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Original Article

# Early prenatal food supplementation ameliorates the negative association of maternal stress with birth size in a randomised trial

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**Abstract**

Low birthweight increases the risk of infant mortality, morbidity and poor development. Maternal nutrition and stress influence birth size, but their combined effect is not known. We hypothesised that an early-invitation time to start a prenatal food supplementation programme could reduce the negative influence of prenatal maternal stress on birth size, and that effect would differ by infant sex. A cohort of 1041 pregnant women, who had delivered an infant, June 2003–March 2004, was sampled from among 3267 in the randomised controlled trial, Maternal Infant Nutritional Interventions Matlab, conducted in Matlab, Bangladesh. At 8 weeks gestation, women were randomly assigned an invitation to start food supplements (2.5 MJ $d^{-1}$; 6 days a week) either early (~9 weeks gestation; early-invitation group) or at usual start time for the governmental programme (~20 weeks gestation; usual-invitation group). Morning concentration of cortisol was measured from one saliva sample/woman at 28–32 weeks gestation to assess stress. Birth-size measurements for 90% of infants were collected within 4 days of birth. In a general linear model, there was an interaction between invitation time to start the food supplementation programme and cortisol with birthweight, length and head circumference of male infants, but not female infants. Among the usual-invitation group only, male infants whose mothers had higher prenatal cortisol weighed less than those whose mothers had lower prenatal cortisol. Prenatal food supplementation programmes that begin first trimester may support greater birth size of male infants despite high maternal stress where low birthweight is a public health concern.

*Keywords:* maternal nutrition, stress, low birthweight, prenatal food supplement, low-income countries, gestational age.

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## Introduction

Improving birthweight to reduce infant mortality and morbidity is a priority worldwide (Black *et al*. 2008), particularly in Asia where ~30% of infants are born with low birthweight (LBW) (UNICEF 2009). Fetal growth restriction that leads to LBW is associated with adverse neurodevelopmental outcomes (Many *et al*. 2005; Geva *et al*. 2006), lower intelligence quotient (Many *et al*. 2005), reduced immunocompetence (Raqib *et al*. 2007), increased risk of chronic diseases (Hales & Barker 2001; Martin-Gronert & Ozanne 2007; Grigore *et al*. 2008) and reduced human capital (Victora *et al*. 2008). Prenatal stress and depression are associated with reduced birth size (Rini *et al*. 1999; Diego *et al*. 2006, 2009; Field *et al*. 2008; Valladares *et al*. 2009; Dunkel-Schetter 2011). In low- and middle-income countries, many women suffer

from not only high stress and depression (Rahman *et al*. 2007; Nasreen *et al*. 2010), but also poor diets, leading to inadequate weight gain during pregnancy, that also contributes to LBW (Kramer 1987; Hosain *et al*. 2006). The combined influence of prenatal maternal nutrition and stress on birth size is not known, but is important to understand to develop effective interventions to prevent LBW.

Wadhwa *et al*. proposed a biopsychosocial model whereby greater prenatal stress reduces birthweight through neuroendocrine, immune and cardiovascular systems (Wadhwa *et al*. 1996). Prenatal stress increases the activity of the hypothalamic-pituitary-adrenal axis (Field *et al*. 2008; Dunkel-Schetter 2011); thereby, elevating maternal cortisol (Diego *et al*. 2009) and reducing birthweight (Diego *et al*. 2006; Field *et al*. 2008) either through reducing uterine blood flow and nutrient delivery to the fetus (Teixeira *et al*. 1999; Vythilingum *et al*. 2010) or by direct effects on the fetus (Diego *et al*. 2009). Poor maternal nutritional status may further increase the exposure of the fetus to cortisol by reducing the enzyme 11$\beta$-hydroxysteroid dehydrogenase in the placenta (Langley-Evans *et al*. 1996; Shams *et al*. 1998; Lesage *et al*. 2001). This enzyme converts maternal cortisol to cortisone and protects the fetus from maternal cortisol (Benediktsson *et al*. 1997). In one observational study, prenatal maternal stress was associated with birthweight only in the infants of less well-nourished women (Cliver *et al*. 1992).

Prenatal food supplementation programmes provide food containing nutrients that can prevent fetal growth restriction in populations that suffer from a high prevalence of LBW (Bitler & Currie 2005; Osrin *et al*. 2005; Bhutta *et al*. 2008; Khatun & Rahman 2008; Hoynes *et al*. 2011). In general, the more food supplement consumed or the longer the participation in the programme (beginning in the second rather than third trimester) the larger the infant at birth, yet the effects of prenatal food interventions on birth size have been mixed (Lechtig *et al*. 1975; Mora *et al*. 1979; Kardjati *et al*. 1988; Winkvist *et al*. 1998; Bitler & Currie 2005; Shaheen *et al*. 2006; Gueorguieva *et al*. 2009). The effect of these programmes may depend on amount and composition and timing of supplements, maternal nutrition status, seasonal variation, stress and sex of the infant that influence either fetal growth, maternal nutritional status or both (Mora *et al*. 1979; Winkvist *et al*. 1998; Bitler & Currie 2005; Shaheen *et al*. 2006; Clifton 2010; Lampl *et al*. 2010). There are sex-differentials in fetal growth or birthweight that are influenced by maternal nutritional status (Lampl *et al*. 2010), insults (Clifton 2010) and prenatal nutritional supplementation (Osrin *et al*. 2005).

Given that both stress and food supplementation may influence birth size, we examined the combined influence of two different times to invite pregnant women to start a prenatal food supplementation programme (early-invitation group, ~9 weeks gestation; or usual-invitation group, ~20 weeks gestation) and prenatal maternal stress (i.e. concentration of cortisol) on birth size in a cohort of pregnant women in rural Bangladesh. In the early-invitation group, pregnant women received more food overall and earlier in pregnancy than the usual-invitation group. We hypothesised that mothers with high prenatal stress (i.e. high concentration of cortisol) would have smaller infants compared to mothers with low prenatal stress (i.e. low concentration of cortisol) in the

**Key messages**

- Maternal stress in pregnancy limits fetal growth in a population where the prevalence of low birthweight is a public health concern.
- Maternal nutrition and prenatal stress both influence birth size.
- Early food supplementation can promote increased birth size of male infants whose mothers experienced higher prenatal stress.
- Policymakers and programme designers should consider providing food supplements in the first trimester of pregnancy to improve birth size in populations where maternal malnutrition and stress are high and low birthweight is of public health concern.

usual-invitation group, but not in the early-invitation group, and furthermore this effect would differ by sex of the infant.

## Subjects and methods

### Study design

This study was conducted between June 2003 and March 2004 in Matlab, a subdistrict of the Chandpur district that is typical of the rural and riverine delta of Bangladesh (van Ginneken *et al*. 1998), by the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B). Written informed consent was obtained from each woman before enrolment. The institutional review boards of ICDDR, B and Cornell University approved the study protocol.

This study was part of a larger study, Maternal and Infant Nutritional Interventions, Matlab (MINIMat) (Persson *et al*. 2012), registered as an International Standard Randomised Controlled Trial, number ISRCTN16581394. The primary objective of the MINIMat study was to determine the influence of nutritional interventions on infant mortality, birthweight and maternal haemoglobin. MINIMat was a randomised controlled field trial with a $2 \times 3 \times 2$ factorial design. All pregnant women at 8 weeks of gestation were randomly and independently assigned to receive one of each of the three nutritional interventions. Each participant was assigned to a food supplementation group, either invitation and promotion to 'early' start of daily food supplementation (2.5 MJ $d^{-1}$; 6 days a week) (~9 weeks of gestation) or to no such invitation and promotion, which is 'usual' start of participation in the governmental programme (~20 weeks of gestation) until birth. Each participant was also assigned to receive one of two counselling protocols from 30 weeks of gestation until 6 months after giving birth as follows: either usual health messages alone or usual health messages with exclusive breastfeeding counselling. Beginning at 14 weeks of gestation until 3 months post-partum, each participant received one of three daily micronutrient supplements of either 60 mg or 30 mg of iron with 400 $\mu$g folic acid or multiple micronutrients (30 mg iron with the United Nations for Children's Fund formulation) (Frith *et al*. 2009).

The sample for this substudy was recruited from all eligible MINIMat participants who gave birth between June 2003 and March 2004. Of the 1300 pregnant women that were recruited, we collected cortisol from 1041. One hundred and thirteen women had temporarily moved to another location outside of Matlab for the pregnancy and birth; 11 had permanently moved; 20 were absent from their homes and no one reported where they had gone; two women refused to participate; two women had measles; and 111 had either miscarried, dropped out of the MINIMat study, or were pregnant with twins.

### Maternal characteristics

Maternal characteristics including parity, age and wealth index during early pregnancy were assessed by questionnaire at 8 to 10 weeks of gestation. A wealth index was used to assess socio-economic status based on a composite of information about land ownership, characteristics of the household dwelling and household ownership of durables (i.e. bed, quilt, mattress, watch/clock, chair/table, cabinet, bicycle, radio, television, electric fan, cows, goats, chicken/ducks) (Gwatkin *et al*. 2000). Maternal height and weight were measured at 8 to 10 weeks of gestation.

### Food supplement

Pregnant women received and consumed the food supplement that was supplied as individual packets daily for 6 days a week by a community nutrition educator at a community nutrition centre from the assigned invitation to start time (i.e. early or usual) until 8 months of gestation. The community nutrition educators were local women who were trained by the implementing organisation, BRAC, to deliver nutrition education messages and to encourage women to consume food packets completely on site. From 8 months of gestation until birth, food supplement was delivered to participant's homes. The composition of the food supplement was in accordance with the US recommended daily allowance and international recommendations (National Research Council 1989; Institute of Medicine, National Research Council 1999), and the supplement was intended as a snack to

supplement, not to replace, home food consumption. The supplement contained rice, lentils, molasses and oil, contained 2.5 MJ $d^{-1}$ 6 days a week (29% of recommended energy intake), 25% of which was vegetable protein. The consistency was culturally acceptable as it was based on a common type of food. In the main MINIMat study, the early-invitation group began consumption approximately 2.5 months earlier and, on average, consumed more supplement packets over the course of the pregnancy (105 packets) than the usual-invitation group (66 packets). In this substudy, the early-invitation group consumed more packets than the usual-invitation group (86 ± 49 and 57 ± 41, respectively; $P < 0.05$). The difference in packet consumption between the main study and substudy is most likely due to differences in flooding severity during the 3 years of the main study and the 1 year of the substudy (Shaheen *et al*. 2006).

### Prenatal salivary cortisol

Morning cortisol was used as a biomarker of stress with higher concentrations indicating more stress (Pruessner *et al*. 1997; Steptoe *et al*. 2000) as demonstrated in pregnant women (de Weerth & Buitelaar 2005). Concentrations of cortisol are low at awakening, rise to a peak about 30 min after awakening and fall towards baseline concentrations throughout the morning and afternoon (Pruessner *et al*. 1997). The average concentration of cortisol during this 'awakening response' is associated with the person's overall exposure of cortisol during the day, and increased concentrations are associated with more chronic and acute stress (Steptoe *et al*. 2000).

We measured cortisol from 28 to 32 weeks of gestation because, in a previous study, maternal stress at this time of gestation was associated with poor birth outcomes (Copper *et al*. 1996). Community field workers visited the participant's homes and collected one saliva sample from each participant between 7 and 8 am using a salivette (Sarstedt Canada, Inc., St. Laurent, Quebec). These morning samples measured the awakening response as they approximated 30 min to 1 h post-awakening samples, and were highly correlated to morning awakening concentrations of cortisol as determined in a pilot study. In the pilot study we conducted in Matlab, three morning saliva samples were collected, at awakening, 30 min to 1 h post-awakening and 3 h post-awakening, from 27 pregnant women (25–30 weeks gestation) to ascertain the pattern of awakening response of cortisol, and to decide if one morning sample could distinguish those with lower from those with higher awakening responses of cortisol. Concentration of cortisol collected between 7 and 8 am were correlated ($r = 0.75$; $P < 0.01$) with entire area under the curve of the awakening response of cortisol so that one sample per participant could assess whether a mother had a lower or higher concentration of cortisol. The mean concentration of cortisol between 7 and 8 am was similar to mean concentrations reported in published studies that collected samples from pregnant women approximately 1–3 h after awakening (de Weerth & Buitelaar 2005).

Participants were given a cylindrical cotton swab, chewed on it for 30 to 45 s or until it was fully saturated, and placed it in a test tube with cap. Samples were collected daily, frozen and stored at –20°C on the same day. Samples were processed later and were centrifuged for 10 min, 1000× g at 4°C to collect saliva. Concentration of cortisol was measured by a solid-phase $^{125}$ I radioimmunoassay (Coat-A-Count, Diagnostic Products Corp., Los Angeles, CA, USA) by the laboratory of Dirk Hellhammer, University of Trier, Trier, Germany. The assay sensitivity was 1.0 nmol $L^{-1}$. The inter-assay variability was 4.5% and the intra-assay variation was 3.0%.

### Infant characteristics

Trained health workers measured and collected information on infant birth characteristics, including sex, birthweight (g), birth length (cm) and head circumference (cm) in 79.5% of infants within 1 day of birth, and in 90% of infants within 4 days of birth. The other infants in the analysis had their first weight taken within 30 days after birth. Birth-size measurements taken during the first 24 h were used without adjustments. Measurements taken from 24 h to 30 days after birth were adjusted using an SD score transformation with the assumption that infants tend to remain relatively positioned in the anthropometric distribution

during this time period (Arifeen *et al*. 2000). The last menstrual period (LMP) date was used for the calculation of gestational age. When the community health research worker (CHRW) of ICDDR,B visited the participant each month, the CHRW asked the participant when her LPM occurred. If a woman reported to that her LMP was overdue or that she was pregnant, she was offered a pregnancy test (ACON, San Diego, CA, USA) and the date of her LMP was recorded.

### Data analysis

Data were recorded in the field on pretested forms and were checked by the supervisor before and after the data were entered into computers. Analyses were done by SPSS software (version 18; SPSS Inc., Chicago, IL, USA). Univariate analysis was used to identify outliers, which were then checked against the original filed forms and resolved. We used the birth measures as the primary outcomes measures for evaluating the influence of maternal prenatal stress and invitation time to start the food supplement programme on infant outcomes.

Each participant received one type of food, counselling and micronutrient intervention. For this study, the types of counselling and micronutrient supplementation were ignored after we established that these interventions did not modify the relationship of cortisol on birthweight, length or head circumference; for example, using analysis of variance, we found that interaction terms were not significant ($P$-interaction > 0.10) for cortisol and types of counselling or cortisol and types of micronutrient supplement on birthweights of all, female or male infants. The distribution of the sample among micronutrient and counselling groups was equivalent across food supplement groups. We used a *t*-test for continuous variables and a *chi-square* test for categorical variables to determine the following: (1) whether characteristics of participants in this study differed from the larger MINIMat trial; (2) whether values of demographic and anthropometry characteristics and food supplement intake differed between those who participated in the study and those who did not; and (3) whether prenatal maternal or infant characteristics differed by invitation time to start food supplementation, concentration of maternal cortisol (i.e. stress) or sex of the infant.

To test our study hypothesis that the invitation time to start the prenatal food supplementation modifies the relationship of prenatal maternal stress (i.e. concentration of cortisol) with birth size (i.e. birthweight, length, and head circumference), we used a general linear model that included concentration of cortisol, invitation time to start the prenatal food supplementation groups, and the interaction between them, controlling for the design variable for type of micronutrient supplement. The models were conducted separately for each sex, because previous studies have shown sex-differentials in fetal growth or birthweight (Clifton 2010; Lampl *et al*. 2010) including with prenatal nutritional supplementation (Osrin *et al*. 2005). Concentration of cortisol was a continuous variable in the general linear model for all birth measures; a categorical variable for cortisol (i.e. above and below median concentration of cortisol 9.6 nmol $L^{-1}$) was used to examine the difference in birthweight between those with higher and lower cortisol. Concentrations of cortisol were normally distributed so they are reported as means ± SDs. Birth measures are reported as means ± SDs. We reported two-sided $P$-values; a $P$-value of 0.05 was considered significant.

We also tested for potential confounders, i.e. maternal body mass index (BMI), age, wealth and parity (either as a continuous or a bivariate variable), and found that the relationship of food supplementation and cortisol with birth size was the same as when these variables were not added to the model. Timing of food supplementation did not interact with maternal covariates (i.e. BMI, age, wealth and parity) to influence birth size, nor were there significant three-way interactions of timing of food supplementation, cortisol and maternal covariates to influence birth size.

## Results

Demographic and anthropometric characteristics and concentrations of cortisol of the 1041 pregnant women did not differ significantly or substantively between the food supplementation groups or from

**Table 1.** Demographic, anthropometric (8 weeks of gestation) and cortisol characteristics of Bangladeshi pregnant women by concentration of cortisol, invitation time to start food supplementation or sex of infant in the Maternal Infant Nutritional Interventions Matlab study

| | Cortisol* | | Food supplementation† | | Sex | | Total |
|---|---|---|---|---|---|---|---|
| | Lower | Higher | Usual | Early | Male | Female | $n = 1041$ |
| | $n = 527$ | $n = 514$ | $n = 508$ | $n = 533$ | $n = 507$ | $n = 534$ | |
| Body mass index | 20.6 ± 2.7‡§ | 19.8 ± 2.5 | 20.1 ± 2.6 | 20.3 ± 2.8 | 20.2 ± 2.6 | 20.2 ± 2.8 | 20.2 ± 2.7 |
| Parity | 1.5 ± 1.3§ | 1.3 ± 1.3 | 1.4 ± 1.4 | 1.4 ± 1.3 | 1.4 ± 1.4 | 1.4 ± 1.2 | 1.4 ± 1.3 |
| Age (years) | 27.1 ± 5.7§ | 26.1 ± 5.7 | 26.5 ± 5.8 | 26.7 ± 5.6 | 26.7 ± 6.0 | 26.7 ± 6.1 | 26.6 ± 5.7 |
| Wealth index¶ | 3.1 ± 1.4 | 3.0 ± 1.4 | 3.1 ± 1.4 | 3.0 ± 1.4 | 3.1 ± 1.4§ | 2.9 ± 1.4 | 3.0 ± 1.4 |
| Cortisol (nmol $l^{-1}$) | 7.3 ± 3.2* | 12.8 ± 3.8 | 9.9 ± 3.2 | 9.8 ± 3.8 | 9.9 ± 3.4 | 9.7 ± 3.5 | 9.8 ± 3.5 |

*Cortisol obtained at 28–32 weeks gestation was categorised as lower (≤ median value 9.6 nmol $L^{-1}$ of cortisol) to indicate lower prenatal stress or higher (>median value 9.6 nmol $L^{-1}$ of cortisol) to indicate higher prenatal stress. †Invitation time to start food supplementation programme was either early (~9 weeks gestation) or usual (~20 weeks gestation). ‡Means ± SD (all such values). §$P < 0.05$ *t*-test between groups. ¶Wealth Index 1 to 5 with 1 being the poorest and 5 being the wealthiest.

**Table 2.** Infant anthropometric and birth characteristics by concentration of prenatal maternal cortisol, invitation time to start food supplementation, in Bangladeshi pregnant women or infant sex in the Maternal Infant Nutritional Interventions Matlab study

| | Cortisol* | | Food supplementation† | | Sex | |
|---|---|---|---|---|---|---|
| | Lower | Higher | Usual | Early | Male | Female |
| | $n = 527$ | $n = 514$ | $n = 508$ | $n = 533$ | $n = 507$ | $n = 534$ |
| Female (%) | 52.4 | 50.2 | 49.6 | 52.9 | – | – |
| Birthweight (g) | 2744.9 ± 394.6‡§ | 2677.9 ± 418.4 | 2697.2 ± 429.6 | 2728.6 ± 385.2 | 2745.8 ± 411.0§ | 2682.5 ± 402.2 |
| Birth length (cm) | 47.7 ± 2.1 | 47.5 ± 2.3 | 47.5 ± 2.2 | 47.7 ± 2.0 | 47.9 ± 2.2§ | 47.3 ± 2.2 |
| Head circumference (cm) | 32.6 ± 1.5§ | 32.3 ± 1.8 | 32.5 ± 1.7 | 32.4 ± 1.6 | 32.7 ± 1.7§ | 32.2 ± 1.6 |
| LBW (%)¶ | 26.0 | 30.0 | 28.7 | 27.2 | 25.2** | 30.5 |
| Gestational age at birth (weeks) | 39.3 ± 1.5§ | 38.9 ± 1.78 | 39.1 ± 1.7 | 39.1 ± 1.6 | 39.0 ± 1.6 | 39.2 ± 1.6 |

*Cortisol obtained at 28–32 weeks gestation was categorised as lower (≤ median cortisol value 9.6 nmol $l^{-1}$) to indicate lower stress or higher (>median cortisol value 9.6 nmol $L^{-1}$). †Invitation time to start food supplementation programme was either early (~9 weeks gestation) or usual (~20 weeks gestation). ‡Means ± SD (all such values). §$P \leq 0.01$ *t*-test between groups. ¶Low birthweight (LBW) is <2500 g adjusted birthweight. Measurements taken from 24 h to 30 days after birth were adjusted using an SD score transformation with the assumption that infants tend to remain relatively positioned in the anthropometric distribution during this time period. **$P = 0.03$ $\chi^2$ test between groups.

those who had male or female infants (Table 1). Pregnant women who had high cortisol (i.e. cortisol >median value of 9.6 nmol $L^{-1}$) had lower BMI, were younger, and had fewer children than women with low cortisol (i.e. cortisol ≤ median of 9.6 nmol $l^{-1}$), but wealth index did not differ significantly or substantively. There were no significant or substantive differences in maternal characteristics between those who participated in this study and those who had moved or decided not to participate (data not shown).

Infant birthweight, length, head circumference, percentage of LBW and gestational age did not significantly or substantively differ between the food supplementation groups (Table 2). Mothers with higher cortisol had infants with lower birthweights ($P < 0.01$), smaller head circumferences ($P < 0.01$), reduced age at gestation ($P < 0.01$) and a tendency to have shorter length at birth ($P = 0.08$) (Table 2). Overall, female infants had lower birthweights ($P = 0.01$), smaller head circumferences ($P < 0.01$), shorter length at birth ($P < 0.01$) and higher percentage of LBW ($P = 0.03$) than males. The percentage of female infants did not differ significantly or substantively between food supplementation groupsor between those whose mothers had low or high cortisol.

**Table 3.** Interaction of maternal prenatal cortisol and invitation time to start the prenatal food supplementation programme with birthweight (g), length (cm) and head circumference (cm) among Bangladeshi mothers and male infants in the Maternal Infant Nutritional Interventions Matlab study.

| Males ($n = 507$) | Birthweight (g)* | | Birth length (cm)* | | Head circumference (cm)* | |
|---|---|---|---|---|---|---|
| | β | *P* | β | *P* | β | *P* |
| Intercept | 2945.3 | 0.01 | 49.0 | 0.01 | 33.6 | 0.01 |
| Cortisol† | –20.1 | 0.01 | –0.1 | 0.03 | –0.1 | 0.01 |
| Food supplement‡ | | | | | | |
| Early | –259.4 | 0.02 | –1.1 | 0.08 | –1.1 | 0.02 |
| Usual | 0 | 0 | 0 | 0 | 0 | 0 |
| Cortisol*Food Supplement | | | | | | |
| Cortisol * Early | 25.3 | 0.02 | 0.1 | 0.04 | 0.1 | 0.02 |
| Cortisol * Usual | 0 | 0 | 0 | 0 | 0 | 0 |
| $R^2$ | 0.014 | | 0.020 | | 0.018 | |

*Model controlling for type of micronutrient intervention ($P > 0.05$): Iron (60 mg) + 400 μg folic acid (reference); Iron (30 mg) + 400 μg folic acid; and Multiple micronutrients that included 15 recommended micronutrients, including iron 30 mg, as described by Persson *et al*. (2012). †Cortisol obtained at 28–32 weeks gestation and was continuous. ‡Invitation time to start food supplementation programme was either early (~9 weeks gestation) or usual (~20 weeks gestation). Because of the inclusion of the interaction terms in the model, the coefficients for early-invitation food supplementation represent differences in anthropometry between early-invitation and usual-invitation when cortisol is zero.

For male infants, the relationship of maternal cortisol and birthweight and head circumference differed by invitation time to start the food supplementation, and there was a trend for an interaction for birth length (Table 3). In the usual-invitation group, higher cortisol was associated with lower birthweight and head circumference, with a trend for lower length. In contrast, in the early-invitation group, cortisol was not associated with birthweight, length and head circumference. For example, for birthweight, the slope in the usual-invitation group was –20.1 g per nmol $L^{-1}$ of cortisol, whereas the slope in the early-invitation group was close to zero (5.2 g per nmol $L^{-1}$ = 25.3–20.1). In the usual-invitation group, given the SD of cortisol of 3.5 nmol $L^{-1}$, the slope of 20.1 g per nmol $L^{-1}$ represents a difference of about 280 g in birthweight across the range of cortisol in the sample; this means that women in the usual-invitation group with very high concentrations of cortisol would have much lighter male infants than women with very low concentrations of cortisol. For the usual-invitation group, when cortisol was categorised by > or ≤ the median value, there was a 148 g difference in birthweight of males (g; means ± SEM; 2672.5 ± 38.5 and 2820.2 ± 34.9, respectively).

For female infants, the relationship of maternal cortisol and birth size did not differ significantly or substantively by invitation time to start the food supplementation (Table 4). Furthermore, cortisol was not associated with birthweight, length and head circumference in either the usual- or early-invitation group.

We tested for the possibility that gestational age mediated the relationships among invitation time to start the food programme, cortisol and birth size by controlling for gestational age in the models with the three birth-size variables and the interactive term between food group and cortisol. Gestational age did not attenuate the relationship of food group and cortisol on birth size for all infants or for male infants only (data not shown). Gestational age did not differ between male and female infants (Table 1). Cortisol was related negatively with gestational age in both males ($\beta = -0.06$; $P < 0.01$) and females ($\beta = -0.04$; $P = 0.05$).

## Discussion

Early invitation to a prenatal food supplementation programme ameliorated the negative association of prenatal salivary cortisol, a biomarker for stress, on birth size of male, but not female infants in a randomised controlled field trial. In the usual-invitation group, higher maternal cortisol (i.e. higher maternal stress) was associated with reduced birth size of male infants. This relationship was not observed for female infants.

**Table 4.** Interaction of maternal prenatal cortisol and invitation time to start the prenatal food supplementation programme with birthweight (g), length (cm) and head circumference (cm) among Bangladeshi mothers and female infants in the Maternal Infant Nutritional Interventions Matlab study

| Females ($n = 534$) | Birthweight (g)* | | Birth length (cm)* | | Head circumference (cm)* | |
|---|---|---|---|---|---|---|
| | $\beta$ | $P$ | $\beta$ | $P$ | $\beta$ | $P$ |
| Intercept | 2719.1 | 0.01 | 47.6 | 0.01 | 32.6 | 0.01 |
| Cortisol† | –6.6 | 0.39 | –0.1 | 0.68 | –0.1 | 0.24 |
| Food supplement‡ | | | | | | |
| Early | 5.2 | 0.96 | 0.4 | 0.52 | 0.6 | 0.90 |
| Usual | 0 | 0 | 0 | 0 | 0 | 0 |
| Cortisol * Food Supplement | | | | | | |
| Cortisol * Early | 6.8 | 0.50 | –0.1 | 0.76 | –0.1 | 0.96 |
| Cortisol * Usual | 0 | 0 | 0 | 0 | 0 | 0 |
| $R^2$ | 0.011 | | 0.005 | | 0.007 | |

*Model controlling for type of micronutrient intervention ($P > 0.05$): Iron (60 mg) + 400 $\mu$g folic acid (reference); Iron (30 mg) + 400 $\mu$g folic acid and multiple micronutrients that included 15 recommended micronutrients, including iron 30 mg, as described by Persson *et al.* (2012). †Cortisol obtained at 28–32 weeks gestation and was continuous. ‡Invitation time to start food supplementation programme was either early (~9 weeks gestation) or usual (~20 weeks gestation).

Pregnant women with higher prenatal cortisol and in the usual-invitation group had male infants that were 148 g lighter on average than those in with lower level of prenatal cortisol. The magnitude of this effect on birthweight is biologically important as an increase of 100 g in mean birthweight is associated with a 30–50% reduction in neonatal mortality (Shrimpton 2003). In our study, every woman was part of the food supplementation programme, so the influence of prenatal cortisol (i.e. stress) on LBW when there is no food intervention may be even greater than reported here. The reduction in birthweight for male infants in this study is comparable to that reported in observational studies where maternal depression reduced birthweight by 300 g in the United States (Field *et al.* 2008) and 100 g in Bangladesh (Nasreen *et al.* 2010). The large effect of depression on birthweight in the United States is comparable to the difference due to higher altitudes (Haas *et al.* 1980), and may be, in part, a function of the 20% higher average birthweight in the United States compared to Bangladesh. Furthermore, women in Bangladesh are more likely than women in the United States to have low pre-pregnancy BMI and poor energy intake during pregnancy (Kramer 1987; Alam *et al.* 2003; Shaheen & Lindholm 2006). Poor maternal nutrition may limit birthweight to the extent that stress may not have as much influence on birthweight in this study population (Asling-Monemi *et al.* 2009) as in the United States.

## Mechanisms

The mechanisms whereby stress influences birth outcomes may be biological and social. Higher prenatal stress increases maternal concentration of cortisol that could reduce fetal growth through reducing uterine blood flow and nutrient delivery to the fetus, or may influence fetal growth directly (Vythilingum *et al.* 2010; Dunkel-Schetter 2011). In the early-invitation group, high maternal stress was not associated with reduced fetal growth in males. Mothers in the early-invitation group consumed an average of 30 more food packets, and began consuming them earlier (starting at approximately 9 weeks instead of 20 weeks of gestation), thereby, potentially increasing the nutrients available for early fetal growth. This may be important as early growth restriction that has been detected as early as 8 weeks gestation (Smith *et al.* 1998).

Early food supplementation may also promote a healthier placental environment for fetal growth (Clarke *et al.* 1998; Magnusson *et al.* 2004). In an observational study in Bangladesh, earlier start of and longer participation in a food supplement programme (beginning in second trimester) was associated with

heavier infants at birth (Shaheen *et al*. 2006). In sheep, greater energy consumption during early and mid-gestation increases placental size, which is associated with increased birthweight (Clarke *et al*. 1998). Christian (2010) in a recent review outlined several pathways whereby maternal nutrition early in pregnancy could plausibly influence fetal growth and development. In early pregnancy, an increase in maternal plasma volume is necessary to deliver nutrients and oxygen to the developing fetus. Women who are underweight have a higher risk of having inadequate plasma volume leading to poor fetal growth (Rosso *et al*. 1992). Early food supplementation may improve plasma volume resulting in better fetal growth. Another process that occurs early in gestation and may be influenced by maternal nutrition is placental function and development. If early supplementation improves placental weight or vascularisation, then nutrient and oxygen delivery to the fetus could increase resulting in increased fetal growth. A study in India reported that mothers who consumed more nutrient-dense foods had heavier placentas (Rao *et al*. 2001). Furthermore, in animals and humans with fetal growth restriction, the placentas of poorly nourished females have less ability to convert maternal cortisol to the inactive cortisone (Falcone & Little 1994), so that the fetus is not protected from the growth-inhibiting actions of maternal cortisol (Langley-Evans *et al*. 1996; Lesage *et al*. 2001). The result is that a fetus of a poorly nourished woman could be exposed to higher concentrations of maternal cortisol, further reducing fetal growth.

Earlier programme participation may have protected birth size through social pathways. Prenatal food programmes, such as the MINIMat programme or The Supplemental Nutrition Program for Women, Infants and Children programme in the United States provide opportunities for social contact. The early-invitation group likely had more social contact with the local food supplement providers and with pregnant neighbours since they began the programme earlier in pregnancy and consumed more food packets at the nutrition centre. This increased social contact may have improved emotional well-being (Oakley 1988; Collins *et al*. 1993; Shaheen & Lindholm 2006) and social support, which are associated positively with birthweight (Feldman *et al*. 2000) regardless of self-reported stress (Oakley 1988; Collins *et al*. 1993; Nasreen *et al*. 2010; Dunkel-Schetter 2011). The manner in which these social factors influence birth outcomes is not clear, but one possible mechanism is that early-invitation may change health behaviours, such as resting more, that could improve birth outcomes (Ortolano *et al*. 2003).

Invitation time to start a prenatal food supplementation programme did not modify the relationship of stress and birth size in females. Factors that influence fetal growth may differ by sex. The mechanisms for normal sexual dimorphism in birth size (Kraemer 2003; Clifton 2010; Lampl *et al*. 2010; Miles *et al*. 2010) and sex-specific differences in response to adverse events (Lampl *et al*. 2010) are actively being investigated, but they remain largely unknown. These mechanisms may include differences in placental function and structure, hormones and growth factors, and may be Y chromosome-linked (Clifton 2010; Lampl *et al*. 2010; Miles *et al*. 2010). In one study, prenatal food supplements promoted growth and increased birthweight in males to a greater extent than in females (Mora *et al*. 1979), but in another study it did not (Kardjati *et al*. 1988). Under adverse conditions, males and females alter placental function differently leading to different growth and survival patterns. Clifton (2010) provides evidence to support a hypothesis that males respond to one adverse event, such as maternal asthma (Murphy *et al*. 2003), by eliciting placental responses that maintain fetal growth, but increase the risk of intrauterine growth restriction if there is another adverse event. Females change placental genes and proteins to adapt to several insults, and reduce growth by a smaller amount than males. The results from our study are consistent with the pattern proposed by Clifton (2010), yet more research is needed to understand the biological mechanisms underlying sex-specific responses to growth promoting and growth inhibiting events.

## Strengths and limitations

This study was a randomised controlled field trial conducted in community setting using a national

nutrition intervention programme as a type of control group. Additionally, a biomarker was used to measure stress, eliminating the potential for misinformation about sensitive topics that can occur with self-reported stress measures. Given that every pregnant woman received a food supplementation intervention, and social and health conditions may affect participation and response to interventions, generalising to other contexts must be done cautiously. This study was conducted where the community has a long-standing relationship with ICDDR, B. Also, there was a potential to respond to a food intervention in this population as women of childbearing age suffer from chronic energy deficiency, pregnant women consume diets below recommended energy levels (Alam *et al*. 2003) and the prevalence of LBW is high (Khatun & Rahman 2008). Pregnant women could have partially or fully substituted the food packets for food at home, although the nutritional quality of food supplement may have been better than the food at home.

## Conclusion

During pregnancy, poor maternal nutrition (Lechtig *et al*. 1975; Kramer 1987; Kardjati *et al*. 1988; Winkvist *et al*. 1998) and high stress (Field *et al*. 2008; Nasreen *et al*. 2010; Dunkel-Schetter 2011) can limit fetal growth and potentially limit human capital (Victora *et al*. 2008). This study demonstrates that a prenatal food supplement programme, if delivered in the first trimester and of sufficient nutrient value, can ameliorate the negative influence of high maternal prenatal stress on birthweight of male infants. In low-income populations where women routinely face stressful life situations, and these situations are difficult to change, implementing prenatal food programmes in the first trimester, earlier than is normally practised, is one strategy that potentially can support better birth outcomes.

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## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Contributions

ALF led study planning and design, collected data, wrote the manuscript and had primary responsibility for final content; EAF contributed to the study design, statistical analysis of the data, interpretation, and writing of the manuscript; RTN contributed to interpretation of results, and critical revision of the manuscript for important intellectual content. LAP led the MINIMat study and contributed to design and implementation of the study and revision of the manuscript. All authors read and approved the final manuscript.

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