores from poor women who were members of a microcredit programme with that of poor women who were non-members. The non-member poor women attached lower general health scores compared to members (83). This could indicate that these women were able to rate logically their health status as compared to those with another socio-economic status indicated by the membership of credit programme. We used a five dimension scale enabling conversion of answers using a value tariff and a visual analogue scale for measuring women's perception of maternal undernutrition; the results are presented in Paper I.

Interventions to combat the effects of maternal undernutrition on foetal outcomes

In low-income countries, sub-optimal foetal nutrition, originating from maternal undernutrition, and periodic food insecurity have motivated large-scale prenatal food supplementations (1). In recent years, the view that populations in low-resource countries also are deficient in a variety of micronutrients has motivated the need of trials providing multiple micronutrient supplements (MMS) to pregnant women (17).

Prenatal food supplementation

Prenatal food supplementations have been evaluated in high- and low-income countries, mostly with the aim to reduce the occurrence of LBW. The results have varied from no effects (84) to substantial effects (85, 86, 87) depending on the nature, magnitude, and causes of IUGR, maternal undernutrition, food security, and other risk factors such as smoking during pregnancy. Reductions in early neonatal deaths have also been found (32, 88). Cochrane systematic reviews concluded that a balanced protein energy supplementation in pregnancy modestly increased foetal growth and improved foetal and neonatal survival (88), and increased mean BW and reduced the occurrence of SGA (89). A recent review assessing the impact of balanced protein energy supplementation in undernourished pregnant women in low- and middle-income countries showed that a balanced protein energy supplementation significantly improved BW (90). Based on the positive effects of balanced protein energy supplementation in other low-income countries (32, 85, 86, 87), and in the poorer section of a high-income country (84) the Bangladesh Integrated Nutrition Project (BINP) was initiated in 1996 (16) based on the fact that Bangladesh had a very high prevalence of chronic energy deficiency in women and LBW (1). A few years later a number of systematic reviews concluded that a balanced protein energy supplementation during pregnancy reduces the risk of LBW (91, 92, 93).

BINP initially included prenatal food supplementation in six sub-districts. The aim was to incorporate nutrition into the routine heath interventions together with immunization, antenatal care, and family planning (16). Prenatal food supplementation was expected to improve BW and weight gain in pregnancy. As part of the evaluation, several research projects were conducted to provide constructive feedback to the program. The main result of such a project has been presented in paper II. The National Nutrition Program (NNP) was later formed to scale up the efforts of BINP (16). This program may have contributed to the decline in LBW prevalence in Bangladesh from around 50% (68, 69) to 22% (70). Other child health interventions such as oral rehydration solutions (94), case management of pneumonia in accordance with WHO recommended guidelines (95), community based approaches to newborn care (96, 97, 98), and improved socio-economic conditions in general may also have contributed to the overall decline in under-five mortality in Bangladesh and in other low-income countries.

Micronutrients and foetal outcomes

Populations in low-income countries are often deficient not only in iron and folic acid but also in other micronutrients. UNICEF and partners have developed a multiple micronutrient supplement (MMS) for trial purposes in low-income countries (17). A Cochrane systematic review has shown that iron-folic acid supplementation increases BW in high-income countries, but data from low-income countries are inadequate (99). It has been shown that zinc reduced the risk of prematurity and reduced the risk of pre-term mortality by 14% in low-income countries (100). Vitamin A has been shown to reduce maternal mortality, anaemia and night blindness among pregnant women (101). In Nepal, MMS increased BW by 64 g (102) and 77 g (103), and reduced the proportions of LBW, SGA, and maternal anaemia as compared to two or fewer micronutrients, no supplementation, or placebo but not compared to iron and folic acid (102). A Cochrane systematic review including data from India and Tanzania has shown that MMS reduced the risk of LBW (104). Another review has also shown that micronutrient supplementation in pregnancy reduced the risk of LBW (105). However, one trial in Nepal indicated an increased risk of mortality of term infants in the MMS arm (106), while a cluster-randomized trial in Indonesia demonstrated 18% reduced risk of infant mortality by MMS as compared to iron and folic acid supplements (107). A trial in Burkina Faso showed significantly increased birth length from food fortified with MMS compared to MMS alone (108). Recent meta-analyses have shown that MMS compared to iron and folic acid supplementations in pregnancy generate a small increase in BW (109) but no effects on still birth, or neonatal mortality (110). A new review concluded that when given in pregnancy both iron-folic acid and several other micronutrients may improve foetal outcomes (111). Nevertheless, these studies have been performed in populations where both food (macronutrient) and micronutrient deficiencies are common. Except one of these studies (108) in none of the above-mentioned studies MMS was delivered combined with food. Balanced protein-energy supplementation in pregnancy has been found to increase BW and decrease perinatal mortality (88, 89), a result that recently was confirmed in another review (90). In addition to examining the impact of these interventions on mortality, it is essential to investigate if the interventions reduced social inequity in survival and whether it was cost-effective.

Equity issues, concepts and measurements of equity

For a comprehensive evaluation of an intervention, a pertinent question is whether, or not, all social strata have equally benefited, or whether, or not, the most deprived stratum has benefited the most. The definition by Braveman and Gruskin (112) may be the one that covers the core principles defining equity in health. It defines equity in health as "the absence of systematic disparities in health (or in the major social determinants of health) between social groups who have different levels of underlying social advantage/disadvantage, that is different positions in a social hierarchy. Inequities in health systematically put groups of people who are already socially disadvantaged (for example, by virtue of being poor, female, and/or members of a disenfranchised racial, ethnic, or religious group) at further disadvantage with respect to their health; health is essential to well-being and to overcoming other effects of social disadvantage”. Another definition outlines equity in health as, “differences, which are unnecessary and avoidable, but, in addition, are considered unfair and unjust. So, to describe a certain situation as inequitable, the causes need to be examined and judged to be unfair in the context of what is going on to the rest of the society“ (113). This definition, however, lacks the protection of individuals who are disadvantaged due to biologically driven defects such as birth defects.

In recent past, concerns have been raised that during the initial phase of community-based interventions the uptake is usually higher among the more advantaged section of the community that widens the gap between the rich and the poor (114, 115). Research in India has shown that economic development does not automatically lead to a reduction in childhood undernutrition; the authors argued for direct investments in appropriate intervention to reduce undernutrition (116). In recent years, the Commission for Social Determinants of Health (117) has been striving for evidence on health gains from large-scale interventions that also reduce health gaps between social groups. Our results presented in paper III provide such evidence.

Interventions often lead to increasing inequity at the start of activities due to higher uptake by the advantaged groups compared to the disadvantaged groups (114). As time pass by, probably due to saturation in the advantaged group, or increased awareness in the disadvantaged group, this situation may be altered with improved equity in utilization (118) and effect (119). In a quasi-experimental study in Bangladesh comparing health-seeking behaviour for maternal health, it was found that the intervention had an overall positive effect on utilization but also a positive effect on equity due to pro-poor changes (120). Still, persisting inequity is also evident. A study evaluating utilization of maternal care also in Bangladesh showed that despite increased utilization of maternal care among socially disadvantaged mothers in comparison with socioeconomically advantaged counterparts, the absolute gap in utilization of care between socioeconomic groups had increased (121).

Research from the United States has shown that maternal disadvantage leads to the worst health at birth (122). Health at birth is an important indicator of long-term outcomes of education, income, and disability (122). This research also shows that in a situation with overall newborn health improvements due to increasing knowledge and public health policies the most disadvantaged actually benefitted even though those at the bottom of the distribution have the worst economic conditions (122). These findings indicate that despite constraints related to low socio-economic condition reductions in inequity is possible. In a study in India examining the effects of a cash-incentive program for institutional deliveries, the results showed that despite remaining inequality in access to institutional deliveries, this had been reduced after the introduction of the program (123). These findings indicate that reduction in the inequity gap is possible. We have addressed such an issue in Paper III.

Economic evaluation of interventions

In recent years there has been increasing demand that comprehensive evaluations of public health interventions should include economic appraisals. Economic evaluation can be in the form of cost-minimization, cost-effectiveness (CE), cost-utility, and cost-benefit studies (124). The most commonly used analysis is probably CE studies, where the effects in the form of intermediate outcomes are shown in relation to the costs, such as cost per patient, or a final outcome such as cost per death averted, and compares interventions that have the same outcome, such as death averted. When a new program is added, or a new program is launched, a relevant question is whether the extra gain achieved by the additional program or the new program that entails additional costs represents value for money? This is addressed by "incremental CE analyses" such as cost per one extra death averted. In paper IV, we present incremental CE analysis by using cost per extra infant death averted and cost per extra LY saved. In rural areas of low-income countries where problems of sub-optimal maternal and foetal nutrition and child mortality are prevalent, a knowledge gap exists regarding effective and cost-effective interventions.

A CE analysis was performed in Bangladesh assessing a community-based newborn care intervention compared to home care in terms of cost per neonatal death averted (125), and was interpreted in terms of whether the figures are above or below per capita GDP, as per the criteria set by the Commission on Macroeconomics and Health (126). Many of these comparisons are also presented as CE analyses in terms of cost/Disability Adjusted Life Year (DALY) estimates or cost/Quality Adjusted Life Year (QALY) estimates while the latter are based on perceived weights that are subjective. The DALY measure has been criticized on the basis that its conceptual and technical basis is flawed, and value judgment is open to serious question (127).

In this context, we conducted a CE analysis on prenatal food and micronutrient supplementation and presented the results in paper IV in terms of cost/infant death averted and cost/life-year saved. This evaluation was deemed necessary, particularly since other studies provided an incomplete account of the impact of BINP (128).

Rationale for the studies

Given the above background, the MINIMat (Maternal and Infant Nutrition Interventions, Matlab, ISRCTN16581394) trial was implemented in

Chandpur, Bangladesh, considering whether the timing of prenatal food supplementation combined with micronutrient supplements may show new avenues to optimize foetal outcomes (129). A long-time follow-up was planned. The study aimed to assess the effect of the interventions on birth anthropometry including BW, gestational age at birth, change in haemoglobin in pregnancy, and infant and child mortality. Analysis of equity in gains and economic evaluation were integral parts.

Aims

This thesis departs from the situation in Bangladesh with chronic energy deficiency in pregnant women and children, with a high burden of foetal undernutrion in the form of LBW, and increased mortality that occurs due to malnutrition in the woman-child dyad. It explores the life situation of these women, and studies effectiveness, cost-effectiveness and equity of prenatal food and micronutrient supplementations on size at birth and survival of the offspring. The specific aims are

1. To explore women's perceptions of chronic energy deficiency in rural Bangladesh
2. To analyse the effect of prenatal food supplementation on birth weight
3. To analyse whether prenatal food and micronutrient supplementations are able to achieve pro disadvantaged equity in terms of utilisation and effects, and
4. To estimate the incremental CE ratios for moving to an early invitation to prenatal food supplementation combined with MMS compared to the standard practice of invitation to food supplementation at the usual time in pregnancy combined with the standard iron-folic acid supplementation using different delivery strategies.

Subjects and methods

A sub-study that was nested into the MINIMat study provided information on perceptions of women regarding maternal undernutrition and its consequences, and presented in Paper I. The data used in Paper II came from a research project done at the initial stage of BINP activities. The data used in papers III and IV came from the MINIMat study. Cost data for paper IV were derived from the MINIMat study and compiled from a published study and reports.

Study settings

Data for Paper I came from a sub-study (January 1 to November 6, 2002) nested into the MINIMat study (130). The data for Papers III and IV also come from the MINIMat study. The MINIMat study was conducted in Matlab, a sub-district within Chandpur district, where icddr,b has been running an HDSS since 1966. The study was conducted in the area, where icddr,b provides health services covering about 110,000 population. Figure 2 shows the study areas.

Data for Paper II came from a study conducted in Shaharasti, another sub-district within Chandpur district, Bangladesh (Figure 2). In this area, in 1996, BINP initiated nutrition-related activities, including prenatal food supplementation. The studies address relevant program and policy questions that are summarized in Table 1.

Study design Paper I

Paper I was based on interviews of a sub-sample of women who participated in the MINIMat study. It explored women's perceptions of undernutrition.

The MINIMat study was a randomized trial with an invitation to food supplementation early in or at the usual time in pregnancy combined with micronutrient supplementations with planned long-term follow-up. In MINIMat study (n=4436) pregnant women were randomized to early (E – at around 9 weeks of pregnancy), or usual (U - at around 20 weeks) time of invitation to prenatal food supplementation, and to daily doses of either 30 mg iron and 400 μg Folic acid, or 60 mg iron and 400 μg Folic acid, or 15 micronutrients that included 30 mg iron and 400 μg Folic acid. This resulted in six trial arms, EFe30F, EFe60F, EMMS, UFe30F, UFe60F, and UMMS.

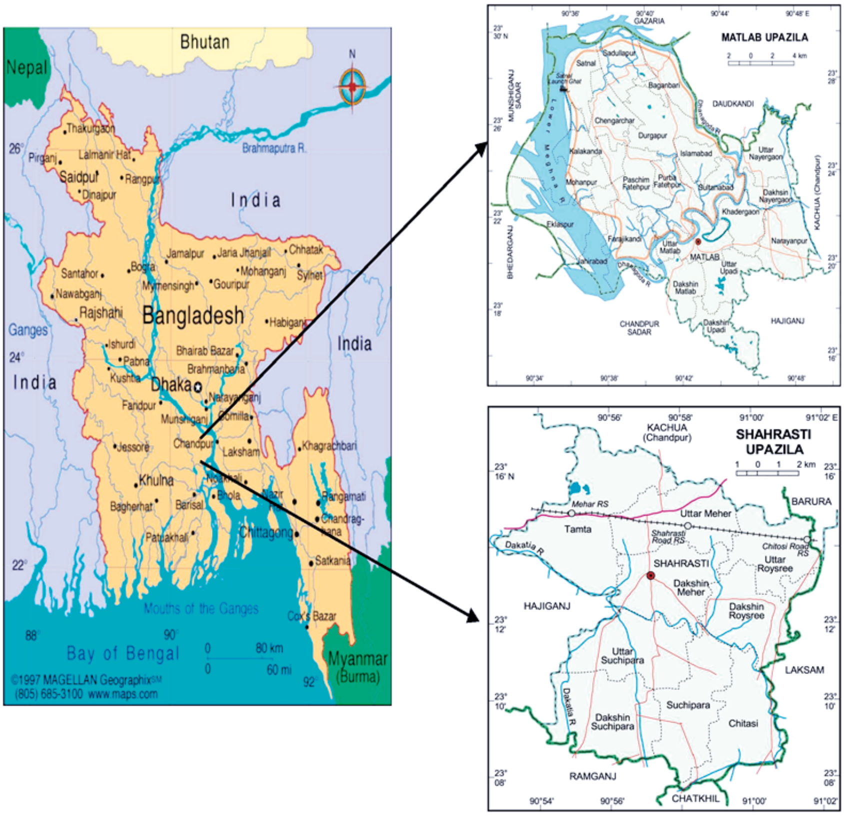

Figure 2. The study sites. Source: Google.

Adherence to food and micronutrient supplements, maternal anthropometry and socio-economic status (SES) were measured. The primary outcomes were maternal haemoglobin in week 30, birth weight and gestational age, and infant mortality. The study was also designed to address a range of secondary outcomes and aimed to measure both short and long-term consequences in the randomized groups (130). The follow-up studies are still continuing.

During the period January 1 to November 6, 2002, 1185 pregnant women were enrolled in the MINIMat trial, and a sub-sample of 285 women having CED at week 8 of pregnancy formed the study group for Paper I. Data were collected in home settings and 261 (91.6%) women were interviewed: 176

were pregnant, and 85 had just given birth, and complete information was available for 236 (83%).

Methods Paper I

Out of all pregnant women enrolled in MINIMat from January 1, 2002 to November 6, 2002 those who had a BMI <18.5 kg/m^2 were selected for the study of paper I. This sample based on a time frame formed the pool of pregnant women to understand women's perceptions of maternal undernutrition presented in Paper I (131).

The EuroQol (EQ)-5D questionnaire and the visual analogue scale (VAS) with endpoints of 1 (full health), and 0 (death) were used for measuring quality of life (QOL) scores (132). The instrument provides a descriptive profile and a score for health status. The questionnaire consists of five dimensions that describe health and a vertical VAS for providing a rating of health. A validation study was conducted for testing whether the instrument was relevant in the study setting. By using semi-structured questionnaires women visiting icddr,b health facility at Matlab were interviewed on how the illnesses they have suffered had affected the dimensions in the questionnaire and if there were other dimensions related to the severity of illness.

A scenario was used to represent CED. The scenario was based on the literature and women's narratives about the consequences of CED. The scenario included information on the burden of CED (133), its link with labour productivity (78, 134, 135), its expression as cumulative effects of malnutrition (133), the fact that it increases the risk of LBW, which maintains the intergenerational cycle of malnutrition (5), and that LBW babies frequently suffer from disability (136), the treatment of which involves considerable costs. The scenario also included information from our formative research related to Paper I (131): the report that low maternal weight is associated with small, undernourished, and weak babies, the probability that LBW babies fall sick more frequently and die more readily, and that malnourished women are often unable to perform adequate household work, and incorporated the effects of the condition on productivity and leisure (137). Although rating of scores were obtained, the study actually addressed women's perceptions of CED. The interviewers were trained on the questionnaire, VAS, to describe the scenario, in providing women with opportunity to reflect on and respond to EQ-5D, and to attach scores to the VAS.

Table 1. *Overview of papers in this thesis.*

Paper	Data sources	Methods	Population	Size	Outcome	Relevance in terms of policy
Paper I	Sub-study to MINIMat	Matlab, Chahdpur, Bangladesh, women with CED, nested into the MINIMat trial	Undernourished women of reproductive age	236	Quality of life scores related to CED	Inform about the public health relevance of CED that has consequences for future generations and economic productivity, as women perceives
Paper II	Shaharasti study	Shaharasti, Chahdpur, Bangladesh, malnourished pregnant women, cohort study	Undernourished women of reproductive age	619	Birth weight (BW)	Inform that BW increases with increasing duration of prenatal food supplementation and suggestion for targeting of prenatal food supplementation
Paper III	MINIMat study	Matlab sub-district, Chandpur, Bangladesh, pregnant women, MINIMat trial	Women of reproductive age	3591 mothers and child pairs	Child mortality and adherence to food and micronutrient supplements	Informs the general public and policy makers that reducing inequity in child mortality is possible through large-scale interventions.
Paper IV	MINIMat study, published data	Matlab sub-district, pregnant women, MINIMat trial	Women of reproductive age	3625 mothers, 3659 children incl. twins	Cost/extra death averted, cost/extra life year saved	Provides information to policy makers to judge whether or not prenatal food and micronutrient supplementations represent value for money

CED=chronic energy deficiency, BMI<18.5 kg/m^2. MINIMat=Maternal and Infant Nutrition Interventions, Matlab.

Analysis Paper I

The respondents' characteristics were compared with the rest of the MINIMat participants, not only with women who were detected pregnant during the study period, i.e., January 1 to November 6, 2002. We examined the distribution of the scores from all three sources and frequencies of answers at different levels of each of the five dimensions. Scores for each woman were calculated using the EQ-5D scoring formulae. Means and SDs are presented of scores from EQ-5D and visual analogue scale (VAS), and 95th percentiles from all three measurements. The scores from EQ-5D were compared with health of a general women population in Sweden (138). Informed written consent was obtained from all participants. The study was approved by the ethical review committee of icddr,b.

Design Paper II

Paper II was based on a cohort study conducted in Shaharasti, a sub-district within Chandpur district, Bangladesh, where BINP initiated nutrition-related activities, including prenatal food supplementation.

Methods Paper II

Four out of nine unions (administrative unit under the sub-district, each covering about 20,000 population) were randomly selected for this study. Pregnant women enrolled in the food supplementation program in these sub-districts were enrolled from the registers of BINP. The BINP activities were performed at Community Nutrition Centres (CNC, 52 in the study area) operated by Community Nutrition Promoters (CNP), who were women with children and a minimum of eight years of schooling. The centres were located in the villagers' houses, and the program activities were run in the morning hours, Saturday through Thursday. Each CNC covered about 1200 population. The promoters paid regular household visits to identify pregnant women and invited them to the activities. Pregnant woman with BMI <18.5 kg/m^2 were eligible to participate. They were invited to visit the CNC early in pregnancy and received health and nutrition education, food supplementation and iron-folate supplementation (supplied monthly, two tablets/day, each tablet containing 60 mg iron and 250 µg folic acid), as per the national recommendations.

Preparatory field activities started in November 1998, and BW measurements were done from December 1998 to October 1999. In 1998, there was a severe flood in Bangladesh. Shaharasti was affected until the end of October 1998. Activities in the field ceased during the peak flood and restarted in mid-November 1998. Women participating in the BINP program with a calculated probable birth (based on last menstrual period, LMP) from December 1998 to October 1999 were invited to take part in the study. Study field workers regularly visited the 52 CNCs to identify new enrolees and to obtain informed consent for the study.

Food supplementation

Village women, employed by the program, prepared the food supplements from local products, and provided this in plastic packets to be mixed with water. The supplement contained 80g roasted rice powder, 40g roasted pulse powder, 20g molasses, and 12 ml (6 g) soybean oil, providing about 608 Kcal and 17.9 g vegetable protein (about 11.5% of the total energy). The supplements were usually eaten at the CNC, but in the third trimester often provided at home by the promoter.

Measurements

Information on participation in the food supplementation was retrospectively collected by three structured interviews performed by study field workers. The respondents were requested to report how many days they had consumed the supplement. Important events in the preceding months were used to improve the recall with additional questions on any 'gap' in supplement intake.

Standard procedures were followed for anthropometric measurements. The training of field workers included standardization of measurements (139). Women's weight was measured after birth with a precision of 100 g (SECA Model 770, Hamburg, Germany), and length by a portable scale, with a precision of 1 mm. 97% of the analysed maternal post-partum weights were assessed within seven days after birth, at the same time as BW was measured. A notification system had been established for births; 23% BWs were measured within 24 hours and 85% within 72 hours. BW was measured by SECA beam scale (Model 725, SECA, Hamburg, Germany) with a precision of 10g. BWs measured later than 24 hours after delivery but within seven days were transformed to standard deviation (SD) scores, using the distribution in this material as the standard. The SD scores obtained were transformed back to the corresponding BW in grams. Gestational age at birth was assessed by date of LMP. Information on maternal age, parity, working hours/day, education, and household income was collected in the first interview.

For this study (Paper II) (140) the sample size was calculated with an aim to be able to show a difference of mean BW of 60 g or more between pregnant women having prenatal food supplements for 60 days or more with 80% power (null hypothesis is not rejected when it is not true) and testing at

0.05 (null hypothesis is rejected when it is true). Initially, about 565 pregnant women were recruited from the registers of the on-going BINP activities within the time frame allocated for the study. However, significant differences were not possible to detect within 60 days of food supplementation. Later, when the time line for the study was increased, a total 777 women were recruited. Out of this cohort of pregnant women 619 mother-infant pairs were included in the multiple regression analysis in Paper II (140). With this sample, a 70 g difference in BW was possible to detect, comparing women having food supplements for <120 days (n=364) and ≥120 days (n=338) at $p<0.02$.

Analysis Paper II

Characteristics were presented for women with and without complete data. Descriptive information on the distribution of days of supplementation and BW were presented. Differences in mean values of BW in relation to season of birth were analysed by ANOVA with F test. We analysed the associations between days of supplementation and BW by linear regressions. We analysed the dose-effect relationship between days of supplementation and BW and tested whether any dose-effect varied with maternal postpartum weight groups (proxy for pre-pregnancy weight). BW was plotted against days of supplementation and Lowess moving average lines were fitted for higher and lower post-partum weight groups based on median value, <42 kg, under the assumption that low weight women would gain weight in pregnancy while BW will improve among higher weight women. Multivariate linear regression analyses were done based on the Lowess curves to test the dose-effect relationship between the days of supplementation and BW. Adjustment for potential confounding and co-factors was considered with a $P < 0.20$ for any linear or non-linear association with BW and days of supplementation. Potential confounding variables were excluded if its influence on the effect estimates was <10%. Informed written consent was obtained from all participants. The study was approved by the ethical review committee of icddr,b.

Design Paper III

Paper III was based on a randomized trial, the MINIMat study.

Methods Paper III

The participants were all pregnant women living in the icddr,b service area at Matlab. If a woman reported to the community health research workers

(CHRW) of icddr,b, who visited her every month, that her last menstrual period (LMP) was overdue, or that she was pregnant, she was offered a pregnancy test. A woman, who tested positive, was invited to join the study after giving written informed consent, and her LMP date was recorded. She was advised to visit the nearby icddr,b clinic at 8-10 weeks of gestation. At clinic visit, if her pregnancy was confirmed by ultrasound and gestational age was <14 weeks, she was individually randomized to early (E) or usual (U) invitation to food supplementation groups, and micronutrient groups. The micronutrient supplementation was double-blinded; food supplementation was randomized but not blinded. Women were advised to revisit the clinic at weeks 14, 19 and 30 of gestation, and were visited on a monthly basis at home by study interviewers.

Interventions

The on-going, government-supported, national nutrition program provided an energy-protein supplement (about 608 kcal/d, the same as in Paper II), 6 d/week to pregnant women having BMI <18.5kg/m^2. In MINIMat, all pregnant women in the study area were offered food supplements irrespective of BMI. Participant women were invited to the feeding program immediately after pregnancy detection, early assignment, or at the time of their choosing, usual assignment. Women randomized to "early assignment" were encouraged to attend nutrition centres (one for 1200 population) and their names were informed to the nutrition programme. Women were also randomized to one of the three types of micronutrient supplements distributed at the icddr,b clinics: (a) 30 mg Fe and 400 µg of folic acid (Fe30F); (b) 60 mg of iron and 400 µg of folic acid (Fe60F); and (c) MMS which contained 15 micronutrients as recommended by UNICEF/WHO/UNU for trial purposes: 30 mg iron, 400 µg folic acid, 800 µg RE vitamin A, 200 IU vitamin D, 10 mg vitamin E, 70 mg vitamin C, 1.4 mg vitamin B1, 1.4 mg vitamin B2, 18 mg niacin, 1.9 mg vitamin B6, 2.6 µg vitamin B12, 15 mg zinc, 2 mg copper, 65 µg selenium and 150 µg iodine (17).

Monitoring of adherence

At every monthly home visit, the interviewers asked a series of questions to assess adherence to food supplements in the previous 30 days. The specific question asked on a monthly basis was "For the last 30 days, how many packages have you eaten?" Data from these interviews were summed up (total 24 weeks, week 10 to 34) and the adherence to food packets over pregnancy was derived. Food supplement data up to week 34 were included to avoid influence on adherence data by preterm delivery.

Daily micronutrient supplements were offered at the 14 weeks clinic visit. The three types of micronutrient supplements looked identical and were distributed in special pill bottles (eDEM®, Aprex, Fremont, California, US). Each bottle contained 35 capsules, and replacement bottles were provided at home during monthly visits by the interviewers. The eDEM® device was used for monitoring of adherence to the micronutrient supplementation. The pill bottle cap was equipped with a counting device and a microprocessor. Each time the pill-bottle was opened and closed, the time and date were recorded. The information in the caps was downloaded into a computer from bottles collected from the enrolled women. Adherence to micronutrient capsules was derived from the total number of openings of pill bottles from week 14 of pregnancy till childbirth.

Notification of birth and measurement of socioeconomic status

A birth notification system was established to make the study staff aware of births as soon as they occurred. Maternal education was assessed as completed years of schooling and dichotomized to <6 and $\geq$6 years. Income-expenditure status and household assets were assessed. The latter included possession of television, radio, domestic animals, chairs, tables, beds, and bicycles, or rickshaw. From these set of variables, an asset score was developed by use of principal component analysis (141).

Mortality outcomes

Mortality outcomes of MINIMat were relevant for both Paper III (142) and Paper IV (143). Information on infant and child mortality was collected at follow-up visits at 7-12 day postpartum, at monthly visits during infancy, and at follow-up studies. This information was verified using HDSS data that were independently collected by CHRWs, who visited households on a monthly basis and collected information on births, deaths, marriage and migration. This information was used to maintain a vital registration system for the population under surveillance. In the MINIMat trial, the cause of death was ascertained by verbal autopsy, which was part of the routine surveillance system, by a team of trained interviewers and a physician and the cause of death assignment was done following international classification of diseases version 10, ICD10 (144). The MINIMat study was approved by the ethical review committee of icddr,b.

In the MINIMat study (130) relevant for Papers III and IV, the sample size was calculated to detect a 70 g difference (a minimum difference that was judged to have a public health importance) in BW between the early and usual invitation to prenatal food supplementation with 90% power with testing at 0.05. The sample size estimated based on this was expected to suffice in demonstrating a mortality difference of 25/1000 live births (that is a difference between 40/1000 live births and 15/1000 live births). The sample size was sufficient to detect a significant difference in infant mortality risk by food and micronutrient groups (130) and by food and micronutrient groups stratified by maternal schooling as a measure of socio-economic status that demonstrated equity gains from the intervention, presented in Paper III (142). The sample for the main study was assumed to be sufficient for CE analyses presented in Paper IV (143).

Analysis Paper III

All mortality analyses were done based on intent-to-treat using dichotomized maternal schooling as the stratifying variable. Analyses were done for women having live births. Baseline characteristics between maternal schooling groups, i.e., <6 and ≥6 years of schooling, were evaluated by student's t-test for continuous variables and chi square test for categorical variables. Adherence to food and micronutrient supplementation for maternal schooling groups was compared by student's t-test and by univariate analysis of variance adjusted for maternal age (years), parity and BMI (kg/m^2) at week 8 of pregnancy. Mean adherence to food and micronutrient supplements by a combination of maternal years of schooling and randomization groups, interactions between food groups and micronutrient groups, between food groups and maternal education groups and between micronutrient groups and maternal education groups were analysed by univariate analysis of variance. Except for those testing interactions, all analyses of adherence to the interventions were adjusted for maternal age (years), parity and BMI (kg/m^2) at week 8 pregnancy. We tested the association between household asset scores and maternal schooling by linear regression. Mortality before the age of five years was analysed across the food and micronutrient supplementation groups and repeated after stratification for groups defined by the level of maternal education. The effect of the interventions on mortality was examined by Cox proportional hazard model by calculating Hazard Ratios (HRs) and 95% confidence intervals (CIs) comparing with the rate in standard intervention, UFe60F (reference category) and other trial arms after stratification by maternal schooling using UFe60F and lower schooling as reference, and taking maternal age (years), parity and BMI (kg/m^2) at week 8 pregnancy as co-variates (142). We tested the analysis by replacing maternal schooling groups by households' asset scores dichotomized based on the median value. Statistical significance was set at p <0.05. Analyses were done using PASW Statistics version 18.0 (IBM Corporation). Informed written consent was obtained from all participants. The study was approved by the ethical review committee of icddr,b.

Design Paper IV

Paper IV was also based on a randomised trial, the MINIMat study, and on published cost data.

Methods Paper IV

Outcome data and alternatives

Outcome data, infant mortality (IM), came from intent-to-treat analysis of the MINIMat trial comparing UFe60F (standard treatment) and EMMS arms, demonstrating a reduced risk of mortality, HR 0.38 (95% CI: 0.18 to 0.78) (130). Therefore, we compared the alternatives UFe60F and EMMS in the MINIMat trial.

Adherence to food and micronutrient data also came from the MINIMat study; 60 food packets and 113 capsules of micronutrients in the UFe60F arm, and 94 food packets and 107 capsules of micronutrients in the EMMS arm (142).

We assumed that the effects of the MINIMat intervention were accumulated from June 2002 through June 2004 and that this could be represented by reductions in IM in the EMMS arm compared to the UFe60F arm.

By using life expectancy (LE) at birth, 70 years in the year 2012 (145), we calculated the average life years (LY) that could be saved by avoiding one infant death; this was 29.99 years when discounted at 3% and 20.31 years when discounted at 5%. Since we adjusted all costs using consumer price index, to remain consistent, we also adjusted the health gains by discounting the LYs gained; this resulted in treating this nutrition intervention similarly in comparison with other sectors of the economy (124, page 108).

Cost data

The direct cost of the intervention included food and micronutrient supplements, staff, training and meetings, administration, capital, community volunteer time, and recurrent activities. The indirect cost included the cost of participants' time.

Most cost data were available from Khan and Ahmed (146), while data on the cost of micronutrients and some staff costs were obtained from the MINIMat project administration. Figures for all cost items from Khan and Ahmed (146) were converted to Bangladeshi Taka (BDT) 79.3823 per US$ 1, the average exchange rate for 2013 (147). Khan and Ahmed reported costs for NGO-run and government-run community nutrition centres (CNCs). We presented all costs for these delivery modes as well as under a hypothetical highest cost scenario combining the highest cost for each item presented for

NGO-run and government-run CNCs. For the last, for example, for food cost we took the figure for NGO-run CNCs but for staff cost we took the figure for government-run CNCs.

CNCs operated for pregnant and lactating women and children under two years of age. At the NGO-run CNCs, there were 9.36 pregnant women per day, 9.71 lactating women, and 10.29 under two-year-olds per day. In total 19.07 pregnant and lactating women represented 19.07 adult equivalents and, 10.29 children represented 5.15 adult equivalents equal to 24.22 adult equivalents. This was because each pregnant or lactating woman was offered four packets and each child was offered two packets of food supplement; thus, two children equals to one adult. There were 7579 (24.22*313) person-days per year (313 working days per year; CNCs were closed on Fridays). Pregnant women represented 2930 (9.36*313) person-days a year and used about 32% (9.36/29.36*100) of working time at the CNC (146). We assumed that pregnant women received comparable services as children did, which we believe was a conservative assumption for CE analysis. Therefore, for calculation of food cost we used adult equivalents and for other costs we used persons contributed by pregnant women. In total, 37.44 packets (9.36*4) were utilized per CNC per day by pregnant women, which were 39% of total 97 (9.36*4+9.71*4+10.29*2) food packets. For all items, we calculated the cost per CNC per year and then cost per pregnant woman per day. Food cost was multiplied by 0.39 (fraction of packets used) and, then, divided by 2930 (person-days) to obtain costs per pregnant woman per day. For other items, costs per CNC per year were multiplied by 0.32 (proportion of working time) to represent pregnant women and, then, divided by 2930 to obtain the cost per pregnant woman per day. In government-run CNCs 6.33 pregnant women, 5.29 lactating women, and 4.38 children were enrolled resulting in 16 persons, 13.81 adult equivalents, and 55.24 food packets consumed. In this situation, pregnant women consumed 46% of food packets [(6.33*4)/55.24*100] and used 40% of time [6.33/16*100]. For the hypothetical highest cost scenario we used the proportions of food consumed and time used in government-run CNCs since this generated the highest cost figures.

Staff cost came from Khan and Ahmed (146), who derived that from the current local salary and benefits of BINP employees, and evaluated volunteers' time using the salary level of similar workers in rural areas. Staff costs included salaries for the manager (BDT 10,000 per month), Community Nutrition Organizers, Community Nutrition Promoters, and helpers. The manager's (responsible for NNP-related activities at sub-district level) salary was retrieved from the cost report of icddr,b. The increase in staff's salaries over time was accounted for by a 40% increase in staff salary from 2002. Training and meeting costs at the sub-district level for 2002 were obtained from BRAC that also provided administrative costs for 2000 to 2003, which were averaged: these costs at CNC levels were available from Khan and Ahmed (146). We ignored administrative costs at BINP/NNP office.

Capitals costs, costs of space for CNCs, and instruments for screening, maternal height and weight measuring scales, were available from Khan and Ahmed (146). From these costs, we deducted the cost for measuring scales (Salter scale and bathroom scale for measuring children's and women's weight, respectively) since all MINIMat participants were offered food supplementation irrespective of their anthropometry. Khan and Ahmed calculated the salary of the Community Volunteers (women for preparing and serving food supplement) as community-donated time at the wage of helpers (146), which we considered appropriate. Recurrent costs at the CNC that represented cost related to the goods procured locally and from outside the local area were available from Khan and Ahmed (146). We ignored such costs for the sub-district and central level in Dhaka.

Participant cost was estimated at the cost of a labourer when labour cost was the lowest (148). UNICEF supplied micronutrient capsules for trial purposes; the price was not subsidized. Assuming economic life of inputs, Khan and Ahmed (146) annualized all capital costs at 5% discount rate, evaluated donated materials and resources using the market price of similar resources in the local area. We did not do any further discounting but adjusted all costs to the price levels of 2013 using consumer price index (145, 149). All costs are presented in Table 1 of Paper IV.

Analysis Paper IV

Incremental cost-effectiveness ratios (ICERs) were calculated for switching from the standard intervention (UFe60F) to EMMS using MINIMat trial results by dividing the differences in costs with the differences in effects and costs/one extra infant death averted and cost/one extra LY saved were calculated. For sensitivity analyses, we used the lower and upper limits of 95% CI of HR from the intent-to-treat analyses comparing EMMS and UFe60F arms in MINIMat, and converted the resulted number of infant deaths to IM rates. The above-described steps for calculating ICERs were then followed and ICERs for extra IM averted and extra LY gained were calculated. The study was approved by the ethical review committee of icddr,b.

Ethical considerations

The Shaharasti study was an observational study with a cohort of pregnant women, already enrolled by the BINP nutrition interventions, was followed to childbirth. These women were not allocated to different durations of prenatal food supplementation; rather their own choice of consumption of food supplements was observed. Therefore, they were not deprived of an intervention that could benefit them and their newborns in the context when studies in other low-income countries have shown that prenatal food supplementation could increase BW (32, 86, 87) and reduce neonatal mortality (32).

MINIMat was an experimental study, where pregnant women were randomly allocated to an early or usual timing of invitation to prenatal food supplementation combined with micronutrient supplementations around week 14. At detection of pregnancy, women allocated to early invitation (average entry week 9 pregnancy) were suggested to participate in food supplementation sessions at the nearby CNCs and their names were informed to the nutrition programme while those on the usual invitation (average around week 20 pregnancy) did not receive such a suggestion but was invited by the normally operating nutrition program ran by BRAC. At the time of study start, the additional benefits of allocation to food supplementation early in pregnancy was not known, although it was presumed that an early allocation would benefit the foetus development from early pregnancy and entail a longer duration of food supplementation that would result in higher BW. Although it was desirable to have a "no intervention" arm, because of the known benefits of prenatal food supplementation (32, 86, 87) it was considered unethical to include such a group. Therefore, the MINIMat study did not deprive the participating women from any known benefit of prenatal food supplementation.

Micronutrient supplementations were given at doses equivalent to daily allowances. No published harmful effects of any micronutrients used in the trial were available at the time of initiation of the MINIMat study, nor are such results available at present. Till now, all meta-analyses conclude that micronutrients supplementation during pregnancy have some beneficial effects on infants and sometimes on mothers (109, 110, 111). The rates of infant mortality in the MINIMat trial ranged from 16.8 per 1000 live births in the EMMS arm to 47.1 per 1000 live births in UMMS arm (130). That is, infant mortality rates in all trial arms were below the level reported for the same year, 2004, in the adjacent government service area, i.e. 48.5 per 1000 live births (150). This may indicate, to a varying extent, that all women in the MINIMat trial may have benefited from the interventions although other activities in the icddr,b service area may have contributed. Anyhow, the MINIMat trial did not expose women in any trial arm to an increased risk of infant death compared to what was happening in the adjacent area at the time of the intervention.

Results

The studies presented in this thesis address public health questions related to maternal suboptimal nutrition, and interventions to combat its effects on offspring outcomes. The studies also deal with issues of equity in gains from the interventions and cost of the interventions in relation to the benefits in terms of prevention of death and life-years gained.

Quality of life among pregnant women with chronic energy deficiency in rural Bangladesh (Paper I)

The participants of Paper I were less educated, poorer and were less frequently employed compared to the average of women in the MINIMat trial. These unfavourable characteristics were also reflected in their nutritional status. In this study, women related maternal undernutrition to small, undernourished, weak babies and stated that LBW babies fall sick more frequently and die more often, and undernourished women are unable to perform adequate work (131). In this study, in EQ-5D terms, most women reported level 2 for mobility, self-care and usual activities; a few reported level 3. For the dimensions pain/discomfort and anxiety/depression a large proportion of women reported level 3 (Fig. 2, Paper I) indicating the poor health of women with CED, as perceived by the study participants. The main finding of this paper is that women attached very low scores to maternal undernutrition and the scores were mainly driven by their concerns for the health and wellbeing of their offspring.

Effect of prenatal food supplementation on birth weight: an observational study from Bangladesh (Paper II)

In Paper II (140) we presented the characteristics of women included and not included in analysis to display the possible consequences of incomplete data (Table 1, Paper II) (140). We evaluated the association between prenatal food supplementation and BW by simple linear regressions. In this thesis, we examined the distribution of key variables (Figure 3).

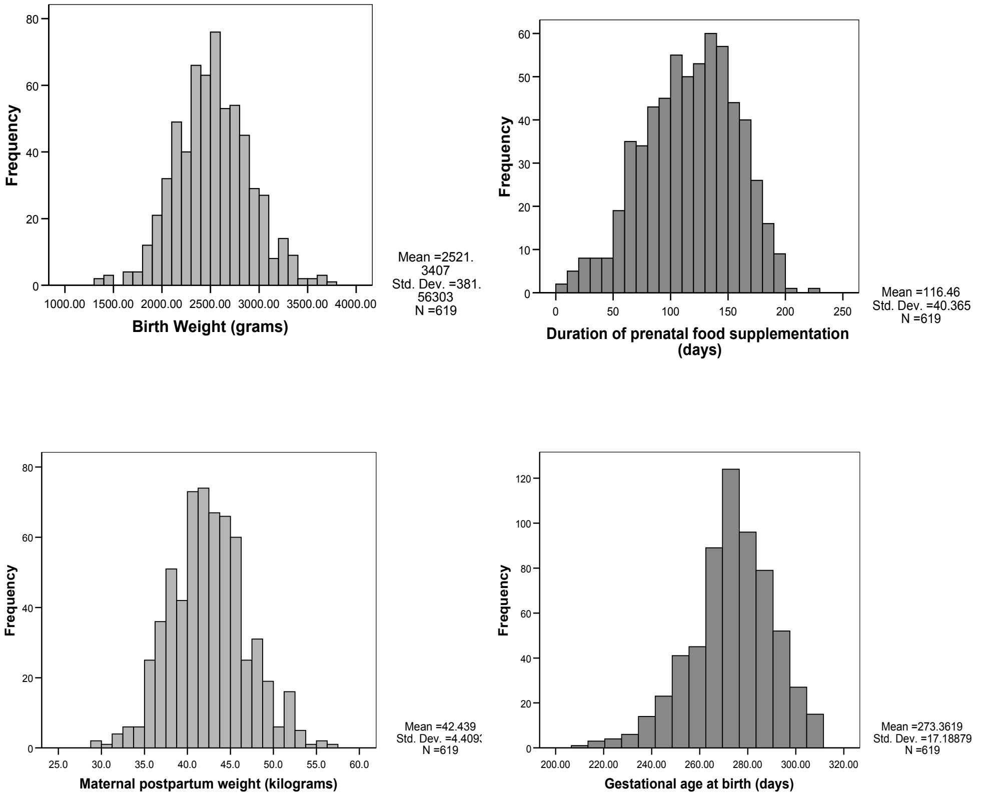

Figure 3. Presented clockwise: birth weight (grams), prenatal food supplementation duration (days), gestational age at birth (days) and maternal postpartum weight (kg): Shaharasti study

A positive association was found between prenatal food supplementation and BW. Among mostly undernourished women, an average of four months of supplementation increased BW by 118 g (about 1g/day of supplementation, adjusted for gestational age at birth). We observed larger effects of prenatal food supplementation on BW, 2.2 g/d of supplementation adjusted for gestational age at birth, for the births that occurred in January -February, i.e., for births occurring after exposure to the hungry season, mid-August to mid-November, 2.2 g/day of supplementation. BW was lowest for births occurring in January-February and highest for births in March to October.

Food supplementation adherence data were derived from one to three interviews in pregnancy and postpartum. Since reporting of adherence may vary by the number of interviews, by *student's t* test we examined if the mean number of interviews varied by postpartum weight groups. The analysis revealed this was not the case (Table 2).

Table 2. *Number of interviews among women with postpartum weight <42 kg and ≥42 kg (n=622): Shaharasti study.*

Postpartum weight	One interview %	Two interviews %	Three interviews %
<42 kg	113/286 (39.5)	86/286 (30.1)	87/286 (30.4)
≥42 kg	132/336 (39.3)	112/336 (33.3)	92/336 (27.4)

Data represents n (%). Chi square test, *P*=0.602

Equity in adherence to and effects of prenatal food and micronutrient supplementation on child mortality: results from MINIMat trial, Bangladesh (Paper III)

Earlier we have presented that in the EMMS arm of the MINIMat trial the under-five mortality was reduced by 66% in comparison with the standard intervention (HR 0.34, 95% CI: 0.18 - 0.65), mainly through reduction of deaths from birth asphyxia, infections associated with preterm birth, and intrauterine growth restriction (130).

In Paper III, we addressed equity in adherence to and effects of prenatal food and micronutrient supplementations on child mortality using maternal schooling as a marker of social groups (142). Women who had less schooling adhered more to food supplementation than women with more schooling (81 vs. 69 packets, p=0.0001). Analysis by the intervention and maternal schooling levels showed that compared to women having more schooling women having less schooling adhered to more food packets while they adhered to less micronutrient capsules (Figure 4).

Within UFe60F adjusted for maternal age, parity and BMI (kg/m^2) at week 8 pregnancy there was no significant difference in food packets between women having less and more schooling (64 vs., 55 packets, p=0.19) but there was significant difference within EMMS (102 vs., 88 packets, p=0.002). Adjusted for maternal age, parity and BMI at week 8 pregnancy, within early food there was a significant difference between women having less and more schooling (99 vs., 83 packets, p=0.0001). A similar difference was found for educational levels within the usual food group (66 vs., 56 packets, p=0.0001).

In Paper III we presented that the reductions in child deaths occurred especially among women having less schooling, i.e., 74% reduction (HR 0.26, 95% CI, 0.11-0.63) (Table 3 of paper III) adjusted for maternal age (years), parity and body mass index (kg/m^2) at week 8 of pregnancy. If also adjusted for the month of conception that relates to food security, this remained true, i.e. 74% reduction (HR 0.26, 95% CI: 0.11 to 0.65).

This effect took the level of child mortality among women with the lower level of education, who had been randomised to EMMS, to the child mortality level of their more educated counterparts, randomized to either UFe60F, or EMMS.

The reduction in deaths was mainly seen in deaths due to intrapartum causes (birth asphyxia) and infections. The main causes of infant mortality were asphyxia, infections, and conditions associated with preterm birth or intrauterine growth restriction as presented in eTable 3 of our main paper (130). The number of neonatal deaths from asphyxia was highest in the usual invitation with MMS group (UMMS, 14 per 595 live births), seven times higher than EMMS (2 per 595 live births, *P*=.004) and double that of the UFe60F group (7 per 612 live births, *P*=.13) (130).

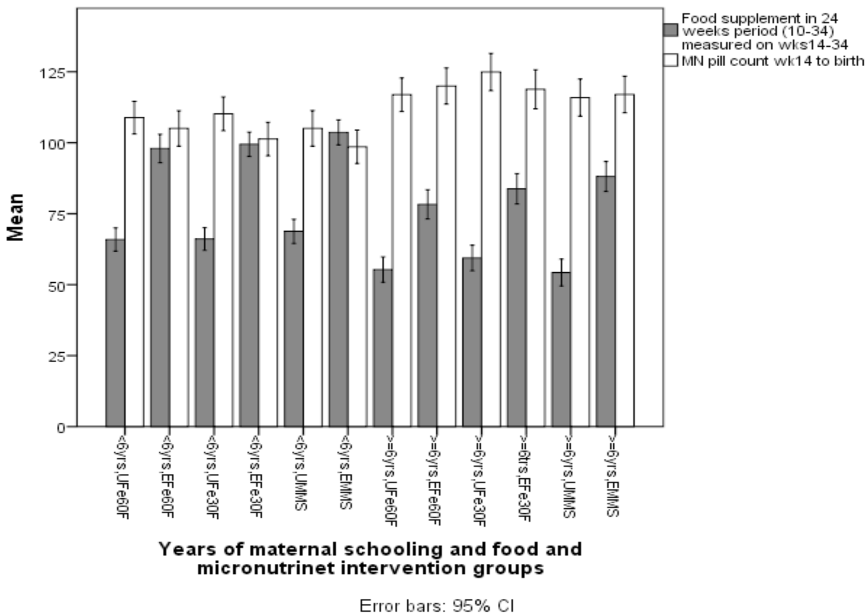

Figure 4. Adherence to prenatal food and micronutrient supplements by intervention and maternal schooling groups: MINIMat study.

Cost-effectiveness of invitation to food supplementation early in pregnancy combined with multiple micronutrients on infant survival: Analysis of data from MINIMat randomized trial, Bangladesh (Paper IV)

In Paper IV we presented the incremental CE ratios for moving from UFe60F to EMMS. We found by replacing UFe60F with EMMS one extra infant death could be averted by US$797 to US$907, and one extra LY could be saved by US$27 to US$30, by government- and NGO-run CNCs, respectively (143). Under a hypothetical scenario of the highest costs these figures were, US$1,024 and US$34, respectively (143). The two major cost components were the food cost and participant cost (Figure 5). The delivery strategy influenced the food cost; lower cost if delivered through government-run CNCs. As the participant cost was same for all three strategies presented in Paper IV, if it is ignored, the food cost remains as the main determinant of the CE ratio. However, the delivery strategy may reduce food cost, since the price of food is lower when delivered through government-run CNCs.

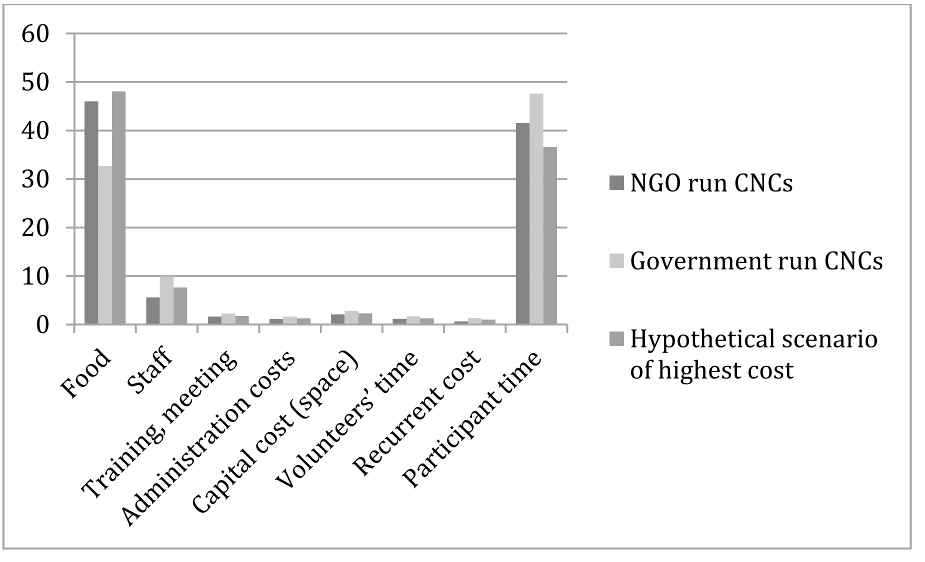

Figure 5. Component costs as a percentage of total cost for prenatal food supplementation.

Discussion

The research presented in this thesis shows that in a low-income country setting, where suboptimal maternal and foetal nutrition and child mortality are prevalent, a longer duration of prenatal food supplementation increased BW, especially for women who were exposed to the lean season in pregnancy, and for women who were marginally malnourished. Prenatal food supplementation early in pregnancy combined with MMS generated pro-disadvantaged equity in child survival and the upgrading of UFe60F to EMMS represents value for money in terms of cost per infant death averted and cost per LY saved, judged in the context of the national per capita gross domestic product. The results also indicate the importance of maternal undernutrion as a public health problem that emerged from women's own voices.

Low health scores related to undernutrition during pregnancy

Paper I shows the QOL scores attached by malnourished pregnant women were very low. These low scores reflect women's concerns about the health their offspring. The description in the scenario presenting the effects of CED on future generations may have resulted in such low scores. The scores from EQ-5D represent the QOL related to CED and its consequences. This indicates that rural women in Bangladesh can logically attach scores to an apparently asymptomatic condition when there are concerns for health of the offspring. The mother's concerns for offspring health are probably a unique phenomenon. From a public health point of view, this indicates that pregnant women's' health should be a priority.

The subjectivity of the measurement and its impact on the acquired scores, however, makes it difficult to use it as QOL scores and places all such QOL measurements in question to use in economic evaluation.

In this study a large proportion of women reported in level 2 or 3 on the dimension for anxiety and depression, which warrants further investigation. In scales having scores ranging from 0 to 1 the scores 0.30 from EQ-5D, 0.27 from VAS for worst health and 0.49 from VAS for current health can be compared to the overall score 0.41 for general health measured by SF-36 among women in a study in Bangladesh (83). The score, 0.41, generated in the study by Ahmed et al., were attached to their own wellbeing by poor women who were not members of BRAC, a micro-credit offering NGO. The scores of VAS current health that is presented in Paper I in this thesis are also low because the scores were based on a heath condition that has impact on the newborn health presented in the scenario. In another study in China that used the EQ-5D instrument women reported worse health status than men (151) indicating that in general women have low health status.

A recent multi-country study has shown that the disability weight for severe wasting was 0.127, i.e., QOL score was 0.87 (1−0.127=0.873) (152). The subjectivity in attaching scores may have resulted in such differences between the results presented in Paper I and this study.

Literature examining perceptions of maternal undernutrion is scarce. However, one study in Bihar, India, explored perception of child undernutrition and found that undernutrition itself was not perceived as a disease but local disease concepts were identified that described undernutrition (81).

For a deeper meaning of maternal undernutrition and its consequences, the study reported in Paper I was nested into the MINIMat study, and a part of the MINIMat cohort was used for this study. The recruitment from the population-based cohort for this sub-study implies that the perceptions reported most likely represent views of the women in the area. The scores represent women's perceptions and weighing of maternal undernutrition in comparison with full health and death.

The questionnaire instrument was tested for face and construct validity, i.e., whether the instrument was measuring what it was expected to measure and whether the measurements were done accurately with sufficient precision. The instrument was judged to have measured what it was intended to measure and the measured scores have moderate accuracy and precision. However, the scores from all the scales were subjective. Due to the selection of a limited number of women residing in one locality the external validity of this study is probably limited. A random sample of women could have been drawn from the MINIMat cohort rather than selecting a sub-sample during a certain time period and this could have enabled to analysis indicating the impact of the intervention regarding improvement in the quality of life of pregnant women.

Nevertheless, the findings of Paper I indicate that women perceived undernutrition during pregnancy as a serious condition since this condition has impact on offspring health and survival.

Improvement of birth weight from longer duration of prenatal food supplementation

Paper II shows that BW improved with increasing duration of prenatal food supplementation. Higher improvements occurred for women who had marginal undernutrition and for women who gave birth in Jan-Feb, i.e., who were exposed to hungry season, mid-August to mid-November, during pregnancy. Among the malnourished women in Shaharasti, mean BW was 2521 g after supplementation and 1 g improvements in BW occurred from each day of prenatal food supplementation (608 kcal per day).

The size of improvements in BW in the Shaharasti study indicates that a relatively large improvement in BW is possible by prenatal food supplementation in a malnourished population. The higher effects among marginally malnourished women and for births after the hungry season indicate that the distribution of effects to mother and foetus depends upon the nutritional status of the women. Larger improvements were possible for women who had medium-level body weight. These findings are consistent with the findings from Guatemala (153, 154) and the Gambia (32).

The energy intake from the food supplements in Shaharasti study was about 70,000 kcal, which was comparable to that in the study in the Gambia, 72,000 kcal, (32, 87) but was higher than that obtained in the EMMS arm in the MINIMat study, which was about 56,000 kcal, from average 91 food packets as presented in Paper III. In a study in Guatemala, the average adherence to food supplementation was about 26,000 kcal (108.6 mega Joule) in malnourished and marginally malnourished women and about 22,000 kcal (90.2 mega Joule) in well-nourished women in low energy supplement group, fresco (154). These figures for women randomised to a high-energy supplement group, atole, were about 110,000 kcal (458 mega Joule) for malnourished and marginally malnourished and 116,000 kcal (487 mega Joule) for well-nourished women (154). In the study in the Gambia the average adherence to food supplementation was 82 days with daily intake of two biscuits of 1015 kcal that provided about 83,000 kcal (32), and a previous paper from this trial reported 72,000 kcal extra energy from the supplement (87).

Lechtig et al. proposed that the size of the effect depends on the previous nutritional status of the mother, the home diet intake, the grade of replacement of home diet, the type of supplementary food, the health status of the mother, and the level of physical activity during pregnancy (85). In Shaharasti study probably the home diet was poor, and a replacement was most likely relatively large; thus, the effects were lower than that could have been achieved, and was evident mostly for marginally malnourished women.

Higher effects were found for births occurring in January-February that is for women who were exposed to hungry season, mid-August to mid-November. This is consistent with research from the Gambia that showed an overall increase of 136 g of BW with higher improvements for births in the hungry season, 201 g, i.e., births in June to October (32). A recent study from India that showed 90 g improvement of BW from full exposure, 26 weeks, to winter when food is relatively abundant (64). Even though the energy did not come from food supplement this latter study (64) showed with relative abundance of food BW improved. In Paper II the higher improvement for those exposed to hungry season during pregnancy was possibly due to higher need that may be related to higher responsiveness.

The results presented in Paper II provide evidence based on analysis of an epidemiological study that may reflect the biological relationship between duration of prenatal food supplementation and BW. This relationship was assessed considering possible confounding factors.

The study women were, in general, poor, had low BMI and participation was higher among women having higher parity and less schooling. This pattern of participation is expected in a community-based intervention in a low-income country like Bangladesh; subjects more in need participate to a larger extent than those who are less in need. The subjects who were lost to follow-up had better socio-economic status, had less frequently given birth in January-February, adhered to food supplementation for longer durations, and gave birth to slightly higher BW babies, but their anthropometry was similar to those who were included in the analysis. This indicates most likely, the loss of women who had incomplete data did not have any major influence on the results.

The duration of food supplementation was measured carefully and the main outcome variable, BW, was measured using standard procedures for high accuracy and precision in anthropometric measurements. The weighing equipment was kept centrally and rotated for the measurement of BW in different areas. Measurement errors, if occurred at all, most likely affected women in higher and lower postpartum weight groups equally. We judge there was very low risk of systematic errors in measurements. The examination of weight data revealed a bell-shaped Gaussian distribution and there was no reporting of duration of food supplementation longer than what was possible. Food supplementation data came from one to three visits with interviews. The number of visits did not vary between maternal postpartum weight groups.

The Shaharasti study was a cohort study, where women enrolled in BINP program were included. The food supplementation program of BINP was already operating and the uptake of the intervention was examined in a natural situation, and the supplement was made of rice, pulses, soybean oil, and molasses, which were locally available. The cohort design and inclusion of mostly malnourished pregnant women offered limited external validity of the effect sizes, although the findings of different effect sizes depending upon maternal weight groups and level of food security may be relevant in other settings. However, other outcomes such as birth length, and birth head circumference were not measured in this study, which can be considered as a missed opportunity.

In essence, Paper II showed in a low-income country mostly among undernourished women BW improved in a dose-response manner with prenatal food supplementation and did so more for marginally malnourished women and for women who were exposed to hungry season during pregnancy.

Pro-disadvantage equity from early invitation to prenatal food supplementation combined with multiple micronutrients

Paper III showed MINIMat intervention of prenatal food and micronutrient supplementation reduced the gap in child survival between the disadvantaged (having less schooling) and advantaged (having more schooling) women. The size of reduction in child mortality among children born to women having less schooling was very substantial. The 66% overall child mortality reduction in the EMMS arm compared to the UFe60F arm was presented in MINIMat main paper (130). This reduction was greater than that found in the Gambia by prenatal food supplementation, i.e., 46% reduction of early neonatal deaths (32) and 22% reduction of child mortality by MMS supplements in a cluster-randomised trial in Indonesia (107).

When compared with other community-based interventions, the reduction of under-five mortality in the MINIMat trial was also higher than that found in a community-based newborn care cluster-randomised trial, 34% reduction in neonatal mortality (155). Similar community-based newborn care interventions in India have shown 62% reduction in neonatal mortality (156, 157), which is also lower than what was found in MINIMat.

Paper III showed reduction in under-five mortality in the MINIMat for women, who had less schooling, was even larger, 74% (142). This figure is larger than all of the studies mentioned above plus showed evidence for reduction in social disparity. The decline in deaths in MINIMat was mainly due to a reduction in deaths from intra-partum-related causes (birth asphyxia), a major cause of neonatal deaths in Bangladesh.

In Paper III, equity in adherence to food and micronutrient supplementation was also assessed that can be compared to other studies that showed adherence to prenatal food and micronutrient supplementation as well as to those that addressed equity in utilization of care. Food supplement intake was much higher in the study in the Gambia (32) as well as in Guatemala (153, 154) compared to the intake of 83 packets for less educated women (50, 464 kcal), 102 packets (62, 016 kcal) for those who were less educated and randomized to the EMMS arm and 97 packets (58, 976 kcal) for those who were less educated and randomised to UFe60F. For more educated women these figures were 68 packets (41, 344 kcal), 88 packets (53, 504 kcal), and 79 packets (48, 032 kcal). That is, overall food supplement intake was low. However, among less educated women those randomised to EMMS consumed 37 more packets (equivalent to 22, 000 kcal) compared to those who were randomized to UFe60F (142). These women having less schooling and randomised to EMMS consumed 14 more packets (8512 kcal) compared to women having more schooling and randomised to EMMS and 23 more packets (13984 kcal) compared to women having more schooling and randomised to UFe60F (142). These indicate women having less schooling randomized to early food availed the opportunity to consume more food and when combined with MMS the effect was such that it took their child survival probability to that of women having more schooling who already have low child mortality rate.

The timing of food supplementation was most likely important in MINIMat since women in the early invitation food group started supplementation at around week 9 in pregnancy, earlier than the study in Guatemala, during the third trimester of pregnancy (154) and the Gambia (32, 87) around week 20 in pregnancy. The early group in MINIMat started food supplementation also much earlier compared to the study conducted in Shaharasti where the starting time in a natural situation was around week 20 (140), comparable to the usual food group in MINIMat. In MINIMat trial in the early invitation food group women indeed started the supplementation before the completion of the development of internal organs. Therefore, as compared to other studies the timing and total dose of food supplements in early pregnancy in the MINIMat is unique and may offer substantial long-term benefits (129).

The average adherence to iron-folic acid supplementation in the MINIMat was lower as presented in Paper III. The highest adherence was 126 capsules in women having more schooling who were randomized to UFe30F, and the lowest, 97 capsules, among women who had less schooling and had been randomized to EMMS (142). The average adherence to micronutrient supplementation in a trial in China was 165 doses (1 capsule=1dose, dose offered for daily consumption), 80% of women consumed more than 120 doses, and 43% consumed more than 180 doses (158, 159). This amount is higher than the average adherence in MINIMat, 111 capsules for all micronutrient groups, and the highest that was 117 capsules in the UFe30F arm, and the highest adherence of 126 capsules among women randomized to UFe30F. The level of adherence in MINIMat is comparable to that found in the experimental arm of a study in Senegal, where the overall compliance to tablets was 69%, equivalent to 97 tablets, with 86% in the experimental group (120 tablets) and 48% in the control group (67 tablets) (160). Higher adherence to micronutrients were observed among more educated women in other settings also (161, 162). However, even few MMS capsules were probably enough to assist less educated women in achieving child mortality reduction when combined with food early in pregnancy as results presented in Paper III showed.

Uptake of services by women having more education was found to be common for other interventions (163). Data on utilization of maternal care in Bangladesh has shown although wealth and education related utilization of antenatal care has reduced that for facility birth delivery has increased (121). That is, more education is related to higher uptake of intervention that is introduced at a later time point since introduction of delivery at facility was started much later than antenatal care.

These indicate relatively modern services delivered at facilities usually benefits the wealthier section of the community. However, food and micronutrient supplementation was delivered at home in MINIMat. Since poorer women having less schooling were at need they availed food more while micronutrient was possibly perceived as an indicator of modern care and thus was mostly utilized by women having more schooling.

Several trials and systematic reviews have shown the effects of multiple micronutrient supplementation compared to iron and folic acid on offspring mortality, BW and other newborn indicators. In a trial in Nepal (106) there was a tendency to increased risk of perinatal mortality in the group randomised to MMS. In a cluster-randomised trial in Indonesia, MMS was found to decrease early infant mortality by 18% and LBW by 14%, as compared to iron and folic acid (107). In a randomized controlled trial in Burkina Faso, an increased risk of perinatal death was found to be associated with MMS allocated to primiparous women (164). In Guinea-Bissau, BW increased with a double the dose of MMS, but there was no effect on perinatal mortality (165). In a trial in Tanzania multivitamin supplementation to HIV negative pregnant women reduced the risk of LBW and small for gestational age and increased BW without any effects on prematurity or mortality (166). A meta-analysis concluded that MMS compared to placebo or iron-folic acid supplementation reduced the risk of LBW by 19% (RR: 0.81) or 17% (RR: 0.83), respectively (167). Other meta-analyses showed increased BW by MMS over iron and folic acid supplementation (109), no effects on stillbirth or neonatal mortality (110), and effect by both iron-folic acid and MMS (111). Another review concluded that prenatal MMS resulted in a decreased incidence of LBW and SGA, but the risk of neonatal death was increased in the subgroup that began the intervention after the first trimester (168). In the context of these studies the overall reduction shown in MINIMat main paper is high, 66% (130) and that shown by Paper III can be considered very substantial, 74% (142). This estimate remains the same when adjusted for season of conception that also represents food security in rural Bangladeshi context.

Data for paper III came from MINIMat randomized trial. Our hypothesis was that women having less schooling would adhere to more food supplements and would benefit more from the intervention. Therefore, whether one type of supplement influenced the adherence to the other type of supplement was not a concern. Selection bias was also not a concern since all pregnant women were invited to participate.

In MINIMat, adherence to food supplement was measured by 30 days recall, “how many packets of food supplement have you eaten during the last 30 days”? The result of these questions was compared with other questions on adherence included in the repeated interviews and was judged to have a good validity. Micronutrient supplement data came from microprocessors embedded in the lids of the pill bottles that recorded each opening of the bottle related to intake of one capsule. This method is a valid way to measure capsule intake without disturbing the participant.

Under-five mortality in MINIMat was verified by information derived from the HDSS. The analysis evaluated the timing of invitation to prenatal food supplementation and type of micronutrients in relation to the outcome, in this case mortality. The intent-to-treat analysis takes into account only the allocations and therefore, the possibility of biased estimates is very low. The external validity may depend on the level of undernutrition, the local food security situations and other contextual factors. Information on level of wealth of the household and level of maternal education was obtained by questioning the participants. Such data collection is routine in Matlab HDSS and is judged to provide good quality data. These validation issues are also relevant for Paper IV where cost effectiveness of prenatal food supplement combined with multiple micronutrients are is presented.

In Paper III, we used maternal schooling as a social stratification variable. Although which marker to use for social stratification is a matter of debate (169, 170, 171), experience from paper III shows that maternal schooling was an appropriate characteristic in the context when evaluation of adherence to an intervention is essential. However, for Paper III and Paper IV due to ethical reasons there were no control groups that received placebo or no food supplements. This limitation is likely to be inherent to this type of interventions where prenatal food and micronutrient is likely to benefit all pregnant women in a low-income setting.

In essence, in Paper III it was shown than although there were complexities in utilization of food and micronutrient supplements, for example more food by less educated women and more micronutrient by more educated women, effects of the intervention generated pro-disadvantaged equity. This finding can be considered as a novel finding that shows in a low-income country situation inequity in child survival can be reduced by a large-scale prenatal food and micronutrient intervention.

Upgrading usual invitation to prenatal food supplementation combined with iron-folic acid to early invitation to prenatal food supplementation combined with multiple micronutrients represents good value for money

Paper IV showed upgrading usual invitation to prenatal food supplementation plus 60 mg iron and 400 microgram folic acid with invitation to prenatal food supplementation early in pregnancy plus MMS was cost effective in terms of per capita GDP for cost per infant death averted. The cost per life year saved figure was also very low.

A community-based newborn care intervention showed 34% reduction in neonatal mortality in the home-care arm that incurred a cost per neonatal death averted US$2939 (125) while the cost per extra death averted figure in MINIMat presented in Paper IV for moving from the standard program UFe60F to EMMS was US$797 to US$1024 (143). The figures from MINIMat were below the per capita GDP in Bangladesh in 2013, US$ 958 (145). The cost per extra LY saved figures were only US$27 to US$34, and lower than per LY saved from participatory women's group intervention in Nepal, US$ 211 per LY saved (172). The cost per infant death averted figure presented in Paper IV was between 1 to 3 times per capita GDP and thus was cost-effective as per the criteria that were set by the Commission on Macroeconomics and Health (126).

The results presented in Paper IV placed the value of prenatal food (macronutrient) and micronutrient supplementation in the context of other public health interventions. That is, CE analysis for an intervention that comprises both quantity and quality of food for pregnant women is now available together with CE analysis for other essential community based interventions. This incorporates cost effectiveness of prenatal food and micronutrient supplementations in the context of cost effectiveness for Haemophilus influenza type b (173) and rotavirus vaccines, in low-income countries, cost of vaccination, US$3.47 per child (174,175) and US$3,015 per life saved (175). These two latter interventions cover two major causes of infant deaths, pneumonia and diarrhoea in low-income countries (176). The results of Paper IV provided a careful account of economic evaluation of prenatal food and micronutrient supplementation when previous studies provided incomplete account of BINP by excluding analysis of the effect of prenatal food supplementation (128).

At the macro-economic level once the income, per capita growth of GDP, is increased, higher revenue can be expected that can be spent to avail better food for women, who are expecting to conceive. A food supplementation program may still be needed since there will be a substantial proportion of women who will benefit from the intervention; such programs are present in high-income countries. In future, a more equitable economic growth should automatically assist in more equitable distribution of child outcomes.

At the microeconomic level, the individual factors and behaviour of families will decide the need of women to participate in this program. Programs that increase societal knowledge on the significance of better food during conception and early pregnancy may influence expenditure at the microeconomic level.

Confounding, selection bias, bias due to loss to follow-up and measurement errors were not concerns for Paper IV since data came from a randomized trial and were addressed in the outcome analysis (130). Khan and Ahmed collected detailed cost data, and these costs were adjusted to the price levels of 2013. Additional data were collected during the MINIMat study. Thus, the costing data presented in Paper IV represented the true cost of the intervention.

Outcome data came from the MINIMat trial that offered the best possible outcome estimates, and therefore the same was true for the CE analysis. The external validity of the CE analysis depends on local price levels, factors influencing those price levels, and outcomes in the local settings, which also depend on different contextual factors.

However, one limitation for Paper IV is that, due to ethical reasons there were no control groups that received placebo or no supplements and therefore the full value of EMMS intervention cannot be judged.

In essence, Paper IV showed that uplifting the usual timing of invitation to prenatal food supplementation combined with 60 mg iron and 400 microgram folic acid to an early invitation to prenatal food supplementation combined with MMS represents good value for money.

The burden of maternal undernutrition and the emerging overweight and obesity

Although the huge burden of undernutriton persists in low-income countries including Bangladesh non-communicable diseases, especially type 2 diabetes, is increasing (177, 178). Many non-communicable diseases are connected to obesity and metabolic disorder related to obesity while emerging obesity is a concern in low- and middle-income countries including Bangladesh, Nepal, and India (179, 180, 181). Data from India showed that underweight and overweight coexists among women, and there are more underweight women in the lower SES group (31). Thus, there are needs for interventions addressing both undernutrition and overnutrition.

Bangladesh experiences a high prevalence of LBW. Many of these children may later be exposed to a relative abundance of food, which may increase the risk of coronary heart disease, type 2 diabetes, and hypertension in adult life (182). These circumstances expose the population to a double burden of under- and overnutrition while infectious and chronic diseases are already persisting.

Therefore, concerted global strategies are needed to increase the access for the poor to health services and other sectors of society, including specific interventions to achieve better health and alleviate poverty. This is because research showed only economic growth cannot ensure health, health indicators vary widely for the same income level (183), and health is now one important aspect of the global sustainable development goals (184).

Conclusions and recommendations

The results presented in this thesis addressed aspects of nutrition that have the potential to influence policy decisions regarding maternal and foetal nutrition and nutrition of women of reproductive age in low-income country settings. To what extent have the results of the studies brought any benefit to the participants, and to rural women in low-income countries? The results should preferably increase the awareness of national and international policy makers on the importance of maternal undernutrition as a public health problem, and the benefits of prenatal food supplementation in improving birth weight, and that large-scale prenatal food and micronutrient supplementations may reduce social inequity in child survival. Policy makers should be made aware of the potential economic value of prenatal food and micronutrient supplementations in preventing infant death and gaining life years when considering and prioritizing child health interventions.

Based on concerns for the health of future generations women in rural Bangladesh perceived maternal undernutrition to be a condition that seriously impaired quality of life, reflecting that health of the offspring should be a priority for the society. Prenatal food supplementation to malnourished women increased BW, especially among the less undernourished women, and among women, who were exposed to the hungry season in pregnancy. These lessons may be helpful in the planning of future interventions.

The costs incurred for food and multiple micronutrients during pregnancy returned the gains regarding deaths averted and LYs saved that represented good value for money.

The early invitation to food supplementation together with multiple micronutrients substantially reduced child mortality, especially among disadvantaged women with lower education level. Therefore, our key conclusions and recommendations are:

1. Undernutrition among women of child bearing age is a key barrier to foetal and child health, development and wellbeing, and a major obstacle to the economic development of the country and the health of future generations. This knowledge was also reflected in the perceptions of rural Bangladeshi women. Political leaders and policymakers must realize the importance of the life-cycle perspective of malnutrition and women's health should be an important priority.
2. In a rural Bangladeshi population, birth weight increased with increasing duration of prenatal food supplementation, and especially so just after the hungry season (mid-August to mid-November). Therefore, in food insecure areas and for poor women of reproductive age dietary aid should be offered with a special focus on women who are expecting to become pregnant and this should cover the hungry season. Families should be advised on the importance of balanced food for women who are expecting to become pregnant.
3. If multiple micronutrients replace iron-folic acid for women who are pregnant in poor populations with food insecurity, this should be combined with ascertaining balanced and sufficient food intake from early pregnancy.
4. Prenatal food supplementation offered from early pregnancy combined with multiple micronutrient supplementation had a major impact on child survival with effect sizes well in parity with other evidence-based interventions for child health and survival. Prenatal food and multiple micronutrient interventions reduced social inequity in child survival chances. Careful and consistent monitoring is needed to ensure that such gains are sustained if better health for future generations has to be achieved.
5. Women's health, food and nutrition should be the highest priority for health planners, policy makers, and governments.

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