Neurodevelopment, vision and auditory outcomes at age 2 years in offspring of participants in the 'Women First' maternal preconception nutrition randomised controlled trial

Michelle Fernandes ,[1,2,3] Nancy F Krebs,[4] Jamie Westcott ,[4] Antoinette Tshefu,[5] Adrien Lokangaka,[5] Melissa Bauserman,[6] Ana L Garcés,[7] Lester Figueroa,[7] Sarah Saleem ,[8] Sumera A Aziz,[8] Robert L Goldenberg,[9] Shivaprasad S Goudar,[10] Sangappa M Dhaded,[10] Richard J Derman,[11] Jennifer F Kemp,[4] Marion Koso-Thomas,[12] Amaanti Sridhar,[13] Elizabeth M McClure,[13] K Michael Hambidge,[4] The Women First Preconception Nutrition Trial Study Group

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/archdischild-2023-325352).

For numbered affiliations see end of article.

Correspondence to
Dr Michelle Fernandes, MRC Lifecourse Epidemiology Centre and Human Development and Health Academic Unit, University of Southampton Faculty of Medicine, Southampton SO16 6YD, UK;
m.c.fernandes@soton.ac.uk

MF and NFK are joint first authors.

Received 21 January 2023
Accepted 10 April 2023
Published Online First
4 May 2023

To cite: Fernandes M, Krebs NF, Westcott J, *et al*. *Arch Dis Child* 2023;**108**:622–631.

ABSTRACT

Background Maternal nutrition in preconception and early pregnancy influences fetal growth. Evidence for effects of prenatal maternal nutrition on early child development (ECD) in low-income and middle-income countries is limited.

Objectives To examine impact of maternal nutrition supplementation initiated prior to or during pregnancy on ECD, and to examine potential association of postnatal growth with ECD domains.

Design Secondary analysis regarding the offspring of participants of a maternal multicountry, individually randomised trial.

Setting Rural Democratic Republic of the Congo, Guatemala, India and Pakistan.

Participants 667 offspring of Women First trial participants, aged 24 months.

Intervention Maternal lipid-based nutrient supplement initiated preconceptionally (arm 1, n=217), 12 weeks gestation (arm 2, n=230) or not (arm 3, n=220); intervention stopped at delivery.

Main outcome measures The INTERGROWTH-21st Neurodevelopment Assessment (INTER-NDA) cognitive, language, gross motor, fine motor, positive and negative behaviour scores; visual acuity and contrast sensitivity scores and auditory evoked response potentials (ERP). Anthropometric z-scores, family care indicators (FCI) and sociodemographic variables were examined as covariates.

Results No significant differences were detected among the intervention arms for any INTER-NDA scores across domains, vision scores or ERP potentials. After adjusting for covariates, length-for-age z-score at 24 months (LAZ_{24}), socio-economic status, maternal education and FCI significantly predicted vision and INTER-NDA scores (R^2=0.11–0.38, p<0.01).

Conclusions Prenatal maternal nutrition supplementation was not associated with any neurodevelopmental outcomes at age 2 years. Maternal education, family environment and LAZ_{24} predicted ECD. Interventions addressing multiple components of the nurturing care model may offer greatest impact on children's developmental potential.

Trial registration number NCT01883193.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Improved maternal nutrition during the preconception and early gestation periods improves fetal and child growth in settings with high rates of stunting.
⇒ Poor physical growth and impairments in early child development (ECD) frequently co-exist.

WHAT THIS STUDY ADDS

⇒ Maternal nutrition supplementation initiated before and early in pregnancy and discontinued at delivery did not improve cognitive, language, gross motor, fine motor, positive and negative behaviour scores; visual acuity and contrast sensitivity scores and auditory evoked response potentials markers in children aged 2 years from Democratic Republic of the Congo, Guatemala, India and Pakistan.
⇒ Maternal education, family environment and child length at 24 months were associated with multiple ECD outcomes in these diverse settings, based on a multidomain, rapid, low-cost ECD assessment tool designed for low-resource settings.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study emphasises that a single nutritional strategy, that is, preconception and prenatal maternal nutrition supplementation, is insufficient to demonstrate positive gains in young children's development.
⇒ Rather, a multisectoral approach is needed to maximise opportunities to improve children's early development.

INTRODUCTION

The first 1000 days of life are a well-established critical window of opportunity for improving child growth and development.[1–3] While numerous early life exposures (ELEs) are associated with delays in early childhood development (ECD),[4] four key

risk factors (stunting, iodine deficiency, iron deficiency anaemia and inadequate cognitive stimulation) have been identified by the *Lancet*'s International Child Development Steering Group as urgent needs for intervention globally.[3] Three of these relate specifically to maternal and child nutrition.[3]

Evidence from both preclinical and human studies indicate that preconception or periconception maternal nutritional status influence fetal growth and development, with life course effects on health and neurocognitive function.[5] Strong associations between intrauterine and extrauterine growth, and ECD, have been demonstrated across disparate populations,[6 7] so that, in some comparisons, childhood stunting is considered a proxy for neurodevelopmental risk.[6] Undernutrition during early life may, therefore, be considered to be a potentially preventable cause of ECD delay. This presents a strong theoretical rationale for the initiation of maternal nutrition supplements prior to conception, to correct both maternal underweight and micronutrient deficiencies before and during sensitive periods of fetal brain development. Preconception and early pregnancy maternal nutritional supplementation are reported to improve birth outcomes and postnatal linear growth, but understanding of its impact on ECD remains limited.[8]

The 'Women First' Preconception Maternal Nutrition Trial (WF) was undertaken in four countries with high rates of childhood stunting.[9] The trial resulted in significant improvements in birth length-for-age z-scores (LAZ), early postnatal growth and linear growth trajectories from birth to 24 months in the offspring of women who received nutritional supplementation initiated preconceptionally (arm 1) or at approximately 12 weeks gestation (arm 2) compared with no supplement (arm 3).[8–10] WF is the first multicountry randomised controlled trial (RCT) to (i) examine associations between preconception maternal nutrition and ECD outcomes in four geographically and culturally disparate low-income and middle-income countries (LMICs) populations; (ii) measure neurocognitive outcomes using a comprehensive, rapid, low-cost ECD assessment (INTERGROWTH-21st Project Neurodevelopment Assessment (INTER-NDA))[4]; (iii) categorise ECD delay based on prescriptive, international standards rather than population-specific references; and (iv) include measurements of vision and cortical auditory processing.

In the present study, we compared multiple domains of neurodevelopment at age 2 years in a randomly selected subset of children in each WF intervention arm. Our aims were to (1) examine associations between WF intervention arm and ECD outcomes and (2) determine which, if any, ELE predict ECD outcomes at age 2. Our a priori trial hypothesis was that the gains previously reported for postnatal growth would be associated with gains in ECD scores at 2 years among the offspring of mothers who received nutritional supplementation.

METHODS

Study design

This analysis included prospectively planned neurodevelopmental testing and anthropometry on live-born infants of WF participants. For this report, these outcomes were obtained on a randomly selected subset of the infants, representing approximately one-third of the WF offspring, evenly distributed across intervention arms and research sites. The remaining offspring were evaluated with the Bayley Scales of Infant Development (Pearson, San Antonio, Texas, USA).[11]

The primary WF trial was a multisite, individually randomised clinical trial of a daily 22-micronutrient fortified small-quantity lipid-based nutrient supplement formulated for pregnancy (Nutriset, Malauney, France; online supplemental material S1). The supplement was initiated at randomisation with continuation for ≥3 months (average ~9 months) before conception through delivery (arm 1), vs initiation of the same supplement late in the first trimester of pregnancy and continued through delivery (arm 2), vs no trial supplement (arm 3).[12] Additionally, women in arms 1 and 2 who were underweight or had inadequate gestational weight gain were provided a balanced protein-energy lipid-based supplement (without additional micronutrients). No postnatal interventions were offered. Details on the trial's protocol and follow-up procedures have been previously published.[8 10 12]

Setting

The study sites were rural communities in India (Belagavi, Karnataka), Pakistan (Thatta, Sindh), Democratic Republic of the Congo (DRC, Sud-Ubangi) and Guatemala (Chimaltenango).[12]

Participants and eligibility

Eligible participants for the primary WF trial were identified through the NICHD Global Network (GN) Maternal and Newborn Health Registry, household surveys and community meetings at each site.[9 12] Infants who completed the birth, 6-month and at least two of the three 12–24 months follow-up visits were assessed for ECD outcomes at 24 months between August 2016 and March 2019.

Enrolment and randomisation

The central data coordinating centre (RTI International, Durham, North Carolina, USA) created the initial randomisation scheme, which included a permuted block design stratified by GN with a trial arm allocation ratio of 1:1:1 within blocks.[9 12] Random assignment to neurodevelopment assessment was made before the 24-month visit and included approximately one-third of infants, evenly distributed across arms and sites.

Follow-up and ECD outcomes

Anthropometric measurements (weight, length and head circumference) were performed on children at 0 (birth), 6, 12, 18 and 24 months according to standardised procedures by trained research team members in the home or clinical environment (online supplemental material S2).[10] Demographic, medical and perinatal information was collected at birth.[9] Using WHO Child Growth Standards,[13] z-scores, accounting for sex and age at time of measurement, were determined for length-for-age (LAZ), weight-for-age (WAZ) and head circumference-for-age (HCAZ). Home environments were assessed with family care indicator (FCI) Questionnaire at 24 months (online supplemental material S2).[14] Assessors were blinded to the original randomisation assignment.

A holistic approach to ECD measurement, involving multiple outcomes, was undertaken at 24 months as follows:

1. *Neurocognitive development:* cognitive, language, fine and gross motor, positive and negative behaviour scores and corresponding risks of delay were measured on INTER-NDA . The INTER-NDA is an international, psychometrically valid, standardised, ECD assessment whose norms (online supplemental file 1) are international ECD standards, constructed according to WHO's prescriptive guidelines.[4]
2. *Vision:* visual acuity (VA; measured in Logarithm of Minimum Angle of Resolution) and contrast sensitivity (CS; %) were assessed using Cardiff tests (PA Vision, UK).[15 16]
3. *Cortical auditory processing:* amplitudes and latencies of auditory evoked response potentials (CA-ERPs) to three types

of auditory stimuli (frequent, infrequent and novel) were measured for three ERP components (P1, N2 and P3a waves) using the 'novelty oddball' ERP task[17] (online supplemental material S4).

The administrative protocols for the ECD assessments are available at: https://www.intergrowth21.org.uk.

Sample size estimations and power calculations

Allowing for multiple comparisons (arm 1 vs arm 2 and arm 1 vs arm 3, within each site; total of 8 comparisons), a conservative sample size of 44 children/arm/site (combined site total of 176/arm) would have allowed detection of a statistically significant mean difference of 1.3 (1.5) or greater with 80% (90%) power (assuming two-sided test with overall 5% type I error). The actual number of infants who survived, were retained for follow-up, and were consented to the INTER-NDA assessment was greater than initial estimates, and included >200 children per arm (combined site).

Statistical methods

Statistical analysis was performed in SPSS V.25.0 (IBM, Armonk, New York, USA). Prenatal, perinatal and postnatal characteristics were compared between arms and for children completing the ECD assessment and those lost to follow-up.

The distributions of ECD outcomes were inspected visually. ERP data were normally distributed; INTER-NDA and vision data were not. No transformation was identified that suited the latter; therefore, we used non-parametric tests (Kruskal-Wallis one-way analysis of variance (ANOVA)) to compare outcomes among arms. ANOVAs were used for ERP comparisons (effect sizes as eta-squared (η^2)). Proportions of ECD delays between arms were compared using χ^2 tests (effect sizes as Cramer's V).

As ELEs were normally distributed, covariate analyses were undertaken to determine if any ELEs were associated (independently of maternal intervention arm) with ECD outcomes using correlations, followed by independent sample t-tests for associations identified as significant. Effect sizes were quantified using Cohen's d and 95% CIs.[18] We used generalised linear regression analysis, adjusting for child sex and age at measurement, to determine exposures that predicted ECD outcomes at 2 years independent of other ELEs. Generalised linear models were selected for their utility when outcome variables (INTER-NDA and vision outcomes) were not normally distributed or when the relationship between the exposure (ELEs) and outcome was non-linear.

RESULTS

Of the 730 children eligible for testing at 2 years, complete INTER-NDA data were obtained for 667 children (91.4% of eligible population), vision data for 613 children (83.9%) and ERP data of sufficient quality for analysis for 123 children (16.8%) (figure 1). Across ECD outcomes, the mean proportional contribution by study arm and site were well balanced (online supplemental material S5).

Characteristics of study population

Prenatal, perinatal and postnatal characteristics of the ECD cohort are presented in table 1. The mean (±SD) age at assessment was 24.6 months (±0.94), with 48% (n=323) male. Mean

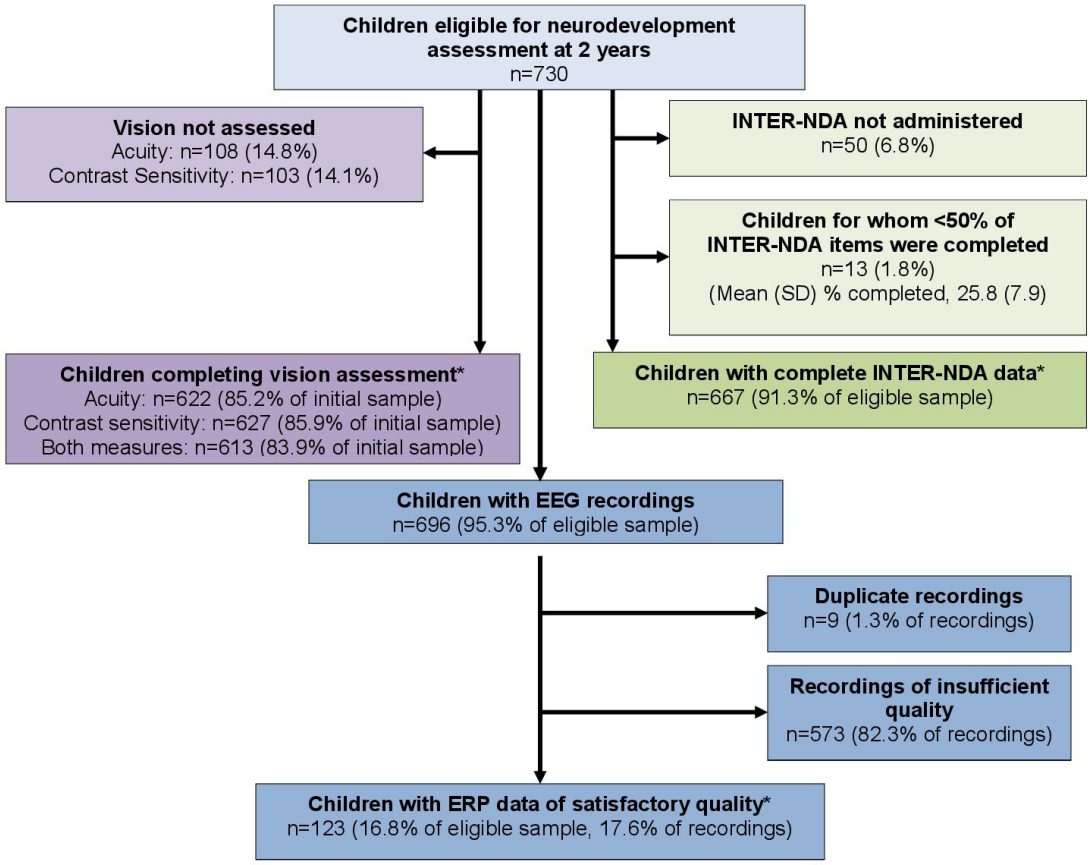

Figure 1 Participant flow. Consolidated Standards of Reporting Trials diagram. EEG, electroencephalogram; ERP, auditory evoked response potential; INTER-NDA, INTERGROWTH-21st Neurodevelopment Assessment. *Sample included in analyses.

Table 1 Sample characteristics

	Pooled cohort (n=667)	Arm 1 (n=217)	Arm 2 (n=230)	Arm 3 (n=220)	Unadjusted pairwise arm comparisons
Age at INTER-NDA assessment, month	24.6±0.9	24.4±0.8	24.4±0.8	24.±0.6	F=0.15, p=0.86
Perinatal characteristics					
Female	344 (51.6)	110 (50.7)	126 (54.8)	108 (49.1)	χ^2=1.56, p=0.46
Male	323 (48.4)	107 (49.3)	104 (45.2)	112 (50.9)	
Maternal age at birth, years	23.3±4.1	23.0±4.0	23.3±4.3	23.4±3.7	F=0.06, p=0.94
Parity					
Nulliparous	135 (20.2)	53 (24.4)	43 (18.7)	39 (17.7)	χ^2=12.76, p=0.24
1	190 (28.5)	63 (29.0)	62 (27.0)	65 (29.5)	
2	159 (23.8)	43 (19.8)	58 (25.2)	58 (26.4)	
3	78 (11.7)	21 (9.7)	30 (13.0)	27 (12.3)	
4	55 (8.2)	19 (8.8)	23 (10.0)	13 (5.9)	
5	28 (4.2)	10 (4.6)	5 (2.2)	13 (5.9)	
Missing	22 (3.3)	8 (3.7)	9 (3.9)	5 (2.7)	
Gestational age* at birth, week	39.2±4.2	39.1±2.2	39.2±1.5	39.4±7.0	F=0.25, p=0.78
Delivery Mode					
Normal	560 (84.0)	178 (82.0)	195 (84.8)	187 (85.0)	χ^2=3.93, p=0.42
Assisted†	6 (0.9)	3 (1.4)	0 (0)	3 (1.4)	
Caesarean section‡	101 (15.1)	36 (16.6)	35 (15.2)	30 (13.6)	
Postnatal health and growth					
Number of children admitted to hospital for ≥3 days in the first 2 years of life	45 (6.7)	19 (8.8)	14 (6.1)	12 (5.5)	χ^2=0.83, p=0.66
Breast fed at 6 months	663 (99.4)	216 (99.5)	227 (98.7)	220 (100.0)	χ^2=3.32, p=0.19
WAZ_{birth}	−1.11±0.92	−1.08±0.93	−1.09±0.92	−1.14±0.91	F=0.23, p=0.79
LAZ_{birth}	−1.06±1.10	−0.94±1.17	−1.07±1.04	−1.15±1.03	F=2.00, p=0.14
$HCAZ_{birth}$	−0.79±1.09	−0.74±1.10	−0.83±1.06	−0.78±1.10	F=0.37, p=0.69
WAZ_{12}	−1.50±1.19	−1.43±1.19	−1.55±1.17	−1.51±1.20	F=0.56, p=0.57
LAZ_{12}	−1.90±1.17	−1.80±1.13	−1.95±1.27	−1.96±1.10	F=1.30, p=0.27
$HCAZ_{12}$	−1.18±1.08	−1.19±1.10	−1.23±1.04	−1.11±1.11	F=0.73, p=0.49
WAZ_{24}	−1.76±1.11	−1.71±1.14	−1.81±1.08	−1.76±1.10	F=0.51, p=0.60
LAZ_{24}	−2.38±1.15	−2.30±1.13	−2.46±1.16	−2.39±1.15	F=1.03, p=0.36
$HCAZ_{24}$	−1.22±1.03	−1.26±1.08	−1.23±0.99	−1.18±1.01	F=0.28, p=0.76
Family environment					
Maternal education, years	4.5±4.2	4.6±4.5	4.7±4.1	4.2±4.0	F=0.47, p=0.62
Socio-economic status§	4.4±2.9	4.4±2.9	4.7±2.9	4.3±2.7	F=0.92, p=0.40
FCI: play activities§	5.5±2.0	5.5±2.1	5.6±1.8	5.4±1.9	F=0.32, p=0.73
FCI: varieties of play materials¶	4.4±1.7	4.4±1.6	4.4±1.7	4.3±1.7	F=0.71, p=0.49
FCI: sources of play materials¶	2.4±0.7	2.4±0.7	2.4±0.7	2.4±0.7	F=0.03, p=0.97
FCI: household books¶	0.3±0.8	0.4±0.9	0.3±0.7	0.3±0.8	F=0.47, p=0.63

Date presented as mean±SD or n (%).
Arm 1: preconception intervention; arm 2: prenatal intervention; arm 3: no intervention.
*Gestational age data not available for Democratic Republic of the Congo.
†Ventouse or forceps-assisted delivery.
‡Emergency or elective caesarean section.
§Socio-economic status tally provides the number of indicators available from the following list: electricity, improved water source, sanitation, synthetic flooring, improved cooking fuels, transportation and household assets.
¶Assessed at 24 months.
F, analysis of variance test statistic; FCI, family care indicators; $HCAZ_{birth}$, $HCAZ_{12}$, $HCAZ_{24}$, WHO z-scores for head circumference at birth, 12 and 24 months; INTER-NDA, INTERGROWTH-21st Neurodevelopment Assessment; LAZ_{birth}, LAZ_{12}, LAZ_{24}, WHO z-scores for length at birth, 12 and 24 months; WAZ_{birth}, WAZ_{12}, WAZ_{24}, WHO z-scores for weight at birth, 12 and 24 months.

maternal education was 4.5 years (±4.2) and 31.9% of the cohort met criteria for low socio-economic status (SES). Forty-five children (6.7%) spent ≥3 days in hospital during the first 2 years, and >99% were breast fed at 6 months.

Comparisons in ECD outcomes between study arms

The associations between ECD outcomes and study arm are presented in table 2. No differences in INTER-NDA, vision and ERP outcomes were detected among treatment arms.

Overall, high rates of cognitive and motor delays and negative behaviour problems were reported: 246 (36.9%), 506 (75.9%) and 379 (56.2%) children, respectively, scored in the INTER-NDA's range for severe delays in these domains; 444 (66.6%), 609 (91.3%) and 615 (92.2%) children scored in the range for *any* delay (table 2). Low VA and CS were reported in 24.0% and 19.3% of the cohort. Delays and behaviours did not consistently differ by maternal intervention arm.

Associations between ECD outcomes and early life exposures

After adjusting for infant sex, age at ECD assessment and multiple covariates (table 3), LAZ at 24 months was the only anthropometric variable that was significantly associated with ECD, including VA, gross motor, language (p<0.001 for all) and positive behaviour (p=0.01). Among other ELEs, maternal education was positively associated with vision, cognition, fine motor and language (p<0.001 for all); FCI (play activities) was associated with language (p<0.001) and SES was marginally

Table 2 All sites unadjusted treatment effects for ECD outcomes at 24 months of age

ECD outcome		Pooled cohort (n=667)	Arm 1 (n=217)	Arm 2 (n=230)	Arm 3 (n=220)	Unadjusted pairwise arm comparisons
INTER-NDA domain scores*, median (IQR)						
Cognitive		30.77 (23.10)	30.77 (25.60)	30.77 (20.50)	36.59 (23.10)	H=1.65, p=0.44 η^2<0.001
Language		50.00 (41.70)	47.22 (41.70)	47.22 (38.90)	51.52 (41.70)	H=2.82, p=0.24 η^2<0.001
Fine motor		11.11 (16.70)	11.11 (16.70)	11.11 (22.20)	11.11 (16.70)	H=0.09, p=0.96 η^2<0.001
Gross motor		11.11 (22.20)	11.11 (22.20)	22.22 (22.20)	22.22 (33.30)	H=0.54, p=0.76 η^2<0.001
Positive behaviour		90.00 (50.00)	100.00 (40.00)	100.00 (50.00)	90.00 (50.00)	H=5.05, p=0.08 η^2=0.004
Negative behaviour		100.00 (25.00)	100.00 (25.00)	100.00 (25.00)	100.00 (50.00)	H=3.44, p=0.18 η^2=0.002
Risk of severe delay/problems†¶, n (%)						
Cognitive		246 (36.9)	89 (41.0)	82 (35.6)	75 (34.1)	χ^2=3.81, p=0.43 Cramer's V=0.05
Language		37 (5.6)	17 (7.8)	9 (3.9)	11 (5.0)	χ^2=3.95, p=0.41 Cramer's V=0.06
Fine motor		506 (75.9)	164 (75.6)	170 (73.9)	172 (78.2)	χ^2=3.98, p=0.41 Cramer's V=0.06
Gross motor		506 (75.9)	166 (76.5)	178 (77.4)	162 (73.6)	χ^2=4.11, p=0.39 Cramer's V=0.06
Positive behaviour		49 (7.4)	15 (6.9)	18 (7.8)	16 (7.3)	χ^2=6.33, p=0.18 Cramer's V=0.07
Negative behaviour		379 (56.8)	136 (62.7)	123 (53.5)	120 (54.6)	χ^2=5.92, p=0.21 Cramer's V=0.07
Risk of *any* delay/problems‡**, n (%)						
Cognitive		444 (66.6)	150 (69.1)	156 (67.8)	138 (62.7)	χ^2=2.26, p=0.32 Cramer's V=0.06
Language		78 (11.7)	30 (13.8)	21 (9.1)	27 (12.3)	χ^2=2.49, p=0.29 Cramer's V=0.06
Fine motor		583 (87.4)	191 (88.0)	202 (87.8)	190 (86.4)	χ^2=0.33, p=0.85 Cramer's V=0.02
Gross motor		609 (91.3)	195 (89.9)	210 (91.3)	204 (92.7)	χ^2=1.13, p=0.56 Cramer's V=0.04
Positive behaviour		173 (25.9)	47 (21.7)	58 (25.2)	68 (30.9)	χ^2=4.96, p=0.08 Cramer's V=0.09
Negative behaviour		615 (92.2)	202 (93.1)	214 (93.0)	199 (90.5)	χ^2=1.40, p=0.50, Cramer's V=0.05
Vision, median (IQR)		(n=613)	(n=206)	(n=205)	(n=202)	
Visual acuity (logMar)		0.40 (0.20)	0.30 (0.20)	0.40 (0.30)	0.40 (0.10)	H=0.33, p=0.85 η^2=0.002
Contrast sensitivity (%)		3.00 (1.00)	3.00 (1.50)	3.00 (1.00)	3.00 (1.00)	H=0.11, p=0.95 η^2=0.003
Risk of low vision, n (%)						
Visual acuity		160 (24.0)	53 (24.4)	58 (25.2)	49 (22.3)	χ^2=0.70, p=0.71 Cramer's V=0.03
Contrast sensitivity		129 (19.3)	46 (21.2)	46 (20.0)	37 (16.8)	χ^2=1.54, p=0.46 Cramer's V=0.05
Cortical auditory ERPs: peak amplitudes (in µV)§, median (IQR)						
		(n=123)	(n=39)	(n=39)	(n=45)	
P1	Frequent	4.65 (4.36)	4.63 (3.84)	4.77 (4.68)	4.05 (3.18)	F=0.39, p=0.67 η^2=0.007
	Infrequent	3.57 (2.27)	3.29 (2.55)	3.96 (2.31)	3.56 (1.93)	F=0.89, p=0.41 η^2=0.015
	Novel	3.74 (2.55)	3.48 (3.07)	3.78 (2.25)	3.85 (2.30)	F=0.23, p=0.79 η^2=0.004
N2	Frequent	4.30 (8.67)	3.31 (3.24)	3.19 (2.20)	4.14 (3.53)	F=1.20, p=0.30 η^2=0.02
	Infrequent	2.81 (1.94)	3.34 (2.00)	2.39 (1.59)	2.62 (2.01)	F=2.69, p=0.07 η^2=0.04
	Novel	2.74 (1.98)	2.48 (2.06)	3.12 (1.30)	2.64 (2.38)	F=1.10, p=0.34 η^2=0.04

Continued

Table 2 Continued

ECD outcome		Pooled cohort (n=667)	Arm 1 (n=217)	Arm 2 (n=230)	Arm 3 (n=220)	Unadjusted pairwise arm comparisons
P3a	Frequent	3.68 (3.28)	3.52 (2.28)	3.90 (3.21)	3.09 (1.74)	F=1.14, p=0.32 η^2=0.02
	Infrequent	2.93 (1.58)	2.65 (1.43)	2.98 (1.64)	3.14 (1.60)	F=1.06, p=0.35 η^2=0.02
	Novel	2.82 (1.70)	3.03 (1.81)	2.64 (1.52)	2.77 (1.78)	F=0.53, p=0.59 η^2=0.009
Cortical auditory ERPs: latencies (in ms)§, median (IQR)						
P1	Frequent	180.73 (37.92)	183.42 (39.22)	181.26 (36.18)	176.23 (37.59)	F=0.40, p=0.67 η^2=0.007
	Infrequent	182.59 (34.01)	181.35 (33.42)	181.05 (32.70)	185.27 (36.57)	F=0.20, p=0.82 η^2=0.003
	Novel	190.16 (34.96)	189.59 (35.13)	181.97 (31.83)	197.65 (36.87)	F=2.11, p=0.13 η^2=0.034
N2	Frequent	294.29 (26.86)	293.13 (30.03)	291.14 (25.69)	297.40 (24.98)	F=0.59, p=0.55 η^2=0.01
	Infrequent	297.78 (30.60)	293.78 (33.91)	304.27 (27.89)	296.23 (29.62)	F=1.27, p=0.29 η^2=0.02
	Novel	298.60 (32.33)	293.89 (31.79)	294.22 (33.51)	306.90 (31.14)	F=2.25, p=0.11 η^2=0.04
P3a	Frequent	389.33 (32.07)	389.86 (36.77)	387.42 (29.82)	390.45 (30.54)	F=0.09, p=0.91 η^2=0.002
	Infrequent	389.32 (34.14)	396.31 (35.55)	392.44 (33.87)	380.08 (32.14)	F=2.64, p=0.08 η^2=0.04
	Novel	387.57 (34.31)	381.68 (34.26)	394.94 (33.71)	386.03 (34.81)	F=1.52, p=0.22 η^2=0.03

Arm 1: preconception intervention; arm 2: prenatal intervention; arm 3: no intervention.
*For all INTER-NDA outcomes, except negative behaviour, higher scores reflect better outcomes.
†For all INTER-NDA outcomes, except negative behaviour, high and *any* risk of delay are defined as domain scores ≤3rd and ≤10th centiles on the INTER-NDA standards, respectively. For negative behaviour, high and *any* risk of problems are defined as domain scores ≥97th and ≥90th centiles on the INTER-NDA standards, respectively.
‡For all INTER-NDA outcomes, except negative behaviour, mild-to-moderate risk of delay is defined as domain scores between the 3rd and 10th centiles on the INTER-NDA standards. For negative behaviour, mild-to-moderate risk of delay is defined as domain scores between the 90th and 97th centiles on the INTER-NDA standards.
§ERP values presented are averaged across the four temporal electrodes (T3–T6).
¶Comparisons made between arms for children with no delay versus mild-to-moderate delay versus severe delay.
**Comparisons made between arms for children with any delay versus no delay. η^2=eta square.
ECD, early child development; ERP, evoked response potentials; INTER-NDA, INTERGROWTH-21st Neurodevelopment Assessment; logMar, logarithm of the minimum angle of resolution.

associated with cognition, fine motor and positive behaviour ($p<0.05$).

Correlations between ECD outcomes and ELEs are presented in online supplemental material S6. Anthropometry z-scores (length, weight and head circumference), SES and play activities (FCI) were positively correlated with all vision and INTER-NDA outcomes. Only 3% (n=11/360) of associations between ERP outcomes and ELEs studied were significant, with no clear pattern of association detected; hence, further analyses were not undertaken. Comparisons of ELEs in children with low vision, and *any* INTER-NDA delay, are presented in online supplemental material S7. Higher maternal age at birth, lower anthropometry z-scores and lower SES, FCI and years of maternal schooling were associated with low VA and CS scores. Effect sizes were small to moderate for all associations (d=0.20–0.45) except for maternal schooling (d=0.99).

Lower anthropometry z-scores at all time points were associated with cognitive delay with moderate effect sizes (d=0.3–0.7). Lower LAZ_{24} and FCI were significantly associated with delays across all INTER-NDA domains. Lower $LAZ_{12,}$ $WAZ_{12\&24}$ and $HCAZ_{12}$ were also significantly associated with delays across all INTER-NDA domains except behaviour problems. Where domains were associated with serial growth measurements, effect sizes increased as children aged. For example, for cognitive delay, LAZ effect sizes were 0.31, 0.56 and 0.69 at 0, 12 and 24 months, respectively. Similar patterns were observed for weight, and for gross motor, fine motor and language delays (online supplemental material S7).

DISCUSSION

To our knowledge, this is the first multicentre RCT to examine the effect of preconception maternal nutrition supplementation on comprehensive ECD outcomes using a standardised ECD measure developed specifically for LMICs. Our key finding was that the benefits of the maternal intervention previously reported for fetal[9] and postnatal growth[8] did not extend to gains in ECD scores or to reduced rates of ECD delays at 2 years among the offspring of mothers who received nutritional supplementation. Linear growth status at 24 months was a significant predictor of scores in several domains, including vision (VA), language, gross motor and positive behaviour. Additionally, indicators of family environment (play activities and play materials) and SES predicted several ECD scores, although differential associations existed between these and ECD domains. Notably, maternal education was a consistent and potent predictor for several domain scores, including vision (VA and CS), cognitive, language and fine motor. High rates of cognitive and motor delays and negative behaviours were observed, as expected in low-resource populations with rates of child stunting≥60%[19 20]; delayed ECD and stunting share many drivers.

Our findings differ only slightly from those of the preconceptual micronutrient supplementation trial (PRECONCEPT) from Vietnam, the only other RCT to report the effects of preconception maternal supplementation on child growth and ECD.[21] PRECONCEPT reported small group differences favouring preconception iron-folate supplementation for fine motor development (effect size 1.3 SD; 95% CI 0.05 to 0.77), but not for

Table 3 Adjusted comparisons: early life exposures as predictors of ECD outcomes at 24 months of age

ECD outcome		Unstandardised coefficients		Standardised coefficients			95% CI	
		Beta	SE	Beta	t	P value	Lower bound	Upper bound
Visual acuity (n=622)								
	Constant	0.34	0.31		1.11	0.27	−0.26	0.95
	Sex	−0.01	0.01	−0.06	−1.26	0.21	−0.04	0.01
	Age at ECD assessment, months	−0.02	0.01	−0.09	2.18	0.03*	−0.03	0.00
	Maternal age at birth, years	0.00	0.00	−0.07	1.46	0.15	0.00	0.01
	Parity	0.00	0.00	0.02	−0.34	0.73	−0.01	0.01
	Gestational age at birth, weeks	0.00	0.00	−0.06	−1.48	0.14	0.00	0.00
	LAZ_{12}	−0.01	0.00	−0.15	1.57	0.12	0.00	0.01
	LAZ_{24}**	−0.01	0.00	−0.31	−2.94	<0.001**	−0.02	0.00
	WAZ_{12}	0.00	0.01	−0.02	−0.20	0.84	−0.02	0.02
	WAZ_{24}	−0.01	0.01	−0.12	1.18	0.24	−0.01	0.03
	$HCAZ_{birth}$	0.00	0.01	−0.05	0.90	0.37	−0.01	0.01
	$HCAZ_{12}$	−0.01	0.01	−0.16	−1.58	0.11	−0.03	0.00
	$HCAZ_{24}$	−0.01	0.01	−0.12	1.19	0.24	−0.01	0.03
	SES	0.00	0.00	−0.03	−0.56	0.57	−0.01	0.00
	Maternal education, years	−0.01	0.00	−0.41	−7.95	<0.001**	−0.01	−0.01
	FCI: play activities	0.00	0.00	−0.01	−0.24	0.81	−0.01	0.01
	FCI: household books	0.00	0.01	−0.02	−0.37	0.71	−0.02	0.01
Contrast sensitivity (n=627)	Constant	2.70	2.36		1.14	0.26	−1.95	7.34
	Sex	−0.06	0.09	−0.03	−0.63	0.53	−0.23	0.12
	Age at ECD assessment, months	−0.05	0.05	0.04	0.86	0.39	−0.06	0.15
	Maternal age at birth, years	−0.01	0.01	0.02	0.60	0.55	−0.01	0.03
	LAZ_{birth}	−0.02	0.03	0.03	0.63	0.53	−0.04	0.07
	LAZ_{12}	−0.01	0.03	0.01	0.17	0.87	−0.06	0.07
	LAZ_{24}	−0.01	0.03	−0.04	−0.38	0.70	−0.06	0.04
	WAZ_{12}	−0.03	0.08	−0.03	−0.38	0.70	−0.20	0.13
	WAZ_{24}	−0.01	0.08	−0.01	−0.07	0.95	−0.16	0.15
	$HCAZ_{birth}$	−0.04	0.04	−0.05	−0.85	0.40	−0.12	0.05
	$HCAZ_{12}$	−0.04	0.06	−0.05	−0.63	0.53	−0.16	0.08
	HAZ_{24}	−0.05	0.06	−0.06	0.76	0.45	−0.07	0.16
	SES	−0.00	0.02	−0.01	0.10	0.92	−0.04	0.04
	Maternal education, years	−0.10	0.01	−0.40	−8.82	<0.001**	−0.12	−0.08
	FCI: varieties of play materials	−0.02	0.03	−0.02	0.47	0.64	−0.05	0.08
	FCI: play activities	−0.03	0.02	−0.05	−1.24	0.22	−0.08	0.02
	FCI: household books	−0.03	0.06	−0.02	−0.49	0.63	−0.15	0.09
Cognition (n=667)	Constant	82.66	43.42		1.90	0.06	−2.67	168.00
	Sex	−3.08	1.51	−0.09	−2.04	0.04*	−6.06	−0.11
	Age at ECD assessment, months	1.94	1.03	0.08	1.88	0.06	−0.09	3.97
	Parity	−0.52	0.56	−0.04	0.92	0.36	−0.59	1.62
	Gestational age at birth, week	0.24	0.17	0.06	−1.43	0.16	−0.09	0.44
	LAZ_{birth}	0.14	0.60	0.02	0.24	0.82	−1.04	1.33
	LAZ_{12}	0.05	0.54	0.01	0.08	0.94	−1.02	1.11
	LAZ_{24}	0.79	0.49	0.17	−1.63	0.10	−0.16	1.74
	WAZ_{birth}	1.27	3.21	0.03	0.39	0.69	−5.05	7.58
	WAZ_{12}	0.80	1.43	0.05	0.56	0.58	−2.02	3.61
	WAZ_{24}	1.09	1.37	0.08	−0.79	0.43	−3.77	1.60
	$HCAZ_{birth}$	0.63	0.76	0.05	−0.83	0.41	−2.11	0.86
	$HCAZ_{12}$	0.08	1.05	0.01	0.07	0.94	−1.98	2.13
	$HCAZ_{24}$	0.14	1.06	0.01	0.13	0.90	−1.94	2.21
	SES	0.68	0.33	0.10	−2.03	0.04*	0.02	1.34
	Maternal education, years	1.09	0.20	0.28	−5.63	<0.001*	0.71	1.48
	FCI: varieties of play materials	1.03	0.56	0.09	−1.84	0.07	0.07	2.14
	FCI: play activities	0.53	0.39	0.06	−1.36	0.18	0.24	1.29
	FCI: household books	0.32	1.03	0.01	−0.31	0.76	1.71	2.35
Fine motor (n=667)	Constant	−1.02	1.36	−0.03	−0.75	0.46	−3.70	1.66
	Sex	0.59	0.81	0.03	0.72	0.47	−1.01	2.19
	Age at ECD assessment, months	0.53	0.45	0.10	1.19	0.24	−0.35	1.41
	LAZ_{12}	0.82	0.41	0.18	−2.02	0.04*	0.02	1.62

Continued

Table 3 Continued

ECD outcome		Unstandardised coefficients		Standardised coefficients			95% CI	
		Beta	SE	Beta	t	P value	Lower bound	Upper bound
	LAZ_{24}	0.00	1.31	0.00	0.00	1.00	−2.57	2.57
	WAZ_{12}	0.83	1.20	0.06	−0.69	0.49	−1.53	3.49
	WAZ_{24}	0.43	0.90	0.04	−0.47	0.64	−2.20	1.35
	$HCAZ_{12}$	0.18	0.91	0.02	0.19	0.85	−1.61	1.96
	$HCAZ_{24}$	0.12	0.28	0.02	−0.45	0.66	−0.66	0.42
	SES	1.14	0.52	0.11	−2.19	0.03*	0.12	2.16
	Maternal education, years	1.14	0.36	0.14	−3.18	<0.001**	0.44	1.83
	FCI: varieties of play materials	0.11	1.03	0.00	0.10	0.92	−1.92	2.13
	FCI: play activities	0.50	0.85	0.02	−0.59	0.56	−2.16	1.16
	FCI: sources of play materials	1.02	1.36	0.03	−0.75	0.46	−3.70	1.66
	FCI: household books	0.59	0.81	0.03	0.72	0.47	−1.01	2.19
Gross motor (n=667)	Constant	148.70	48.52		3.06	0.00	53.41	243.99
	Sex	−1.85	1.79	−0.04	−1.03	0.30	−5.37	1.67
	Age at ECD assessment, months	2.03	1.07	0.08	−1.90	0.06	−0.07	4.13
	LAZ_{birth}	0.68	0.69	0.07	0.98	0.33	−0.68	2.04
	LAZ_{12}	0.62	0.62	0.09	1.00	0.32	−0.59	1.83
	LAZ_{24}	1.71	0.54	0.29	−3.18	<0.001**	0.65	2.77
	WAZ_{birth}	6.23	3.48	0.11	−1.79	0.07	−0.59	13.62
	WAZ_{12}	0.80	1.73	0.04	0.46	0.65	−2.60	4.19
	WAZ_{24}	1.19	1.59	0.07	−0.75	0.46	−4.30	1.93
	$HCAZ_{12}$	1.15	1.19	0.08	0.96	0.34	−1.20	3.49
	$HCAZ_{24}$	0.74	1.20	0.05	−0.61	0.54	−3.09	1.62
	SES	0.34	0.36	0.05	−0.95	0.35	−1.04	0.36
	FCI: varieties of play materials	1.20	0.62	0.09	−1.95	0.05	−0.01	2.42
	FCI: play activities	0.65	0.47	0.06	−1.39	0.16	−0.27	1.57
Language (n=667)	Constant	244.77	52.44		4.67	0.00	141.71	347.82
	Sex	−7.11	1.93	−0.15	−3.69	<0.001**	−10.90	−3.32
	Age at ECD assessment, months	2.02	1.32	0.06	−1.53	0.13	−0.48	4.61
	Gestational age at birth, week	0.12	0.21	0.02	−0.58	0.57	−0.54	0.29
	LAZ_{12}	1.08	0.67	0.13	1.60	0.11	−0.25	2.40
	LAZ_{24}	2.19	0.60	0.34	−3.65	<0.001**	1.01	3.37
	WAZ_{12}	0.45	1.81	0.02	−0.25	0.80	−4.02	3.11
	WAZ_{24}	0.41	1.62	0.02	0.25	0.80	−2.77	3.58
	$HCAZ_{birth}$	0.87	0.78	0.05	−1.12	0.27	−0.66	2.40
	$HCAZ_{12}$	0.43	0.86	0.03	0.50	0.62	−1.26	2.12
	Maternal education, years	2.32	0.21	0.44	−10.82	<0.001**	1.90	2.74
	FCI: play activities	1.63	0.46	0.14	−3.52	<0.001**	0.72	2.54
	FCI: household books	2.23	1.28	0.07	−1.74	0.08	−0.29	4.75
Positive behaviour (n=667)	Constant	−27.63	43.47		−0.64	0.53	−112.99	57.73
	Sex	1.23	2.18	0.02	0.57	0.57	−3.05	5.52
	Age at ECD assessment, months	0.74	1.38	0.02	0.54	0.59	−1.96	3.45
	LAZ_{12}	0.53	0.67	0.06	−0.80	0.42	−1.84	0.77
	LAZ_{24}	1.37	0.56	0.18	2.46	0.01*	0.28	2.46
	SES	1.03	0.46	0.11	2.27	0.02*	0.14	1.93
	FCI: varieties of play materials	1.26	0.87	0.08	1.45	0.15	−0.45	2.95
	FCI: play activities	0.21	0.60	0.02	−0.34	0.73	−1.38	0.97
	FCI: sources of play materials	2.63	1.75	0.06	1.51	0.13	−0.80	6.07
Negative behaviour (n=667)	Constant	−41.72	41.55		−1.00	0.32	−123.31	39.88
	Sex	2.27	2.13	0.04	1.07	0.29	−1.91	6.45
	Age at ECD assessment, months	−2.62	1.32	−0.08	1.98	0.05	−0.02	−5.22
	LAZ_{24}	−0.61	0.30	−0.08	2.01	0.05	−0.02	−1.20
	FCI: varieties of play materials	−1.50	0.69	−0.09	2.18	0.03*	−0.15	2.85

The SES tally provides the number of indicators available from the following list: electricity, improved water source, sanitation, synthetic flooring, improved cooking fuels, transportation and household assets.
*P<0.05, **p<0.001.
ECD, early child development; F, analysis of variance test statistic; FCI, family care indicators; $HCAZ_{birth}$, $HCAZ_{12}$, $HCAZ_{24}$, WHO z-scores for head circumference at birth, 12 and 24 months; LAZ_{birth}, LAZ_{12}, LAZ_{24}, WHO z-scores for length at birth, 12 and 24 months; SES, socio-economic status; WAZ_{birth}, WAZ_{12}, WAZ_{24}, WHO z-scores for weight at birth, 12 and 24 months.

other ECD domains at 2 years, or for any ECD outcomes at 1 year, despite gains in LAZ and lower rates of stunting at 2 years.[21] A prenatal and postnatal maternal multiple micronutrient supplement (MMS) trial from Bangladesh found no impact of maternal supplementation on children's cognitive and motor scores at 2 years.[22] Likewise, a meta-analysis of prenatal MMS trials from LMICs (88 057 women) concluded that prenatal MMS did not lead to a consistent cognitive benefit for children.[23]

It is not clear why previously reported early gains in length and weight following maternal supplementation are not consistently associated with ECD benefits for children.[21 23 24] One reason may be because extant maternal supplementation trials were powered to detect differences in child growth and that larger sample sizes are required to detect differences in ECD outcomes.[23] It is also possible that ECD measures developed for high-income countries may not be sensitive indicators for LMICs.[25] Nevertheless, in our study, even with the use of the INTER-NDA designed specifically for LMICs, we did not detect treatment effects. Some ECD effects may remain latent and manifest at older ages.[21] Additionally, as a screening tool, the INTER-NDA is not intended to detect subtle differences. Although in the WF trial maternal supplementation was associated with improved fetal[9] and postnatal growth,[10] multiple critical aspects of neurological maturation occur postnatally and are influenced by environmental factors, many of which differ among settings.[26] Finally, although poor compliance with the maternal intervention could theoretically explain the lack of ECD differences between arms, overall compliance was ≥80%.[9] The improved birth and postnatal anthropometry reported for both intervention arms (compared with controls) make this explanation unlikely.

Our findings of the associations between general family environment, particularly maternal education and SES, the provision of stimulating environments (as assessed by FCI) and better ECD outcomes are consistent with previous reports[27–29] and emphasise the importance of socio-environmental determinants in addition to biomedical determinants on long-term neurodevelopment.[30 31]

Key strengths of our study are the multicentre design in low-resource populations from four geographically and culturally distinct LMICs; incorporation of measures of vision and cortical auditory processing in ECD measurements; the use of the INTER-NDA and its international ECD standards and our adoption of a LMIC-centric approach to assessment (viz, low cost, rapid assessment time and non-reliance on specialists for administration).

Study limitations include sample size that was insufficient for intersite comparisons within arms. The diverse sites' heterogeneity[20] may have masked treatment-arm effects. The number of auditory ERP assessments of suitable quality for analyses was small due to the technical challenges of collecting high-quality recordings in these field conditions. Our experience emphasises the need for more refined, low-cost tools suitable for large-scale implementation in field settings.

CONCLUSION

In our study, maternal nutrition supplementation initiated either before or early in pregnancy and discontinued at delivery did not improve cognitive, language, gross motor, fine motor, positive or negative behaviour scores; VA or CS scores; or auditory ERP markers in children aged 2 years from diverse low-resource settings. These findings emphasise that a maternal nutritional intervention strategy alone was insufficient to demonstrate positive gains in young children's development. Rather, multiple socio-environmental factors, including family environment, maternal education and children's postnatal linear growth, were positively associated with ECD outcomes.

Author affiliations
[1]MRC Lifecourse Epidemiology Centre and Human Development and Health Academic Unit, University of Southampton Faculty of Medicine, Southampton, UK
[2]Nuffield Department of Women's and Reproductive Health, John Radcliffe Hospital, University of Oxford, Oxford, UK
[3]Oxford Maternal and Perinatal Health Institute, Green Templeton College, University of Oxford, Oxford, UK
[4]Pediatrics, Section of Nutrition, University of Colorado Anschutz Medical Campus School of Medicine, Aurora, Colorado, USA
[5]Kinshasa School of Public Health, Kinshasa, The Democratic Republic of the Congo
[6]The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, North Carolina, USA
[7]Instituto de Nutricion de Centroamerica y Panama, Guatemala, Guatemala
[8]Community Health Sciences, Aga Khan University, Karachi, Sindh, Pakistan
[9]Columbia University, New York, New York, USA
[10]KLE Academy of Higher Education and Research (Deemed-to-be-University) Jawaharlal Nehru Medical College, Belagavi, Karnataka, India
[11]Thomas Jefferson University, Philadelphia, Pennsylvania, USA
[12]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, Maryland, USA
[13]RTI International, Durham, North Carolina, USA

Twitter Michelle Fernandes @DR_MCFernandes

Acknowledgements The Women First Maternal Preconception Nutrition Trial Study Group consists of the following additional members: Carl L Bose (University of North Carolina, Chapel Hill, NC, USA); neurodevelopment assessors: Aura Arevalo, Gelen Gomez, and Marta Lidia Aguilar (INCAP, Guatemala); Zahid Abbasi, Sumera Ali and Sumaira Fatima (AKU, Pakistan); Deepa Metgud and Spurthi Mastiholi (JNMC, India); Robert Kpado, Croco Gbenge, Matthieu Gbozo, Philippe Zolia, Papy Fakadanga, and Joel Eay (KSPH, DRC); Vanessa R Thorsten, Dhuly Chowdhury, Abhik Das, and Kristen Stolka (RTI International, Durham, NC, USA); and Omrana Pasha (AKU, Pakistan).

Collaborators The Women First Maternal Preconception Nutrition Trial Study Group consists of the following additional members: Carl L. Bose (CLB) (University of North Carolina, Raleigh, North Carolina, USA); neurodevelopment assessors: Aura Arevalo (AA), Galen Gomez (GG) and Marta Lidia Aguilar (MLA) (INCAP, Guatemala); Zahid Abbasi (ZA), Sumaira Fatima (SF) (AKU, Pakistan); Deepa Metgud (DM) and Spurthi Mastiholi (SM) (JNMC, India); Robert Kpado (RK), Croco Bgenge (CB), Matthieu Gbozo (MG), PhilippeZolia (PZ), Papy Fakadanga (PF) and Joel Eay (JE) (KSPH, DRC); Vanessa R.Thorsten (VRT), Dhuly Chowdhury (DC), Abhik Das (AD) and Kristen Stolka (KS) (RTI International, Durham, North Carolina, USA) and Omrana Pasha (OP) (AKU, Pakistan).

Contributors NFK, MF and MH conceived and designed the study; MF, NFK and JW wrote the final protocol in collaboration with all members of the trial group (AT, AL, MB, ALG, LF, SS, SAA, RLG, SSG, SMD, RJD, MK-T, AS, EMMcC and members of the Women First Preconception Nutrition Trial Group listed above); MF provided expert training to research assessors in each site; AT, AL, ALG, LF, SS, SAA, SSG and SMD coordinated implementation of the study at the country level; NFK, CLB, RLG and RJD provided overall supervision of study conduct; AA, GG, MLA, ZA, SA, SF, SM, RK, CG, MG, PZ, PF and JE performed developmental assessments; MF and NFK drafted the manuscript with critical input from all authors for subsequent revisions; JFK supported data base management and statistical analyses; MF, AS, EMMcC, DC, VRT and AD provided statistical analyses. All authors read and approved the final version of the manuscript. NFK acts as guarantor for the manuscript.

Funding The Thrasher Research Foundation funded this study; the Bill & Melinda Gates Foundation, the Eunice Kennedy Shriver National Institutes of Child Health and Human Development and the NIH Office of Dietary Supplements funded the primary Women First trial. MF is supported by a Clinical Research Training Fellowship from the Medical Research Council, UK.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The Women First trial was approved by the Colorado Multiple Institutional Review Board (#13-2160); Comité de Ética Universidad Francisco Marroquin (CE-FM/UFM 059-17, Guatemala); JNMC Institutional Ethics Committee on Human Subjects Research and the Indian Council of Medical Research (KAHER/EC/2018-19/D3017, India); Comité D'Ethique, Ecole De Sante Publique, University of Kinshasa (ES/CE/102B/14, Democratic Republic of the Congo); the Aga Khan

University Ethical Review Committee (2753-CHS-ERC-13, Pakistan) and RTI International (North Carolina, USA). Mothers provided written informed consent for themselves and their children.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available on reasonable request. On publication of study findings, de-identified study data will be available through the NICHD Data and Specimen Hub (N-DASH) at https://dash.nichd.nih.gov.

ORCID iDs
Michelle Fernandes http://orcid.org/0000-0002-0051-3389
Jamie Westcott http://orcid.org/0000-0002-0549-3145
Sarah Saleem http://orcid.org/0000-0002-6797-8631

REFERENCES

1 Black MM, Walker SP, Fernald LCH, *et al*. Early childhood development coming of age: science through the life course. *The Lancet* 2017;389:77–90.
2 Black MM, Behrman JR, Daelmans B, *et al*. The principles of nurturing care promote human capital and mitigate adversities from preconception through adolescence. *BMJ Glob Health* 2021;6:e004436.
3 Walker SP, Wachs TD, Gardner JM, *et al*. Child development in developing countries 2-child development: risk factors for adverse outcomes in developing countries. *Lancet* 2007;369.
4 Fernandes M, Villar J, Stein A, *et al*. INTERGROWTH-21st project international INTER-NDA standards for child development at 2 years of age: an international prospective population-based study. *BMJ Open* 2020;10:e035258.
5 King JC. A summary of pathways or mechanisms linking preconception maternal nutrition with birth outcomes. *The Journal of Nutrition* 2016;146:1437S–1444S.
6 Grantham-McGregor S, Cheung YB, Cueto S, *et al*. Developmental potential in the first 5 years for children in developing countries. *The Lancet* 2007;369:60–70.
7 Belfort MB, Rifas-Shiman SL, Sullivan T, *et al*. Infant growth before and after term: effects on neurodevelopment in preterm infants. *Pediatrics* 2011;128:e899–906.
8 Krebs NF, Hambidge KM, Westcott JL, *et al*. Growth from birth through six months for infants of mothers in the "women first" preconception maternal nutrition trial. *J Pediatr* 2021;229:S0022-3476(20)31165-3:199–206.:.
9 Hambidge KM, Westcott JE, Garcés A, *et al*. A multicountry randomized controlled trial of comprehensive maternal nutrition supplementation initiated before conception: the women first trial. *Am J Clin Nutr* 2019;109:457–69.
10 Krebs NF, Hambidge KM, Westcott JL, *et al*. Birth length is the strongest predictor of linear growth status and stunting in the first 2 years of life after a preconception maternal nutrition intervention: the children of the women first trial. *The American Journal of Clinical Nutrition* 2022;116:86–96.
11 Krebs N, Hambidge M, Westcott J, *et al*. Neurodevelopment scores at 24 months are associated with maternal education, home environment, and linear growth in offspring of the women first trial. *Current Developments in Nutrition* 2022;6:585.
12 Hambidge KM, Krebs NF, Westcott JE, *et al*. Preconception maternal nutrition: a multi-site randomized controlled trial. *BMC Pregnancy Childbirth* 2014;14:111.
13 World Health Organization. *The WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-height and body mass index-for-age. Methods and development*. Geneva: WHO, 2006.
14 Hamadani JD, Tofail F, Hilaly A, *et al*. Use of family care indicators and their relationship with child development in Bangladesh. *J Health Popul Nutr* 2010;28:23–33.
15 Adoh TO, Woodhouse JM. The Cardiff acuity test used for measuring visual acuity development in toddlers. *Vision Res* 1994;34:555–60.
16 Adoh TO, Woodhouse JM, Oduwaiye KA. The Cardiff test: a new visual acuity test for toddlers and children with intellectual impairment. A preliminary report. *Optom Vis Sci* 1992;69:427–32.
17 Kihara M, Hogan AM, Newton CR, *et al*. Auditory and visual novelty processing in normally-developing Kenyan children. *Clin Neurophysiol* 2010;121:564–76.
18 Cohen J. A coefficient of agreement for nominal scales. *Educational and Psychological Measurement* 1960;20:37–46.
19 Vaivada T, Akseer N, Akseer S, *et al*. Stunting in childhood: an overview of global burden, trends, determinants, and drivers of decline. *The American Journal of Clinical Nutrition* 2020;112:777S–791S.
20 Gil JD, Ewerling F, Ferreira LZ, *et al*. Early childhood suspected developmental delay in 63 low- and middle-income countries: large within- and between-country inequalities documented using National health surveys. *J Glob Health* 2020;10:010427.
21 Nguyen PH, Gonzalez-Casanova I, Young MF, *et al*. Preconception micronutrient supplementation with iron and folic acid compared with folic acid alone affects linear growth and fine motor development at 2 years of age: a randomized controlled trial in Vietnam. *The Journal of Nutrition* 2017;147:1593–601.
22 Christian P, Kim J, Mehra S, *et al*. Effects of prenatal multiple micronutrient supplementation on growth and cognition through 2 Y of age in rural Bangladesh: the jivita-3 trial. *The American Journal of Clinical Nutrition* 2016;104:1175–82.
23 Devakumar D, Fall CHD, Sachdev HS, *et al*. Maternal antenatal multiple micronutrient supplementation for long-term health benefits in children: a systematic review and meta-analysis. *BMC Med* 2016;14:90.
24 Nguyen PH, Young MF, Tran LM, *et al*. Preconception micronutrient supplementation positively affects child intellectual functioning at 6 Y of age: a randomized controlled trial in Vietnam. *Am J Clin Nutr* 2021;113:1199–208.
25 Fernandes M, Stein A, Newton CR, *et al*. The INTERGROWTH-21st project neurodevelopment package: a novel method for the multi-dimensional assessment of neurodevelopment in pre-school age children. *PLoS ONE* 2014;9:e113360.
26 Clark H, Coll-Seck AM, Banerjee A, *et al*. A future for the world's children? A WHO–UNICEF–lancet Commission. *The Lancet* 2020;395:605–58.
27 Duncan GJ, Magnuson K, Votruba-Drzal E. Boosting family income to promote child development. *Future Child* 2014;24:99–120.
28 Conger KJ, Rueter MA, Conger RD. The role of economic pressure in the lives of parents and their adolescents: the family stress model. In: Crockett LJ, Silbereisen RK, eds. *Negotiating adolescence in times of social change*. Cambridge University Press, 2000.
29 Jeong J, McCoy DC, Fink G. Pathways between paternal and maternal education, caregivers' support for learning, and early child development in 44 low- and middle-income countries. *Early Childhood Research Quarterly* 2017;41:136–48.
30 Prado EL, Alcock KJ, Muadz H, *et al*. Maternal multiple micronutrient supplements and child cognition: a randomized trial in Indonesia. *Pediatrics* 2012;130:e536–46.
31 Richter LM, Daelmans B, Lombardi J, *et al*. Investing in the foundation of sustainable development: pathways to scale up for early childhood development. *Lancet* 2017;389:103–18.