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Cohort Profile: The Maternal and Infant Nutrition Interventions in Matlab (MINIMat) cohort in Bangladesh

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Why was the cohort set up?

Proportions of malnourished mothers and children remain high, especially in South Asia.[1] In countries like India, Pakistan and Bangladesh, underweight and stunted linear growth frequently start in fetal life. This is reflected in a high proportion of children who are small for their gestational age at birth and experience continued stunted growth.[2–4] A life cycle perspective is needed to address these intergenerational problems.[1,5]

Trials that have provided pregnant women in undernourished populations with balanced protein-energy supplementations demonstrated increased birthweight.[6] Most food supplementation programmes have reached pregnant women in mid or late pregnancy[6] for practical reasons. In the first trimester, organs develop and fetal plasticity is pronounced. A balanced dietary intake including micronutrients is needed beginning in the first trimester, to ensure fetal health, growth and later health.[7–10]

To prevent anaemia and promote fetal health, the World Health Organization has recommended iron-folate supplementation during pregnancy. Based on the notion that iron and other micronutrient deficiencies often coexist, a group of experts developed the composition of a multiple-micronutrient supplement for trial purposes.[11] A series of prenatal multiple micronutrient trials were initiated in different countries, with maternal haemoglobin and birthweight as outcomes.[12]

Nutritional imbalance or insult in fetal or early life may alter later disease risk. This concept, later labelled the Developmental Origin of Health and Disease (DOHaD), has been underpinned by epidemiological and biomedical studies.[13–15] Few prenatal nutritional intervention studies have been done, however, to assess the effect of prevention of nutritional imbalance or insult on developmental trajectories at a stage when developmental plasticity is great.[16]

Based on these considerations, the designers of the Maternal and Infant Nutrition Interventions in Matlab trial

(MINIMat, ClinicalTrials.gov identifier ISRCTN16581394) hypothesized that prenatal multiple-micronutrient supplementation (MMS), as well as an early invitation (around gestational week 9) to receive a daily food supplement, would increase maternal haemoglobin concentration at 30 weeks' gestation, birthweight, and infant survival. The designers also hypothesized that a combination of these interventions (early invitation with MMS) would further improve these outcomes compared with the usual timing of invitation to food supplementation (around week 20) and supplementation with the standard programme of iron-folic acid supplements.

At an early stage in the planning of the MINIMat cohort, the perspective that events in early fetal life might have longer-term consequences provided a rationale for a long-term follow-up. Secondary outcomes listed at the time of the trial registration were: child growth and cognitive development; child micronutrient status; child immune function and morbidity; blood pressure; metabolic markers; and mothers' anthropometric development up to the next pregnancy, when applicable.

The trial was carried out in Matlab, Bangladesh, a rural sub-district 57 km south of the capital Dhaka, a setting where child and maternal undernutrition remain widespread. In this area, the International Centre for Diarrhoeal Disease Research, Bangladesh (iccdr, b) has been running a Health and Demographic Surveillance System (HDSS) since 1966. Through monthly household visits, community health research workers (CHRW) collect data on demographic and selected health information, on a population of about 220 000 in more than 140 villages. The use of a unique identification system allows tracking over time and across studies and databases.

The initial funding of the MINIMat trial (up to birth) was provided by the United Nations Children's Fund (UNICEF), followed by many funders, as described below.

Who is in the cohort?

Participants were recruited from 11 November 2001 to 30 October 2003 (Figure 1). CHRW visited all households monthly. If a woman of reproductive age reported that her last menstrual period (LMP) was overdue or that she was pregnant, she was offered a pregnancy test and the date of her LMP was recorded. A woman who tested positive was encouraged to visit the icddr, b clinic, where an ultrasound examination was offered. Dating based on ultrasound examination at week 8 was used if LMP date was missing Women were eligible for the study if they had a viable fetus and gestational age less than 14 weeks on ultrasound, no severe illness and provided written consent for participation. In total, 5880 women were assessed for eligibility, 1444 were excluded, and 4436 women were randomized to the different nutrition interventions. There were 3625 live births. The MINIMat cohort study and the Health and Demographic Surveillance System in the area have closely monitored these children.

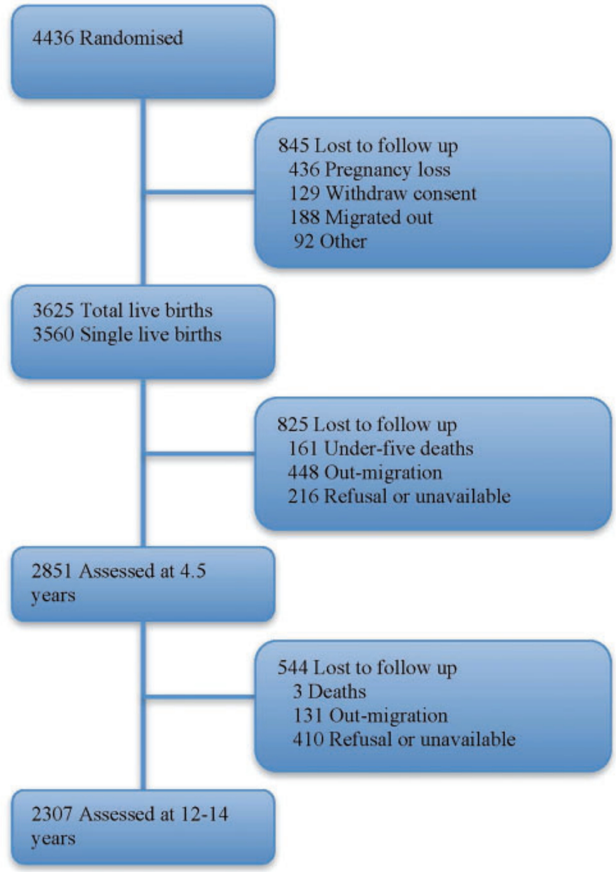

Figure 1. Study flow.

The MINIMat trial participants were randomized into six groups in a 3 x 2 design. A double-masked supplementation with capsules of 30 mg iron and 400 μg of folic acid, 60 mg of iron and 400 μg of folic acid or multiple micronutrients (MMS) containing a daily allowance of 15 micronutrients, including 30 mg of iron and 400 μg of folic acid, was combined with food supplementation (608 kcal/day on 6 days per week) randomized to either early invitation (9 weeks' gestation) or usual invitation (20 weeks' gestation). Primary outcomes were maternal haemoglobin concentration at 30 weeks' gestation, birthweight, gestational age at birth and infant mortality. The pregnant women who participated in the MINIMat trial were also randomly allocated in the third trimester to receive either the usual health messages from the antenatal services or to receive exclusive breastfeeding counselling.

At baseline, the pregnant women in this cohort had an average weight of 45 kg and mean height of 150 cm,[17] see Table 1. One-third of these women were in their first

Table 1. Background characteristics of the pregnant women at recruitment, for those with a live birth, and for those where the child also participated at follow-up at 12–14 years. MINIMat cohort, Bangladesh, 2001–17

Characteristic	Levels	Recruitment	Live birth	12-14 years
			(*n* 3625)	(*n* 2307)
Total		4415	3587	2306
Age at recruitment	<20	711 (16)	563 (16)	331 (14)
	20–29	2521 (57)	2067 (57)	1312 (57)
	>30	1183 (27)	957 (27)	663 (29)
		4416	3619	2307
Parity	First	1479 (33)	1184 (33)	662 (29)
	Second or more	2937 (67)	2435 (67)	1645 (71)
Total		4462	3580	2300
BMI kg/m^2	<18.5	1228 (28)	1000 (28)	669 (29)
	>18.5	3234 (72)	2580 (72)	1631 (71)
Total		4431	3591	2307
Educational level	No schooling	1427 (32)	1135 (32)	795 (34)
	1–4 years	479 (11)	400 (11)	298 (13)
	5 or more years	2525 (57)	2506 (57)	1214 (53)
Total		4431	3591	2307
Household asset score at recruitment	Lowest third	1476 (33)	1195 (33)	821 (36)
	Middle	1483 (34)	1209 (34)	812 (35)
	Highest third	1472 (33)	1187 (33)	674 (29)
Total		4429	3589	2305
Household surplus at recruitment	Surplus	1199 (27)	976 (27)	585 (25)
	Equal	2367 (53)	1917 (53)	1254 (54)
	Occasional deficit	727 (16)	586 (16)	393 (17)
	Constant deficit	125 (3)	102 (3)	66 (3)
	Don't know	11 (0.2)	8 (0.2)	7 (0.3)
Total		4436	3625	2307
Trial randomization[a]	E+Fe30	739 (16.7)	608 (16.8)	389 (16.9)
	E+Fe60	738 (16.6)	610 (16.8)	387 (16.8)
	E+MMS	740 (16.7)	595 (16.4)	404 (17.5)
	U+Fe30	741 (16.7)	605 (16.7)	374 (16.2)
	U+Fe60	738 (16.6)	612 (16.9)	387 (16.8)
	U+MMS	740 (16.7)	595 (16.4)	366 (15.9)

Data are *n*/*n* (%).

BMI, body mass index; U = start of food supplementation at the standard programme start (week 20); Fe30= 30 mg Fe with 400 µg folic acid; Fe60 = 60 mg Fe with 400 µg folic acid; MMS= 15 micronutrients including 30 mg Fe and 400 µg folic acid.

[a]E = Early invitation to daily prenatal food supplementation (gestational week 9).

pregnancy and four out of 10 were in their third or later pregnancies. One-third had no formal education, and slightly more than half had attended school for 5 years or more. One-quarter had some surplus in the perceived status of income compared with expenditure, and one-fifth had some deficit. The attrition during the follow-up period did not change the general characteristics and proportions allocated to the different interventions of the population being studied, see Table 1.

How often have they been followed up?

After recruitment at around gestational week 8, women were assessed at gestational weeks 9, 14, 19 and 30 (measurements listed in Table 2). Mothers and newborn children were assessed at birth, followed by monthly examinations of the dyads up to 12 months. During the second year of life, the children were assessed quarterly. The next follow-ups were performed at 4.5 and 10 years of age. At 12.3 to 14.5 years of age, assessments of pubertal development, anthropometry and body composition were performed.

Of the 5880 pregnant women who were initially assessed, 4436 were eligible and consented to participate in the trial (Figure 1). These women had 3625 live births, of which 3560 were singleton live births. For the follow-up at 4.5 years of age, 2851 children participated (80% of the single live births). For the follow-up at 12.3–14.5 years of

Table 2. Measurements in the MINIMat trial and follow-up

	Pregnancy	Birth	0–24 months	4.5 years	10 years	12–14 years
Interventions						
Compliance food supplementation	+					
Compliance micronutrients (eDEM)	+					
Anthropometry etc.						
Gestational age (LMP, ultrasound)	+					
Maternal anthropometry	+		+	+	+	+
Fetal growth (ultrasound)	+					
Child anthropometry		+	+	+	+	+
Skinfolds, body composition				+	+	+
Child development						
Motor and cognitive development			+	+	+	
Language development			+	+		
Motor milestones			+			
Mother-child interaction			+			
IQ				+	+	
Home environment			+	+	+	
Infections, immune function						
Morbidity	+	+	+	+	+	
Thymus size (ultrasound)			+			
Food, diet, feeding						
Food security	+		+	+	+	+
Diet	+			+	+	
Diet diversity				+	+	
Breastfeeding		+	+			
Reproductive history						
Previous pregnancies, outcomes	+					
Follow-up to next pregnancy			+	+		
Social conditions						
Household asset score	+			+	+	+
Parents' education	+					
Parents' occupation	+			+	+	
Marital status						
Partner violence	+				+	
Depressive symptoms/distress	+		+		+	
Biomarkers						
Haematology	+		+	+	+	
Micronutrients	+		+	+	+	
Oxidative stress	+					
Toxic exposure (urine)	+		+	+	+	
Metabolic markers				+	+	
Blood pressure				+	+	+
Salivary cortisol	+		+			

age, 2307 children participated (64% of the singleton live births). Out-migration and unavailability because of other activities were the main explanations for non-participation by these schoolchildren. Children who did not attend the latest follow-up more frequently came from wealthier households (asset score in the highest tertile, 42% lost to follow up, as compared with the lower two tertiles with 31% attrition). They also more frequently had mothers with some formal education (37% attrition) in comparison with children of mothers with no formal schooling (30% attrition).

What has been measured?

This cohort was established within the Matlab HDSS, which implies that the cohort data may be linked to family,

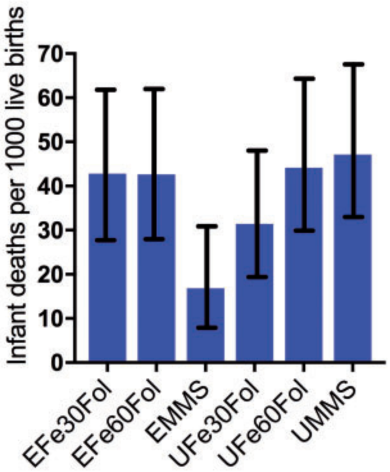

Figure 2. Infant deaths per 1000 live births in the MINIMat trial with 95% confidence intervals. E = early (around week 9) invitation to daily balanced food supplementation, 600 kcal, 6 days per week; U = the usual timing (around week 20) of start of this food supplementation; Fe30Fol = 30 mg iron and 400 µg of folic acid; Fe60Fol = 60 mg of iron and 400 µg of folic acid; MMS = multiple micronutrients containing a daily allowance of 15 micronutrients, including 30 mg of iron and 400 µg of folic acid.

sociodemographic and reproductive information on mothers and grandmothers if these relatives stayed within the Matlab HDSS the years before. Valid data on important demographic and health-related events are available, such as last menstrual period, date of birth, out-migration, in-migration, death and causes of death.

The pregnancy cohort was followed from about gestational week 9 (Table 1). Fetal growth was monitored by repeated ultrasound assessments. Infant and young child anthropometric measurements were carefully monitored up to 2 years of age and after that at ages 4.5 and 10.0 years. Body composition was assessed by bioelectrical impedance measurements at 4.5, 10.0 and 12.3–14.5 years of age.

The quality of maternal-infant interaction was measured at 4 months of age. Child development was assessed when the participants were 7 and 18 months as well as 5 and 10 years old. These assessments included Bayley Scales of Infant Development, behaviour ratings, language development, IQ and motor milestones.

Morbidity was assessed by 7-day recalls throughout infancy up to 2 years of age, and after that at 4.5 and 10 years of age. At 8, 24 and 52 weeks of age, thymic volume was assessed by ultrasound.

The social conditions of the members of the MINIMat cohort have been carefully and repeatedly assessed. These indicators include household characteristics (including asset scores), food security, educational level of parents and a wide range of characteristics of the mother and the child. Participating women also responded to questions regarding exposure to physical, sexual and emotional violence and levels of controlling behaviour. Women's levels of stress were measured.

Haemoglobin has been measured repeatedly in mothers and their children. In sub-samples, assessments have been made of iron and other micronutrient status, markers of oxidative stress, toxic exposure including arsenic, metabolic markers and salivary cortisol (Table 2).

What has been found? Key findings and publications

To date, more than 100 scientific publications and 20 PhD dissertations have been completed based on data from the MINIMat cohort. See [http://www.kbh.uu.se/Research/International+Child+Health+and+Nutrition/main-fields-of-research-and-projects/global-nutrition] for a complete publication list.

There was a pronounced effect on infant survival in line with the hypothesis. With early invitation to food supplementation with MMS, this group had an infant mortality rate of 16.8 per 1000 live births, versus 44.1 per 1000 live births among the group with the usual later invitation to food supplementation with 60 mg of iron and 400 µg of folic acid [hazard ratio (HR) 0.38, 95% confidence interval (CI) 0.18–0.78], Figure 2.[17] Adjusted maternal haemoglobin concentrations at 30 weeks' gestation were 115.0 g/L with no differences among treatment groups. Mean birthweight was 2694 g with no difference among groups. An equity analysis revealed that the intervention reduced the gap in child survival between social groups.[18] The interventions were also judged to be cost-effective in reducing mortality.[19] The early invitation to food supplementation in pregnancy reduced the occurrence of stunting at 0–54 months of age.[20] In contrast, prenatal MMS increased the proportion of stunting,[20] a finding that also was supported by corresponding IgF1 levels.[21]

The prenatal supplementations had also effects on metabolic markers at 4.5 years of age.[21] These effects were judged to be of public health importance and suggest programming effects in early fetal life.

What are the main strengths and weaknesses?

The MINIMat cohort is a well-characterized cohort with information from early pregnancy to puberty. Plans are under way for a new update at 15 years of age. The randomized prenatal food and micronutrient interventions have enabled analyses of short- and medium-term effects and will provide opportunities to address the question whether long-term (adulthood) negative consequences of early nutritional insults may be prevented by this type of prenatal intervention. The context of this cohort is characterized by widespread undernutrition of mothers and children, and almost two-thirds of these children were born small for their gestational-age. This is important to consider when making inferences to other low-income settings. There was no follow-up between 5 and 10 years. For some rare outcomes, the sample size may be too small.

Can I get hold of the data? Where can I find out more?

Several researchers and research groups have so far analysed MINIMat data to address new research questions that could be answered by the available databases. If you are interested, please contact Qazi Sadeq-ur Rahman at [qsrahman@icddrb.org].

Profile in a nutshell

- The rationale for the MINIMat cohort in Bangladesh was the high prevalence of maternal malnutrition and intrauterine growth restriction. It was hypothesized that prenatal multiple micronutrient supplementation, as well as an early invitation to a daily food supplementation, would increase maternal haemoglobin concentration, birthweight and infant survival, and that a combination of these interventions would further improve these outcomes. Secondary outcomes were linked to the Developmental Origin of Health and Disease perspective.
- A total of 4436 women were recruited from 2001 to 2003. There were 3625 live births, and 2307 children participated in the latest follow-up at 12.3–14.5 years of age.
- Fetal growth was monitored. Further assessments include child growth, body composition, child development, morbidity and mortality. Sociodemographic information included household characteristics, food security and educational levels. Haemoglobin was measured repeatedly. Sub-sample information is available on iron and other micronutrients, markers of oxidative stress, toxic exposure, metabolic markers and salivary cortisol.
- The early invitation to prenatal food supplementation combined with multiple micronutrients lowered infant mortality substantially. Among the 100 publications to date, several reports address feeding, growth, development, micronutrients, immunological development, social conditions and the Developmental Origins of Adult Disease perspective.
- If interested in the MINIMat cohort data, please contact [qsrahman@icddrb.org].

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