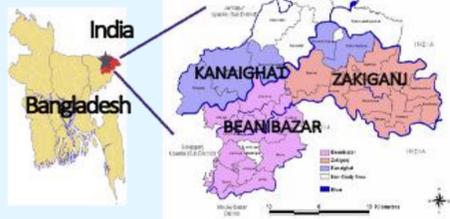


BACKGROUND

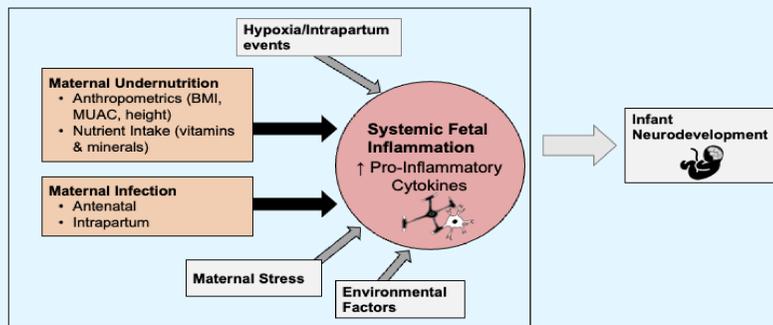


- Perinatal inflammation may adversely affect early human brain development and contribute to the large burden of neurodevelopmental impairment concentrated in low-income countries.
- Identifying and addressing modifiable pregnancy risk factors associated with fetal inflammation may help optimize neurodevelopment among children worldwide.

OBJECTIVE



To investigate the association between maternal pregnancy undernutrition and infections and offspring inflammation, as measured by pro-inflammatory immune mediators in umbilical cord blood in a pregnancy-birth cohort in rural Bangladesh.



METHODS

- For this sub-study, we included 251 consecutively enrolled women and their healthy, term infants from a parent pregnancy-birth cohort ("Projahnmo") in rural Sylhet district, Bangladesh.
 - Infants stillborn, preterm, or who had neonatal encephalopathy were excluded.
- Maternal and infant health data including maternal food frequency questionnaire (FFQ) responses were prospectively collected during pregnancy and at delivery.
 - Relative levels of nutrient intake was calculated utilizing Indian and Bangladeshi food composition tables.
- Umbilical cord blood at birth was analyzed for IL-1 α , IL-1 β , IL-6, IL-8, and CRP.
- The associations between exposures (maternal undernutrition [underweight (BMI) <18.5 kg/m², mid-upper arm circumference (MUAC) <22 cm, height < 145 cm (stunting), anemia], tertiles of nutrient intake, and antenatal and intrapartum infection) and outcome (elevated cytokine levels [$>75\%$ vs $\leq 75\%$]) were evaluated using logistic regression models adjusted for potential confounding:
 - Socioeconomic status, primiparity, MUAC < 22 cm, maternal education, tobacco or betel nut use, and season of initial antenatal assessment

RESULTS

Demographic and Clinical Characteristics

- Women were on average 23.7 years old (SD 4.6) with primary level education (mean years of schooling 6 (SD 2.9)).
- Rates of maternal undernutrition were high: 20.1% of women were stunted, 31.7% underweight at enrollment visit (mean GA 12.1 weeks), 34.5% had a MUAC <22 cm, and 47.4% were anemic (Hg < 11 g/dL).
- Mean birthweight was 2749.9 g (SD 413.7) and rates of term low birth weight (22.9%) and small for gestational age (43.9%) were high, similar to national rates in Bangladesh

Maternal Dietary Intake (Figure 1)

- Maternal diet primarily consisted of fish, milk, green leafy vegetables, green pepper, and mango
- Diet was relatively consistent with little variation across pregnancy
- Nutrient intake in this population was substantially lower than recommended intake in pregnancy for most nutrients

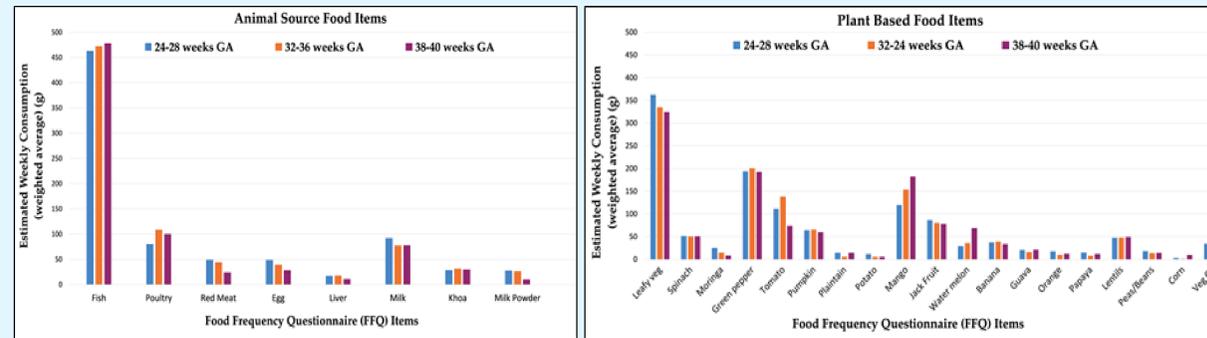


Figure 1. Estimated average weekly consumption (g) of food items through the course of gestation for animal source (top) and plant-based (bottom) items

Maternal nutrition, infection and odds of elevated inflammation

- Maternal anemia was significantly associated with greater odds of elevated IL-1 α (aOR = 1.92, 95% CI: 1.04, 3.54) (Figure 2)
- No other statistically significant results ($p < 0.05$) were observed among Figure 2 exposures, though ORs tended to be greater than one.
- Greater odds of elevated IL-6 had a borderline significant association with stunting (aOR = 1.97, 95% CI: 0.97, 4.02) and intrapartum infections (aOR = 2.07, 95% CI: 0.95, 4.54).
- Vitamins.** Lowest tertile levels (< 33rd%) of B vitamins (B1, B2, B3, B6, B9 (folate), B12) were associated with increased odds of inflammation, notably IL-1 α , IL-8 and IL-6, with aORs greater than 2 times the reference (33rd% - 67th%) (Table 1)
- For fat soluble vitamins D and E, a relatively higher intake ($> 67\%$) was associated with lower aOR for IL-1 α and IL-8 elevation, respectively. Higher B12 intake was associated with lower odds of elevated IL-6 and IL-8
- Minerals & LCPUFAs.** Low intake of iron and linoleic acid was associated with elevated IL-8, while low zinc and iron intake were associated with elevated IL-1 β .

CONCLUSIONS

Among pregnant women in Sylhet, Bangladesh who delivered healthy, term infants, improving micronutrient intake (e.g., B vitamins, fat-soluble vitamins D & E, minerals iron & zinc, LC PUFA linoleic acid) and preventing anemia and perinatal infections are potential targets for reducing systemic fetal inflammation, including elevation in IL-8, which has been reported as a risk factor for adverse developmental outcomes.

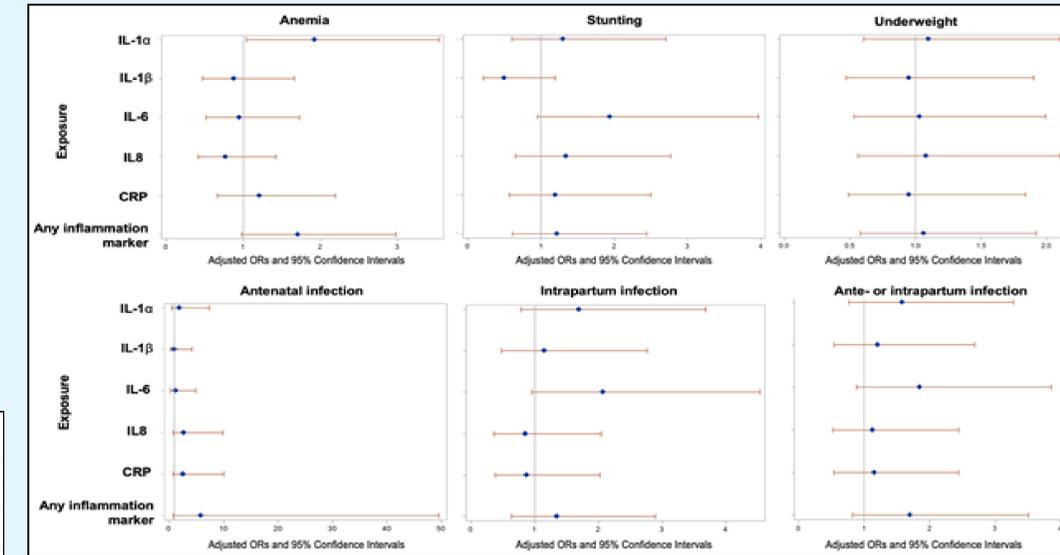


Figure 2. Association between maternal anthropometry, anemia, and perinatal infections and newborn inflammation: ORs are for outcome of elevation in inflammation protein above the 75% (vs <75%).

Nutrient ¹	Tertiles of Intake	IL-1 α	IL-1 β	IL-6	IL-8	CRP
		aOR ¹ [95%CI]				
Vit A (mcg)	<33%	1.50 [0.70 - 3.21]	2.13 [0.93 - 4.87]	1.18 [0.56 - 2.52]	1.76 [0.81 - 3.79]	1.16 [0.56 - 2.41]
	>67%	0.96 [0.44 - 2.10]	1.81 [0.80 - 4.10]	0.78 [0.36 - 1.69]	0.79 [0.35 - 1.78]	0.62 [0.29 - 1.35]
Vit B1 (mg)	<33%	2.13 [0.98 - 4.65]	1.76 [0.79 - 3.95]	2.07 [0.95 - 4.48]	2.27 [1.05 - 4.91]	1.11 [0.52 - 2.34]
	>67%	1.30 [0.59 - 2.85]	0.75 [0.34 - 1.68]	1.02 [0.46 - 2.26]	0.74 [0.32 - 1.67]	1.01 [0.48 - 2.12]
Vit B2 (mg)	<33%	3.17 [1.39 - 7.19]	2.11 [0.93 - 4.80]	2.25 [1.03 - 4.94]	2.45 [1.12 - 5.37]	2.52 [1.17 - 5.45]
	>67%	1.86 [0.83 - 4.15]	1.14 [0.52 - 2.51]	1.10 [0.05 - 2.41]	0.74 [0.33 - 1.68]	1.10 [0.50 - 2.42]
Vit B3 (mg)	<33%	2.30 [1.03 - 5.12]	2.94 [1.25 - 6.9]	1.60 [0.74 - 3.46]	3.23 [1.42 - 7.31]	0.96 [0.46 - 2.02]
	>67%	1.61 [0.72 - 3.58]	1.70 [0.75 - 3.84]	0.80 [0.36 - 1.78]	1.32 [0.57 - 3.06]	0.62 [0.29 - 1.34]
Vit B6 (mg)	<33%	1.78 [0.82 - 3.87]	1.92 [0.85 - 4.34]	2.47 [1.12 - 5.44]	2.35 [1.08 - 5.13]	1.56 [0.74 - 3.30]
	>67%	1.20 [0.55 - 2.61]	0.75 [0.34 - 1.67]	1.09 [0.49 - 2.44]	0.71 [0.31 - 1.63]	0.90 [0.41 - 1.95]
Vit B9 (Folate) (mcg)	<33%	1.60 [0.73 - 3.51]	2.04 [0.88 - 4.71]	1.16 [0.54 - 2.47]	2.28 [1.04 - 5.02]	1.36 [0.64 - 2.89]
	>67%	1.28 [0.60 - 2.73]	1.26 [0.57 - 2.76]	0.55 [0.25 - 1.19]	0.78 [0.35 - 1.76]	0.86 [0.40 - 1.85]
Vit B12 (mcg)	<33%	0.60 [0.28 - 1.30]	0.49 [0.21 - 1.13]	0.42 [0.19 - 0.92]	0.49 [0.23 - 1.07]	0.75 [0.35 - 1.60]
	>67%	0.63 [0.29 - 1.37]	0.54 [0.24 - 1.24]	0.38 [0.17 - 0.84]	0.42 [0.19 - 0.95]	0.71 [0.33 - 1.56]
Vit C (mg)	<33%	1.28 [0.59 - 2.80]	1.23 [0.57 - 2.89]	1.31 [0.61 - 2.81]	1.23 [0.57 - 2.62]	0.65 [0.31 - 1.38]
	>67%	1.18 [0.56 - 2.48]	0.76 [0.35 - 1.65]	0.82 [0.38 - 1.74]	0.52 [0.24 - 1.15]	0.52 [0.25 - 1.10]
Vit D (mcg)	<33%	0.66 [0.29 - 1.52]	1.44 [0.59 - 3.52]	1.33 [0.57 - 3.07]	1.18 [0.51 - 2.73]	0.90 [0.39 - 2.06]
	>67%	0.48 [0.23 - 0.99]	0.65 [0.31 - 1.37]	0.80 [0.39 - 1.67]	0.57 [0.27 - 1.20]	0.86 [0.42 - 1.77]
Vit E (mg)	<33%	0.91 [0.42 - 1.98]	1.00 [0.43 - 2.34]	0.82 [0.38 - 1.79]	1.06 [0.49 - 2.03]	0.90 [0.43 - 1.90]
	>67%	0.79 [0.38 - 1.65]	0.76 [0.36 - 1.61]	0.60 [0.28 - 1.26]	0.42 [0.19 - 0.92]	0.56 [0.26 - 1.19]
Iron (mg)	<33%	1.57 [0.73 - 3.38]	2.37 [1.03 - 5.45]	1.52 [0.72 - 3.25]	2.28 [1.05 - 4.97]	0.94 [0.45 - 1.94]
	>67%	1.30 [0.61 - 2.78]	1.52 [0.68 - 3.37]	0.96 [0.45 - 2.05]	1.01 [0.45 - 2.24]	0.70 [0.34 - 1.48]
Selenium (mg)	<33%	1.43 [0.67 - 3.06]	1.62 [0.72 - 3.66]	1.01 [0.48 - 2.16]	1.79 [0.84 - 3.83]	0.95 [0.46 - 1.97]
	>67%	1.23 [0.58 - 2.62]	1.43 [0.66 - 3.10]	1.01 [0.48 - 2.11]	1.02 [0.47 - 2.23]	0.65 [0.30 - 1.37]
Zinc (mg)	<33%	2.10 [0.95 - 4.65]	2.52 [1.07 - 5.91]	2.08 [0.93 - 4.65]	2.20 [1.00 - 4.86]	1.60 [0.73 - 3.47]
	>67%	1.23 [0.56 - 2.70]	1.26 [0.56 - 2.82]	1.24 [0.57 - 2.73]	0.68 [0.30 - 1.55]	1.06 [0.49 - 2.28]
Linoleic acid (mg) ²	<33%	1.72 [0.81 - 3.67]	1.73 [0.76 - 3.90]	1.35 [0.63 - 2.09]	2.35 [1.07 - 5.15]	1.47 [0.69 - 3.12]
	>67%	0.78 [0.36 - 1.69]	1.10 [0.51 - 2.38]	0.85 [0.40 - 1.80]	0.96 [0.43 - 2.12]	0.87 [0.41 - 1.85]

Table 1. The adjusted odds of cord blood inflammation ($>75^{\text{th}}$ percentile) by tertile of maternal nutrient (Reference is the middle tertile of nutrient intake (33rd-67th percentile))