

Neurodevelopment, Vision, and Auditory Outcomes at Age 2 Years in Offspring of Participants in the “Women First” Maternal Preconception Nutrition Randomized Controlled Trial

Michelle Fernandes^{‡1,2,3}, Nancy F Krebs^{‡4}, Jamie E Westcott⁴, Antoinette Tshetu⁵, Adrien Lokangaka⁵, Melissa Bauserman⁶, Ana Garcés⁷, Lester Figueroa⁷, Sarah Saleem⁸, Sumera A Ali⁸, Robert L Goldenberg⁹, Shivaprasad S Goudar¹⁰, Sangappa M Dhaded¹⁰, Richard J Derman¹¹, Jennifer F Kemp⁴, Marion Koso-Thomas¹², Amaanti Sridhar¹³, Elizabeth M McClure¹³, and K Michael Hambidge⁴, and the Women First Preconception Nutrition Trial Study Group

[‡]Designates shared first authorship

¹MRC Lifecourse Epidemiology Centre and Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, Southampton, UK

²Nuffield Department of Women’s and Reproductive Health, John Radcliffe Hospital, University of Oxford, Oxford, UK

³Department of Neonatology, Princess Anne Hospital, University Hospitals Southampton NHS Foundation Trust, Southampton, UK

⁴Department of Pediatrics, Section of Nutrition, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

⁵Kinshasa School of Public Health (KSPH), Kinshasa, Democratic Republic of the Congo

⁶University of North Carolina, Chapel Hill, NC, USA

⁷Instituto de Nutrición de Centro América y Panamá (INCAP), Guatemala City, Guatemala

⁸Aga Khan University, Karachi, Pakistan

⁹Columbia University, New York, NY, USA

¹⁰KLE Academy of Higher Education and Research (Deemed-to-be-University) Jawaharlal
Nehru Medical College, Belagavi, India

¹¹Thomas Jefferson University, Philadelphia, PA, USA

¹²National Institute of Child Health and Human Development/NIH, Bethesda, MD, USA

¹³RTI International, Durham, NC, USA

Correspondence to:

Dr. Michelle Fernandes, MRC Lifecourse Epidemiology Centre, University of Southampton,
Southampton SO16 6YD, UK.

E: m.c.fernandes@soton.ac.uk

@Dr_MCFernandes

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- and middle-income countries (LMIC) 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 multi-country, individually randomized trial.

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

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

Intervention: Maternal lipid-based nutrient supplement (LNS) 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 behavior 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 (LAZ₂₄), 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

LAZ₂₄ predicted ECD. Interventions addressing multiple components of the nurturing care model may offer greatest impact on children's developmental potential.

Trial Registration: ClinicalTrials.gov #NCT01883193;

<https://clinicaltrials.gov/ct2/show/NCT01883193?term=01883193&rank=1>

Key Words: Early child development, INTER-NDA, developmental delay, maternal nutrition, preconception nutrition, linear growth, family environment, lipid nutrient supplement (LNS)

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.¹
- 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 behavior scores; visual acuity and contrast sensitivity scores; and auditory evoked response potentials markers in 2-year-old children 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 multi-domain, rapid, low-cost ECD assessment tool designed for low resource settings.

How this study might affect research, practice or policy

- Our study emphasizes that a single nutritional strategy, i.e., preconception and prenatal maternal nutrition supplementation, is insufficient to demonstrate positive gains in young children's development. Rather, a multi-sectoral approach is needed to maximize 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.²⁻⁴ While numerous early life exposures (ELEs) are associated with delays in early childhood development (ECD),⁵ four key risk factors (stunting, iodine deficiency, iron deficiency anemia, and inadequate cognitive stimulation) have been identified by the Lancet's International Child Development Steering Group as urgent needs for intervention globally.⁴ Three of these relate specifically to maternal and child nutrition.⁴

Evidence from both preclinical and human studies indicate that pre- or periconception maternal nutritional status influence fetal growth and development, with life course effects on health and neurocognitive function.⁶ Strong associations between intra- and extra-uterine growth, and ECD, have been demonstrated across disparate populations,^{7 8} so that, in some comparisons, childhood stunting is considered a proxy for neurodevelopmental risk.⁷ 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.⁹

The "Women First" Preconception Maternal Nutrition Trial (WF) was undertaken in four countries with high rates of childhood stunting.¹ 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).¹⁹⁻¹⁰ WF is the first multi-country RCT to (i) examine associations between preconception maternal nutrition and ECD outcomes in four geographically and culturally disparate LMIC populations; (ii) measure neurocognitive outcomes using a comprehensive, rapid, low-cost ECD assessment (INTERGROWTH-21st Project Neurodevelopment Assessment; INTER-NDA);⁵ (iii) categorize 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, TX).¹¹

The primary WF trial was a multisite, individually randomized clinical trial of a daily 22-micronutrient fortified small-quantity lipid-based nutrient supplement formulated for pregnancy (Nutraset, Malauney, France; supplemental material S1). The supplement was initiated at randomization 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.^{9 10 12}

Setting: The study sites were rural communities in India (Belagavi, Karnataka), Pakistan (Thatta, Sindh), Democratic Republic of 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 Maternal and Newborn Health Registry, household surveys, and community meetings at each site.^{1 12} Infants who completed the birth, 6-month, and at least two of the three 12–24-month follow-up visits were assessed for ECD outcomes at 24 months between August 2016 and March 2019.

Enrollment and Randomization: The central data coordinating center (RTI International, Durham, NC) created the initial randomization scheme, which included a permuted block design stratified by GN with a trial arm allocation ratio of 1:1:1 within blocks.^{1 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 standardized procedures by trained research team members in the home or clinical environment (supplemental material S2).¹⁰ Demographic, medical and perinatal information was collected at birth.¹ 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 (supplemental material S2).¹⁴ Assessors were blinded to the original randomization 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 behavior scores and corresponding risks of delay were measured on INTER-NDA. The INTER-NDA is an international, psychometrically valid, standardized, ECD assessment whose norms are international ECD standards, constructed according to the WHO's prescriptive guidelines.⁵
- 2) **Vision:** Visual acuity (VA; measured in Logarithm of Minimum Angle of Resolution) and contrast sensitivity (CS; %) were assessed using Cardiff tests (PA Vision Ltd, UK).^{15 16}
- 3) **Cortical auditory processing:** Amplitudes and latencies of auditory evoked response potentials (CA-ERPs) to 3 types of auditory stimuli (frequent, infrequent and novel) were measured for three ERP components (P1, N2, and P3a waves) using the 'novelty oddball' ERP task¹⁷ (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. 2 and Arm 1 vs. 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 more than 200 children per arm (combined site).

Statistical Methods

Statistical analysis was performed in SPSS V.25.0 (IBM, Armonk, NY). Pre-, peri- 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 1-way 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 Chi-square 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 generalized 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) are not normally distributed or when the relationship between the exposure (ELEs) and outcome is 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 (supplemental material S5).

Characteristics of Study Population

Prenatal, perinatal, and postnatal characteristics of the ECD cohort are presented in table 1. The mean (\pm SD) age at assessment was 24.6 months (\pm 0.94), with 48% (n=323) male. Mean maternal education was 4.5 years (\pm 4.2) and 31.9% of the cohort met criteria for low SES. Forty-five children (6.7%) spent \geq 3 days in hospital during the first 2 years, and >99% were breastfed 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 behavior 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 behaviors 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 visual acuity, gross motor, language ($p < 0.001$ for all) and positive behavior ($p = 0.01$). Among other early life exposures, 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 associated with cognition, fine motor, and positive behavior ($p < 0.05$).

Correlations between ECD outcomes and ELEs are presented in 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 evoked response potentials 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 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 LAZ₂₄ and FCI were significantly associated with delays across all INTER-NDA domains. Lower LAZ₁₂, WAZ_{12&24}, and HCAZ₁₂ were also significantly associated delays all INTER-NDA domains except behavior 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 (supplemental material S7).

DISCUSSION

To our knowledge, this is the first multicenter RCT to examine the effect of preconception maternal nutrition supplementation on comprehensive ECD outcomes using a standardized ECD measure developed specifically for LMICs. Our key finding was that the benefits of the maternal intervention previously reported for fetal¹ and postnatal growth⁹ 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 behavior. 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 behaviors were observed, as expected in low-resource populations with rates of child stunting $\geq 60\%$;^{19 20} delayed ECD and stunting share many drivers.

Our findings differ only slightly from those of the PRECONCEPT Study 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 favoring preconception iron-folate supplementation for fine motor development (effect size 1.3 SD; 95% CI: 0.05, 0.77), but not for 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 WF maternal supplementation was associated with improved fetal¹ 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 $\geq 80\%$.¹ The improved birth and postnatal anthropometry reported for both intervention arms (compared to 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 reports²⁷⁻²⁹ and emphasize the importance of socioenvironmental determinants in addition to biomedical determinants on long-term neurodevelopment.^{30 31}

Key strengths of our study are the multicenter 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 inter-site 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 emphasizes 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 behavior scores; visual acuity or contrast sensitivity scores; or auditory ERP markers in 2-year-old children from diverse low resource settings. These findings emphasize that a maternal nutritional intervention strategy alone was insufficient to demonstrate positive gains in young children's development. Rather, multiple socioenvironmental factors, including family environment, maternal education, and children's postnatal linear growth, were positively associated with ECD outcomes.

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Contributors: NFK, MF, and KMH 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, AG, LF, SS, SAA, RLG, SSG, SMD, RJD, MKT, AS, EMM and members of the Women First Preconception Nutrition Trial Group listed above); MF provided expert training to research assessors in each site; AT, AL, AG, 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, DP, 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; JLK supported data base management and statistical analyses; MF, AS, EMM, DC, VRT and AD provided statistical analyses. All authors read and approved the final version of the manuscript.

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Competing interests: None to declare.

Ethical Considerations: 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 (NC, USA). Mothers provided written informed consent for themselves and their children.

Data availability statement: Upon 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>.

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ORCID iDs

Michelle Fernandes	0000-0002-0051-3389
Nancy F Krebs	0000-0001-5652-7547
Jamie E Westcott	0000-0002-0549-3145
Antoinette Tshetu	0000-0001-7657-6901
Adrien Lokangaka	0000-0002-8609-5877
Carl L Bose	0000-0002-8727-8640
Melissa Bauserman	0000-0002-4992-9895
Ana Garcés	0000-0002-0878-5274

Lester Figueroa	0000-0003-1732-0361
Sarah Saleem	0000-0002-6797-8631
Sumera A Ali	0000-0001-8996-7995
Robert L Goldenberg	0000-0002-1283-8340
Shivaprasad S Goudar	0000-0002-8680-7053
Sangappa M Dhaded	0000-0001-9575-5251
Richard J Derman	0000-0003-1148-1594
Carl L Bose	0000-0002-8727-8640
Jennifer F Kemp	0000-0001-6495-9104
Marion Koso-Thomas	0000-0003-2417-3101
Vanessa R Thorsten	0000-0003-4430-1473
Amaanti Sridhar	0000-0001-7216-7713
Abhik Das	0000-0003-2722-0479
Elizabeth M McClure	0000-0001-8659-5444
K Michael Hambidge	0000-0003-0017-5444

REFERENCES

1. Hambidge KM, Westcott JE, Garces 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 doi: 10.1093/ajcn/nqy228 [published Online First: 2019/02/06].
2. Black MM, Walker SP, Fernald LCH, et al. Early childhood development coming of age: science through the life course. *Lancet.* 2017;389:77-90 doi: 10.1016/S0140-6736(16)31389-7 [published Online First: 2016/10/09].
3. 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 doi: 10.1136/bmjgh-2020-004436 [published Online First: 2021/04/21].
4. 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;369:145-57 doi: Doi 10.1016/S0140-6736(07)60076-2.
5. 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 doi: 10.1136/bmjopen-2019-035258 [published Online First: 2020/06/10].
6. King JC. A summary of pathways or mechanisms linking preconception maternal nutrition with birth outcomes. *J Nutr.* 2016;146:1437S-44S doi: 10.3945/jn.115.223479 [published Online First: 2016/06/10].
7. Grantham-McGregor S, Cheung YB, Cueto S, et al. Developmental potential in the first 5 years for children in developing countries. *Lancet.* 2007;369:60-70 doi: 10.1016/S0140-6736(07)60032-4 [published Online First: 2007/01/09].

8. 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 doi: 10.1542/peds.2011-0282 [published Online First: 2011/09/29].
9. 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;229:199-206 e4 doi: 10.1016/j.jpeds.2020.09.032 [published Online First: 2020/09/22].
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. *Am J Clin Nutr*. 2022;116:86-96 doi: 10.1093/ajcn/nqac051 [published Online First: 2022/06/11].
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. *Curr Dev Nutr*. 2022;6:585- doi: 10.1093/cdn/nzac060.043.
12. Hambidge KM, Krebs NF, Westcott JE, et al. Preconception maternal nutrition: a multi-site randomized controlled trial. *BMC Pregnancy Childbirth*. 2014;14:111 doi: 10.1186/1471-2393-14-111 [published Online First: 2014/03/22].
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, Huda SN, Engle P, Grantham-McGregor SM. Use of Family Care Indicators and their relationship with child development in Bangladesh. *J Health Pop 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 doi: 10.1016/0042-6989(94)90168-6 [published Online First: 1994/02/01].

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 doi: 10.1097/00006324-199206000-00003 [published Online First: 1992/06/01].
17. Kihara M, Hogan AM, Newton CR, Garrashi HH, Neville BR, de Haan M. Auditory and visual novelty processing in normally-developing Kenyan children. *Clin Neurophysiol.* 2010;121:564-76 doi: 10.1016/j.clinph.2009.11.086 [published Online First: 2010/01/19].
18. Cohen J. A coefficient of agreement for nominal scales. *Educational Psychological Measurement.* 1960;20:37-46 Online.
19. Vaivada T, Akseer N, Akseer S, Somaskandan A, Stefopoulos M, Bhutta ZA. Stunting in childhood: an overview of global burden, trends, determinants, and drivers of decline. *Am J Clin Nutr.* 2020;112:777S-91S doi: 10.1093/ajcn/nqaa159 [published Online First: 2020/08/30].
20. Gil JD, Ewerling F, Ferreira LZ, Barros AJ. 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 doi: 10.7189/jogh.10.010427 [published Online First: 2020/06/23].
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. *J Nutr.* 2017;147:1593-601 doi: 10.3945/jn.117.250597 [published Online First: 2017/06/16].
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. *Am J Clin Nutr.* 2016;104:1175-82 doi: 10.3945/ajcn.116.135178 [published Online First: 2016/09/09].

23. Devakumar D, Fall CH, 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 doi: 10.1186/s12916-016-0633-3 [published Online First: 2016/06/17].
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 doi: 10.1093/ajcn/nqaa423 [published Online First: 2021/03/06].
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 doi: 10.1371/journal.pone.0113360 [published Online First: 2014/11/26].
26. Clark H, Coll-Seck AM, Banerjee A, et al. A future for the world's children? A WHO-UNICEF-Lancet Commission. *Lancet.* 2020;395:605-58 doi: 10.1016/S0140-6736(19)32540-1 [published Online First: 2020/02/23].
27. Duncan GJ, Magnuson K, Votruba-Drzal E. Boosting family income to promote child development. *Future Child.* 2014;24:99-120 doi: 10.1353/foc.2014.0008 [published Online First: 2014/12/19].
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 Child Res Q.* 2017;41:136-48 doi: 10.1016/j.ecresq.2017.07.001.

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 doi: 10.1542/peds.2012-0412 [published Online First: 2012/08/22].
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 doi: 10.1016/S0140-6736(16)31698-1 [published Online First: 2016/10/09].

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, mo	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)	X ² =1.56, p=0.46
Male	323 (48.4)	107 (49.3)	104 (45.2)	112 (50.9)	
Maternal age at birth, y	23.3 ± 4.1	23.0 ± 4.0	23.3 ± 4.3	23.4 ± 3.7	F=0.06, p=0.94
Parity					X ² =12.76, p=0.24
Nulliparous	135 (20.2)	53 (24.4)	43 (18.7)	39 (17.7)	
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 ¹ at birth, wk	39.2 ± 4.2	39.1 ± 2.2	39.2 ± 1.5	39.4 ± 7.0	F=0.25, p=0.78
Delivery Mode					X ² =3.93, p=0.42
Normal	560 (84.0)	178 (82.0)	195 (84.8)	187 (85.0)	
Assisted ²	6 (0.9)	3 (1.4)	0 (0)	3 (1.4)	
Caesarean section ³	101 (15.1)	36 (16.6)	35 (15.2)	30 (13.6)	
Postnatal Health and Growth					
Number of children admitted to hospital for ≥3 d in the first 2 y of life	45 (6.7)	19 (8.8)	14 (6.1)	12 (5.5)	X ² =0.83, p=0.66
Breastfed at 6 mo	663 (99.4)	216 (99.5)	227 (98.7)	220 (100.0)	X 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, y	4.5 ± 4.2	4.6 ± 4.5	4.7 ± 4.1	4.2 ± 4.0	F=0.47, p=0.62
Socioeconomic status ⁴	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 ⁴	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 ⁵	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 ⁵	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 ⁵	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 (%)

¹ Gestational age data not available for Democratic Republic of the Congo

² Ventouse or forceps assisted delivery

³ Emergency or elective caesarean section

⁴ 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

⁵ Assessed at 24 mo

Arm 1: Preconception intervention; Arm 2: Prenatal intervention; Arm 3: No intervention; SD: standard deviation; FCI: Family Care Indicators; LAZ_{birth}, LAZ₁₂, LAZ₂₄: WHO z scores for length at birth, 12, and 24 mo; WAZ_{birth}, WAZ₁₂, WAZ₂₄: WHO z scores for weight at birth, 12, and 24 mo; HCAZ_{birth}, HCAZ₁₂, HCAZ₂₄: WHO z scores for head circumference at birth, 12, and 24 mo; F: ANOVA test statistic; X²: Chi-Square test statistic.

Table 2 All sites unadjusted treatment effects for Early Child Development (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 scores¹, 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 $\eta^2 < 0.001$
Language	50.00 (41.70)	47.22 (41.70)	47.22 (38.90)	51.52 (41.70)	H=2.82, p=0.24 $\eta^2 < 0.001$
Fine Motor	11.11 (16.70)	11.11 (16.70)	11.11 (22.20)	11.11 (16.70)	H=0.09, p=0.96 $\eta^2 < 0.001$
Gross Motor	11.11 (22.20)	11.11 (22.20)	22.22 (22.20)	22.22 (33.30)	H=0.54, p=0.76 $\eta^2 < 0.001$
Positive Behavior	90.00 (50.00)	100.00 (40.00)	100.00 (50.00)	90.00 (50.00)	H=5.05, p=0.08 $\eta^2 = 0.004$
Negative Behavior	100.00 (25.00)	100.00 (25.00)	100.00 (25.00)	100.00 (50.00)	H=3.44, p=0.18 $\eta^2 = 0.002$
Risk of severe delay/problems^{2*}, n (%)					
Cognitive	246 (36.9)	89 (41.0)	82 (35.6)	75 (34.1)	$X^2 = 3.81$, p=0.43 Cramer's V=0.05
Language	37 (5.6)	17 (7.8)	9 (3.9)	11 (5.0)	$X^2 = 3.95$, p=0.41 Cramer's V=0.06
Fine Motor	506 (75.9)	164 (75.6)	170 (73.9)	172 (78.2)	$X^2 = 3.98$, p=0.41 Cramer's V=0.06
Gross Motor	506 (75.9)	166 (76.5)	178 (77.4)	162 (73.6)	$X^2 = 4.11$, p=0.39 Cramer's V=0.06
Positive Behavior	49 (7.4)	15 (6.9)	18 (7.8)	16 (7.3)	$X^2 = 6.33$, p=0.18 Cramer's V=0.07
Negative Behavior	379 (56.8)	136 (62.7)	123 (53.5)	120 (54.6)	$X^2 = 5.92$, p=0.21 Cramer's V=0.07
Risk of any delay/problems^{3**}, n (%)					
Cognitive	444 (66.6)	150 (69.1)	156 (67.8)	138 (62.7)	$X^2 = 2.26$, p=0.32 Cramer's V=0.06
Language	78 (11.7)	30 (13.8)	21 (9.1)	27 (12.3)	$X^2 = 2.49$, p=0.29 Cramer's V=0.06
Fine Motor	583 (87.4)	191 (88.0)	202 (87.8)	190 (86.4)	$X^2 = 0.33$, p=0.85 Cramer's V=0.02
Gross Motor	609 (91.3)	195 (89.9)	210 (91.3)	204 (92.7)	$X^2 = 1.13$, p=0.56 Cramer's V=0.04
Positive Behavior	173 (25.9)	47 (21.7)	58 (25.2)	68 (30.9)	$X^2 = 4.96$, p=0.08 Cramer's V=0.09
Negative Behavior	615 (92.2)	202 (93.1)	214 (93.0)	199 (90.5)	$X^2 = 1.40$, 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 $\eta^2 = 0.002$
Contrast Sensitivity (%)	3.00 (1.00)	3.00 (1.50)	3.00 (1.00)	3.00 (1.00)	H=0.11, p=0.95 $\eta^2 = 0.003$
Risk of low vision, n (%)					
Visual Acuity	160 (24.0)	53 (24.4)	58 (25.2)	49 (22.3)	$X^2 = 0.70$, p=0.71 Cramer's V=0.03
Contrast Sensitivity	129 (19.3)	46 (21.2)	46 (20.0)	37 (16.8)	$X^2 = 1.54$, p=0.46 Cramer's V=0.05

Cortical Auditory ERPs: Peak Amplitudes (in microvolts) ⁴ , 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 $\eta^2=0.007$
	Infrequent	3.57 (2.27)	3.29 (2.55)	3.96 (2.31)	3.56 (1.93)	F=0.89, p=0.41 $\eta^2=0.015$
	Novel	3.74 (2.55)	3.48 (3.07)	3.78 (2.25)	3.85 (2.30)	F=0.23, p=0.79 $\eta^2=0.004$
N2	Frequent	4.30 (8.67)	3.31 (3.24)	3.19 (2.20)	4.14 (3.53)	F=1.20, p=0.30 $\eta^2=0.02$
	Infrequent	2.81 (1.94)	3.34 (2.00)	2.39 (1.59)	2.62 (2.01)	F=2.69, p=0.07 $\eta^2=0.04$
	Novel	2.74 (1.98)	2.48 (2.06)	3.12 (1.30)	2.64 (2.38)	F=1.10, p=0.34 $\eta^2=0.04$
P3A	Frequent	3.68 (3.28)	3.52 (2.28)	3.90 (3.21)	3.09 (1.74)	F=1.14, p=0.32 $\eta^2=0.02$
	Infrequent	2.93 (1.58)	2.65 (1.43)	2.98 (1.64)	3.14 (1.60)	F=1.06, p=0.35 $\eta^2=0.02$
	Novel	2.82 (1.70)	3.03 (1.81)	2.64 (1.52)	2.77 (1.78)	F=0.53, p=0.59 $\eta^2=0.009$
Cortical Auditory ERPs: Latencies (in milliseconds) ⁴ , 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 $\eta^2=0.007$
	Infrequent	182.59 (34.01)	181.35 (33.42)	181.05 (32.70)	185.27 (36.57)	F=0.20, p=0.82 $\eta^2=0.003$
	Novel	190.16 (34.96)	189.59 (35.13)	181.97 (31.83)	197.65 (36.87)	F=2.11, p=0.13 $\eta^2=0.034$
N2	Frequent	294.29 (26.86)	293.13 (30.03)	291.14 (25.69)	297.40 (24.98)	F=0.59, p=0.55 $\eta^2=0.01$
	Infrequent	297.78 (30.60)	293.78 (33.91)	304.27 (27.89)	296.23 (29.62)	F=1.27, p=0.29 $\eta^2=0.02$
	Novel	298.60 (32.33)	293.89 (31.79)	294.22 (33.51)	306.90 (31.14)	F=2.25, p=0.11 $\eta^2=0.04$
P3A	Frequent	389.33 (32.07)	389.86 (36.77)	387.42 (29.82)	390.45 (30.54)	F=0.09, p=0.91 $\eta^2=0.002$
	Infrequent	389.32 (34.14)	396.31 (35.55)	392.44 (33.87)	380.08 (32.14)	F=2.64, p=0.08 $\eta^2=0.04$
	Novel	387.57 (34.31)	381.68 (34.26)	394.94 (33.71)	386.03 (34.81)	F=1.52, p=0.22 $\eta^2=0.03$

¹ For all INTER-NDA outcomes, except negative behavior, higher scores reflect better outcomes.

² For all INTER-NDA outcomes, except negative behavior, high and any risk of delay are defined as domain scores $\leq 3^{\text{rd}}$ and $\leq 10^{\text{th}}$ centiles on the INTER-NDA standards, respectively. For negative behavior, high and any risk of problems are defined as domain scores $\geq 97^{\text{th}}$ and $\geq 90^{\text{th}}$ centiles on the INTER-NDA standards, respectively.

³ For all INTER-NDA outcomes, except negative behavior, mild-to-moderate risk of delay is defined as domain scores between the 3^{rd} and 10^{th} centiles on the INTER-NDA standards. For negative behavior, mild-to-moderate risk of delay is defined as domain scores between the 90^{th} and 97^{th} centiles on the INTER-NDA standards.

⁴ ERP values presented are averaged across the 4 temporal electrodes (T3-T6).

[^] Comparisons made between arms for children with no delay vs. mild-to-moderate delay vs. severe delay.

^{^^} Comparisons made between arms for children with any delay vs. no delay. η^2 = eta square.

Arm 1: Preconception intervention; Arm 2: Prenatal intervention; Arm 3: No intervention; ECD: Early child development; ERP: Evoked response potentials; logMar: Logarithm of the Minimum Angle of Resolution; IQR: Inter-quartile range.

Table 3 Adjusted comparisons: Early life exposures (ELE) as predictors of Early Child Development (ECD) outcomes at 24 months of age

ECD Outcome		Unstandardized coefficients		Standardized coefficients			95% Confidence Interval for B	
		B	Std. Error	Beta	t	Sig.	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, mo	-0.02	0.01	-0.09	2.18	0.03*	-0.03	0.00
	Maternal age at birth, y	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, wk	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, y	-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, mo	-0.05	0.05	0.04	0.86	0.39	-0.06	0.15
	Maternal age at birth, y	-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, y	-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, mo	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, wk	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, y	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, mo	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
	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, y	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, mo	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, mo	2.02	1.32	0.06	-1.53	0.13	-0.48	4.61
	Gestational age at birth, wk	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, y	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 Behavior (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, mo	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 Behavior (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, mo	-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

**p<0.001; *p<0.05.

ECD: Early child development; FCI: Family Care Indicators; LAZ_{birth}, LAZ₁₂, LAZ₂₄: WHO z scores for length at birth, 12 and 24 mo; WAZ_{birth}, WAZ₁₂, WAZ₂₄: WHO z scores for weight at birth, 12 and 24 mo; HCAZ_{birth}, HCAZ₁₂, HCAZ₂₄: WHO z scores for head circumference at birth, 12 and 24 mo; SES: Socio-economic status, 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; F: ANOVA test statistic; X²: Chi-Square test statistic.

FIGURE LEGEND

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram of participant flow.