Early exposure, future health

Maternal and Infant Nutrition Interventions in Matlab (MINIMat trial), Bangladesh

A brief annotated bibliography June 2019

International Centre for Diarrhoeal Disease Research (icddr,b), Dhaka, Bangladesh

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The MINIMat trial (Maternal and Infant Nutrition Interventions in Matlab, ClinicalTrials.gov identifier ISRCTN16581394) was a randomised factorial experiment that was performed in pregnant women in rural Bangladesh where food insecurity and malnutrition of women and children still are prevalent. The hypothesis was that early (first trimester) invitation to daily prenatal food supplementation combined with multiple micronutrient supplementation improve foetal growth, infant survival and later selected functional outcomes as compared to usual (third trimester) invitation to food supplementation and standard program iron-folate supplements. Participants were randomized into six groups; a double-masked supplementation with capsules of 30 mg iron and 400µg of folic acid, 60 mg of iron and 400µg of folic acid or multiple micronutrients (MMS) containing a daily allowance of 15 micronutrients, including 30 mg of iron and 400µg of folic acid, was combined with food supplementation (608 kcal 6 days per week) randomized to either early invitation (9 weeks’ gestation) or usual invitation (20 weeks’ gestation). Primary outcomes were maternal haemoglobin level at 30 weeks’ gestation, birth weight, and gestational age at birth and infant mortality. Secondary outcomes listed at the time of trial registration were child growth and cognitive development, child micronutrient status, child immune function and morbidity, blood pressure, metabolic markers, and regarding mothers development of anthropometric measurements beyond a next pregnancy, when applicable.

The pregnant women participating in the MINIMat trial were also randomly allocated in the third trimester to either receive the usual health messages of the antenatal services, or to receive exclusive breastfeeding (EBF) counselling.

Women aged 14-50 years in Matlab subdistrict, Bangladesh, with pregnancy confirmed by a urine test and ultrasound with gestational age less than 14 weeks were invited to participate. Between November 11, 2001 and October 30, 2003, 4436 pregnant women were recruited into the trial. There were 3625 live births, and the MINIMat study, as well as the Health and Demographic Surveillance System in the area, have carefully monitored these children. In 2013 the 10-year follow-up of these children was completed and in 2016-17 the puberty follow-up when the children were 11.5-14.5 years old. A 15 year’s follow-up has been completed in June 2019.

**Primary outcomes**

The effects of the interventions on primary outcomes were reported in JAMA 2012, including an analysis of effects on mortality up to the age of 5 years (Persson et al., 2012). Adjusted maternal haemoglobin levels at 30 weeks’ gestation were 115.0 g/L with no significant differences among treatment groups. Mean birth weight was 2694 g with no significant difference among groups. The early invitation with MMS group had an infant mortality rate of 16.8 per 1000 live births vs. 44.1 per 1000 live births for usual invitation with 60 mg of iron and 400µg of folic acid (HR 0.38, 95% CI 0.18-0.78). The usual invitation with MMS group had the highest incidence of spontaneous abortions and the
Table 1. Measurements in the MINIMat trial and follow-up.

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<th>Pregnancy</th>
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The early invitation to food supplementation with MMS seems to have influenced foetal and infant health without differential effects on size at birth. An equity analysis revealed that the intervention reduced the gap in child survival between social groups (Shaheen, Streatfield, Naved, Lindholm, & Persson, 2014). A health economics analysis of the effect on survival revealed that the interventions are cost-effective (Shaheen, Persson, Ahmed, Streatfield, & Lindholm, 2015).
Measurements
Above the main measurements in the MINIMat trial and follow-up to 10 years of age are displayed (Table 1).

Feeding, growth and body composition
Foetal growth was monitored by repeated ultrasound assessments, infant and young child anthropometric measurements were carefully monitored up to 2 years of age, after that at ages 4.5 years and 10.0 years. Body composition has been assessed by leg-to-leg bioelectrical impedance at 4.5 and 10.0 years of age. Early invitation to food supplementation in pregnancy reduced the occurrence of stunting 0-54 months of age, and prenatal MMS increased the proportion of stunting. These effects were judged to be of public health importance and suggest programming effects in early foetal life (Khan et al., 2011). There were no effects of the food and micronutrient interventions on body composition at 4.5 years (Khan, Kabir, et al., 2012b). The breastfeeding counselling increased the duration of exclusive breastfeeding by 60 days. This duration was not influenced by the supplementation (Khan et al., 2017). The exclusive breastfeeding intervention did neither result in differential growth trajectory in infancy and childhood nor differences in body composition at 4.5 years (Khan et al., 2013). There was an interaction between the exclusive breastfeeding intervention and multiple micronutrient supplementation with unfavourable linear growth 0-54 months, which raises questions about possible negative effects of MMS.

Paramedics performed the sonographic foetal biometry, and in a methodological paper, the accuracy and precision were judged to be good (Neufeld, Wagatsuma, Hussain, Begum, & Frongillo, 2009). The effects of the prenatal interventions on foetal biometry have not yet been reported. The validity of the leg-to-leg bioelectrical impedance assessment was evaluated by deuterium dilution as the reference method, and new prediction equations were produced for 4-10 year old Bangladeshi children (Khan, Hawkesworth, et al., 2012a). In a sub-study, the associations were analysed between oxidative parameters in pregnancy and birth anthropometry (Lindström et al., 2012). Calcium levels in cord blood were also shown to be associated with birth length (Doi et al., 2011).

In a subset of the cohort, analyses were performed on food security, infant feeding, and growth. A food security measure was developed (Frongillo, Chowdhury, Ekstrom, & Naved, 2003). Household food security was associated with infant feeding practices (Saha, Frongillo, Alam, Arifeen, Persson, & Rasmussen, 2008b). Appropriate infant feeding practices, as reflected in current recommendations, were linked to better growth (Saha, Frongillo, Alam, Arifeen, Persson, & Rasmussen, 2008a). As expected of the previously mentioned results, food security was also a determinant of subsequent weight and length gain, and stunting was more prevalent in food insecure households (Saha, Frongillo, Alam, Arifeen, Persson, & Rasmussen, 2009a). Maternal, infant and household factors were associated with breast-feeding trajectories in the first half of infancy (Rasheed, Frongillo, Devine, Alam, & Rasmussen, 2009). It was also shown that the growth pattern of the MINIMat children more closely tracked the new WHO child growth standards as compared to earlier references (Saha, Frongillo, Alam, Arifeen, Persson, & Rasmussen, 2009b).
Stable-isotope techniques were employed to validate reports on infant feeding practices. Reports were accurate at the group level but misreporting was found both among mothers who had received exclusive breastfeeding counselling and among those who had received the routine health education (S. E. Moore et al., 2007).

MINIMat growth data were included in a recent analysis of 19 longitudinal birth cohorts. Results showed that childhood undernutrition might have its origins in the foetal period, suggesting a need to intervene early, ideally during pregnancy (Christian et al., 2013). Half of the MINIMat children were stunted at two years, decreasing to 29% at ten years. Height growth trajectories and prevalence of stunting in pre-adolescence showed strong intergenerational associations, social differentials, and environmental (seasonal) influence from foetal life to pre-pubertal age (Svefors et al., 2016).

Child development
Child development has been assessed at seven months, 18 months and five years, and recently at ten years. These assessments have included Bayley Scales of Infant Development, behaviour ratings, language development, IQ, but also motor milestones. Effects on poverty on children’s cognition were shown to be mediated through parental education, birth size, growth in the first 24 months, and home stimulation in the first five years (Hamadani et al., 2014).

Reports of effects of prenatal food and micronutrient supplementation on development have so far only covered 7-months data. There were small benefits from early invitation to food supplementation and MMS in infants of more malnourished mothers (Tofail et al., 2008). In a substudy, it was shown that early invitation to prenatal food supplementation ameliorated the negative association of food insecurity with quality of maternal-infant interaction (Frith, Naved, Persson, Rasmussen, & Frongillo, 2012). There were also associations between prenatal micronutrient alternatives and the quality of maternal-infant interaction and maternal early postpartum distress (Frith, Naved, Persson, & Frongillo, 2013).

Household food security was shown to be associated with early childhood language development (Saha et al., 2010). Mothers’ reports of their children’s language development were judged to be reliable and to have an acceptable validity (Hamadani, Baker-Henningham, et al., 2010a). In a methodological analysis of attainment of motor milestones and future cognitive and motor development, it was judged that milestone age of attainment might not be an appropriate way to predict later IQ (Hamadani, Tofail, Cole, & Grantham-McGregor, 2013). Family Care Indicators were evaluated and considered to be a promising survey-based indicator of the quality of children’s home environment (Hamadani, Tofail, et al., 2010c).

Micronutrients
The prevalence of anaemia and micronutrient deficiencies in early pregnancy was assessed; 28% was anaemic, 55% were zinc deficient, 46% were vitamin B12 deficient, and 18% were folate deficient. Anaemia was not associated with iron deficiency, rather with B12 deficiency. Ascaris infestation was common and associated with folate and B12 deficiency (Lindström et al., 2011). Urinary iodine concentrations in pregnancy were to
a large extent reflecting adequate intake (Rydbeck, Bottai, Tofail, Persson, & Kippler, 2013) and was positively associated with size at birth of the male offspring (Rydbeck et al., 2014). Maternal multiple micronutrient supplementation increased the level of B12 in last trimester (Ziaei, Rahman, Raqib, Lönnnerdal, & Ekstrom, 2016b) but had limited impact on micronutrient status of 6-months old infants; some beneficial effect on B12 status (Eneroth et al., 2010). Anaemia at six months of age was common and associated with infection, low birth weight and iron deficiency (Eneroth, Persson, Arifeen, & Ekstrom, 2011). The duration of exclusive breastfeeding was not associated with plasma ferritin, haemoglobin levels, iron deficiency or anaemia at six months of age (Eneroth et al., 2009). The association between the prenatal micronutrient supplementations and different health indicators at 4.5 and ten years have also been reported (Mannan et al., 2016).

Immunological development and morbidity
Morbidity was assessed throughout infancy up to two years of age, and after that at 4.5 and ten years. At 8, 24 and 52 weeks of age thymic volume were assessed by ultrasound. Disproportionate early foetal growth was shown to predict postnatal thymic size (Fulford et al., 2013). Longer duration of exclusive breastfeeding resulted in a larger thymic index. The thymic size was not affected by the prenatal supplementations but associated with arsenic exposure via drinking water during pregnancy (S. Moore et al., 2009). Thymus size in early infancy predicted subsequent survival (S. E. Moore et al., 2013). In a sub-study of children at 4.5 years, it was shown that stunting was a risk factor for wheezing (Hawlader et al., 2013), and Ascaris lumbricoides infestation was a risk factor for asthma and atopy (Hawlader et al., 2014).

Social conditions and health
The MINIMat cohort has been very carefully and repeatedly assessed as to social conditions. These indicators include household characteristics (e.g. asset scores), food security, educational level of parents, and a wide range of characteristics of the mother and the child. Participating women were also responding to questions regarding exposure to physical, sexual and emotional violence and level of controlling behaviour. Any lifetime family violence against women and controlling behaviour were associated with smaller size at birth and growth impairment in early childhood (Asling-Monemi, Naved, & Persson, 2009a) Violence against women was also associated with an increased risk of diarrhoea and respiratory tract infection in childhood (Asling-Monemi, Naved, & Persson, 2009b). Women who experienced either emotional violence or controlling behaviour had the highest levels of emotional distress (Ziaei, Frith, Ekstrom, & Naved, 2016a).

Toxic and other environmental exposures
Bangladesh has a major public health problem with arsenic-contaminated drilled water tube-wells. In Matlab major studies and mitigation activities were initiated in parallel with the MINIMat trial (Gardner, Hamadani, et al., 2011b; Vahter et al., 2006). The MINIMat cohort has been extensively used for studies on arsenic and health effects as well as on other toxic exposure. Arsenic exposure during pregnancy increased the risk of infant mortality (A. Rahman et al., 2010a). Analyses of arsenic-associated oxidative stress, inflammation and immune disruption in human placenta and cord blood
indicated that effects of arsenic on immune function contribute to impaired foetal and infant health (Sultan Ahmed et al., 2011; Raqib et al., 2009). Arsenic exposure was associated with lower size at birth (A. Rahman et al., 2009) and later growth (Gardner et al., 2013; Saha et al., 2012). Arsenic exposure in early pregnancy was also shown to alter genome-wide DNA methylation in cord blood, particularly in boys (Broberg et al., 2014). The arsenic-related growth impairment could, at least partly, be mediated through suppressed IGF-1 levels (Sultan Ahmed et al., 2013). Breast-feeding was shown to be a protection against arsenic exposure (Fängström et al., 2008) and arsenic methylation efficiency decrease during weaning (Fängström et al., 2009). Prenatal arsenic exposure was also associated with an impaired thymic function in newborns (Sultan Ahmed et al., 2012) and with increased morbidity in infectious diseases during infancy (A. Rahman, Vahter, Ekstrom, & Persson, 2010b). There was no association between prenatal arsenic exposure and infant development at seven months, (Tofail et al., 2009) or between pre- and postnatal exposure and development at 18 moths(Hamadani, Grantham-McGregor, et al., 2010b), but some effect on IQ at five years (Hamadani et al., 2011). Arsenic exposure in early life was also associated with increased blood pressure. (Hawkesworth, Wagatsuma, Kippler, et al., 2013b). Elevated childhood arsenic exposure appeared to reduce cell-mediated immunity (Sultan Ahmed et al., 2014). Elevated arsenic exposure in childhood appeared to reduce cell-mediated immunity, possibly linked to reduced concentrations of Th1 cytokines (Sultan Ahmed et al., 2014). Prenatal arsenic exposure was related to impaired lung function in schoolchildren, while childhood exposure was associated with increased airway inflammation, particularly in boys (Sultan Ahmed et al., 2017). Despite decreased water arsenic concentrations in rural Bangladesh, the children still have elevated exposure, largely from food (Kippler, Skröder, Rahman, Tofail, & Vahter, 2016).

A number of papers deals with arsenic metabolism (Gardner et al., 2012; Gardner, Nermell, et al., 2011 a; L. Li et al., 2008; Nermell et al., 2006; Raml et al., 2007) and with gene expression (Engström et al., 2013; Engström, Vahter, Mlakar, et al., 2010b; H. Li, Engström, Vahter, & Broberg, 2012). Children methylated arsenic more efficiently than their mothers (Skröder Löveborn et al., 2016).

Cadmium exposure and its health consequences have been covered in a series of publications (Engström, Vahter, Johansson, et al., 2010a; Kippler et al., 2007; 2013; Kippler, Goessler, et al., 2009a; Kippler, Hoque, et al., 2010a; Kippler, Hossain, et al., 2012a; Kippler, Lönnerdal, et al., 2009b; Kippler, Nermell, et al., 2010b; Kippler, Tofail, Gardner, et al., 2012b; Kippler, Tofail, Hamadani, et al., 2012c; Kippler, Wagatsuma, et al., 2012d; Rentschler et al., 2013). Cadmium concentrations in human blood and urine were associated with polymorphisms in zinc transporter genes (Rentschler et al., 2014). Prenatal lead exposure and childhood blood pressure and kidney function are explored in one paper (Skröder et al., 2016). In another paper, the effects of exposure to arsenic and cadmium on kidney function and blood pressure in pre-school-aged children are analysed, and the possible protection by selenium (Skröder et al., 2015).

Exposure to manganese (Ljung et al., 2009; S. M. Rahman et al., 2013), lead (Bergkvist et al., 2010) and organochlorine compounds (Bergkvist et al., 2012) has been reported in other papers. Elevated drinking water levels of manganese were associated with foetal survival (S. M. Rahman et al., 2013) but may impair foetal growth (S. M. Rahman et al., 2015). Elevated water manganese levels during pregnancy were positively associated with cognitive function at ten years in girls (S. M. Rahman et al., 2016).
Low prenatal selenium status may be detrimental to cognitive development at 1.5 years of age (Skröder et al., 2014).

The temperature during pregnancy was shown to foetal growth and size at birth (Rashid et al., 2017).

**Developmental Origin of Health and Disease (DOHaD)**
The MINIMat trial evaluates effects of prenatal nutrition supplementation alternatives in a population of pregnant women where undernutrition of the women and the child is common. So far we have (see above) documented improved survival (Persson et al., 2012), effects on stunting (Khan et al., 2011), some effects on child development (Tofail et al., 2008) and mother-child interaction (Frith et al., 2012; Frith, Naved, Ekstrom, Rasmussen, & Frongillo, 2009). The prenatal supplementations were associated with levels of metabolic markers at 4.5 years (Ekstrom et al., 2016). An early invitation to food supplementation was associated with a small lowering effect on diastolic blood pressure at 4.5 years (Hawkesworth, Wagatsuma, Kahn, et al., 2013a), and MMS with marginally higher diastolic blood pressure (Hawkesworth, Wagatsuma, Kahn, et al., 2013a). The DOHaD perspective dominates the currently completed follow-up at 10 years of age.

**Completed Ph.D. theses based on MINIMat data**


3. **Kuntal Kumar Saha** (2007). Household food security, infant feeding practices and growth of infants and young children in rural Bangladesh. Cornell University, USA.


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17. **Shirin Ziaie** (2016). Women’s status and child nutrition Findings from community studies in Bangladesh and Nicaragua. Uppsala University, Sweden

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