क्षेत्रीय आयुर्विज्ञान संस्थान, इंफाल: मणिपुर
REGIONAL INSTITUTE OF MEDICAL SCIENCES, IMPHAL, MANIPUR
(स्वास्थ्य और परिवार कल्याण मंत्रालय,भारत सरकार के अंतर्गत एक स्वायत्त संस्थान)
(An Autonomous Institute under the Ministry of Health & Family Welfare, Govt. of India

Phone : 0385- 2414720
0385-2414750
e-mail : rims@rims.edu.in
website : www.rims.edu.in

CIRCULAR

Imphal, the 22nd October, 2025

No. 218/RIMS-MRU/2025: It is to notify that the 6th **Research Masterclasses 2025**, of the Department of Health Research, Ministry of Health and Family Welfare, Government of India, will be conducted virtually, **on 31st October, 2025 (Friday).**

2. All the faculties (RIMS, Dental College, College of Nursing), members of EC, LRAC of MRU, Principal Investigators undertaking MRU funding projects (including under process projects) and residents are invited to attend the session at Banting Hall, RIMS, Imphal.

Date: 31.10.2025 (Friday)
Time: 3:00 PM onwards
Venue: Banting Hall, RIMS, Imphal (ONLY SITE FOR PARTICIPATION FOR RIMS)
Resource Person: Dr. Nita Bhandari, Chief Scientist & Chairman, Society for Applied Studies, New Delhi.
Event name: Research Masterclass under DHR-ICMR Research Grand Rounds

3. As per the directives issued by the DHR, **maximum participation** from our institute is highly encouraged. MRU is submitting the attendance sheet to the DHR after the session concludes.

4. The research papers to be discussed during the research masterclass are available in the RIMS website: https://www.rims.edu.in/secure/ and also being shared with all concerned through their respective (personal/ departmental/ college) e-mail IDs.

22.10.25

Prof. T. Jeetenkumar Singh,
Nodal Officer,
Multi-Disciplinary Research Unit,
RIMS, Imphal

Copy to:

1. The P.S. to Director, RIMS, for kind information of Director
2. The P.A. to Medical Superintendent, RIMSH, for kind information
3. The Dean (Academic), RIMS, for kind information & permission to utilize the facilities at Banting Hall.
4. The Principal, Dental College, RIMS
5. The Principal, College of Nursing, RIMS — with a request for ensuring maximum participation.
6. The Head of Department, RIMS, Imphal .....
7. The Chairperson/Co-Chairperson/Member, LRAC, MRU, RIMS.....
8. The Member, EC, MRU, RIMS, Imphal.....
9. The Principal Investigator, RIMS .....
10. The IT Cell, RIMS – with a request for uploading the notice in the website & technical support on 31.10.25
11. Asst. Engineer (Elect./Civil), RIMS - with a request for ensuring uninterrupted power supply & optimum AC functioning.
12. The Care Taker, Banting Hall, RIMS, Imphal- for proper upkeep of the venue & the accompanying facilities.
13. Guard file.

JAMA | Original Investigation

Child Neurodevelopment After Multidomain Interventions From Preconception Through Early Childhood
The WINGS Randomized Clinical Trial

Ravi Prakash Upadhyay, MD; Sunita Taneja, PhD; Ranadip Chowdhury, PhD; Neeta Dhabhai, MD; Savita Sapra, PhD; Sarmila Mazumder, PhD; Sitanshi Sharma, MD; Mark Tomlinson, PhD; Tarun Dua, PhD; Harish Chellani, MD; Rupali Dewan, MD; Pratima Mittal, MD; M. K. Bhan, MD; Nita Bhandari, PhD; for the Women and Infants Integrated Interventions for Growth Study (WINGS) Group

Editorial page 25

Supplemental content

IMPORTANCE Multidomain interventions in pregnancy and early childhood have improved child neurodevelopment, but little is known about the effects of additional preconception interventions.

OBJECTIVE To evaluate the effect of a multifaceted approach including health; nutrition; water, sanitation, and hygiene (WASH); and psychosocial support interventions delivered during the preconception period and/or during pregnancy and early childhood on child neurodevelopment.

DESIGN, SETTING, AND PARTICIPANTS In this randomized trial involving low- and middle-income neighborhoods in Delhi, India, 13 500 participants were assigned to preconception interventions or routine care for the primary outcome of preterm births and childhood growth. Participants who became pregnant were randomized to pregnancy and early childhood interventions or routine care. Neurodevelopmental assessments, the trial's secondary outcome reported herein, were conducted in a subsample of children at age 24 months, including 509 with preconception, pregnancy, and early childhood interventions; 473 with preconception interventions alone; 380 with pregnancy and early childhood interventions alone; and 350 with routine care. This study was conducted from November 1, 2000, through February 25, 2022.

INTERVENTIONS Health, nutrition, psychosocial care and support, and WASH interventions delivered during preconception, pregnancy, and early childhood periods.

MAIN OUTCOMES AND MEASURES Cognitive, motor, language, and socioemotional performance at age 24 months, assessed using the Bayley Scales of Infant and Toddler Development 3 tool.

RESULTS The mean age of participants at enrollment was 23.8 years (SD, 3.0 years). Compared with the controls at age 24 months, children in the preconception intervention groups had higher cognitive scores (mean difference [MD], 1.16; 98.3% CI, 0.18-2.13) but had similar language, motor, and socioemotional scores as controls. Those receiving pregnancy and early childhood interventions had higher cognitive (MD, 1.48; 98.3% CI, 0.49-2.46), language (MD, 2.29; 98.3% CI, 1.07-3.50), motor (MD, 1.53; 98.3% CI, 0.65-2.42), and socioemotional scores (MD, 4.15; 98.3% CI, 2.18-6.13) than did controls. The pregnancy and early childhood group also had lower incidence rate ratios (RRs) of moderate to severe delay in cognitive (incidence RR, 0.62; 98.3% CI, 0.40-0.96), language (incidence RR, 0.73; 98.3% CI, 0.57-0.93), and socioemotional (incidence RR, 0.49; 98.3% CI, 0.24-0.97) development than did those in the control group. Children in the preconception, pregnancy, and early childhood intervention group had higher cognitive (MD, 2.60; 98.3% CI, 1.08-4.12), language (MD, 3.46; 98.3% CI, 1.65-5.27), motor (MD, 2.31; 98.3% CI, 0.93-3.69), and socioemotional (MD, 5.55; 98.3% CI, 2.66-8.43) scores than did those in the control group.

CONCLUSIONS AND RELEVANCE Multidomain interventions during preconception, pregnancy and early childhood led to modest improvements in child neurodevelopment at 24 months. Such interventions for enhancing children's development warrant further evaluation.

TRIAL REGISTRATION Clinical Trials Registry–India CTRI/2017/06/008908

JAMA. 2024;331(1):28-37. doi:10.1001/jama.2023.23727

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The members of the Women and Infants Integrated Interventions for Growth Study (WINGS) Group appear in Supplement 4.

Corresponding Author: Sunita Taneja, PhD, Centre for Health Research and Development, Society for Applied Studies, 45, Kalu Sarai, New Delhi 110016, India (sunita.taneja@sas.org.in).

© 2024 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Universitetet i Bergen, Ranadip Chowdhury on 01/03/2024

More than 200 million children younger than 5 years in low- and middle-income countries do not reach their full developmental potential due to poor nutrition among multiple other factors.[1] Substantial brain development occurs from gestation through the first 2 to 3 years of childhood.[2] Stand-alone nutritional and nonnutritional interventions aimed at mothers and/or offspring have shown relatively small effects on child neurodevelopment.[3-9] These interventions have encompassed a variety of approaches, including promotion of breastfeeding, supplementation with macronutrients and micronutrients, improving water and sanitation, interventions for promotion of child play and responsive stimulation, and parenting interventions.[3-9]

The effects of interventions during the preconception period have received comparatively less attention than interventions during pregnancy or early childhood. To our knowledge, no previous study has attempted to deliver evidence-based interventions to improve child growth and neurodevelopment throughout the continuum from preconception to pregnancy through a child's first 2 years of life. This study aimed to evaluate the effect of an integrated package of health; nutrition; psychosocial support; and the water, sanitation, and hygiene (WASH) interventions delivered during preconception, pregnancy, and early childhood periods on child neurodevelopmental outcomes at 24 months of age.

Key Points

Question How does a package of multidomain interventions addressing health, nutrition, psychosocial care and support, and environmental hygiene delivered during preconception, pregnancy, and early childhood affect child neurodevelopment at 24 months?

Findings In this second report of a randomized trial in India assessing interventions during preconception, pregnancy, and early childhood on childhood preterm births and childhood growth as primary outcomes, the secondary outcome was neurodevelopment at 24 months. Among 1712 children assessed, preconception, pregnancy, and early childhood interventions were associated with modest improvements in scores and lower incidence of moderate to severe neurodevelopmental delay in the cognitive, language, and socioemotional domains.

Meaning Multidomain interventions in the preconception period, along with those in pregnancy and early childhood, may be beneficial for child neurodevelopment.

Methods

This study was part of the Women and Infants Integrated Interventions for Growth Study (WINGS), a randomized trial whose primary outcomes were preterm birth and child growth outcomes at birth and 24 months, reported separately.[10,11] Neurodevelopment at ages 12 and 24 months were prespecified secondary outcomes.[11]

Ethical approvals were obtained from the Ethics Review Committee of the Society for Applied Studies (SAS/ERC/LG/2017), New Delhi, India; Vardhman Medical College and Safdarjung Hospital, New Delhi, India (IEC/SJH/VMMC/PROJECT-2017/694), and the World Health Organization, Geneva, Switzerland (ERC.0002934).

Study Design and Participants

This individually randomized trial with a factorial design was conducted in urban low- and middle-income populations in Delhi, India.[10,11] Participants were 18- through 30-year-old married women identified via house-to-house survey who had 0 or 1 child and who intended to have more children. Detailed methods are described in the protocol (Supplement 1) and a publication that reports on the primary outcomes on growth.[10,11]

Because neurodevelopment was a secondary outcome in this trial, assessments for the current study were conducted in a subsample of children. All children who turned 24 months of age between November 1, 2020, and February 25, 2022, were eligible. Within this cohort, all families were approached consecutively for assessment as soon as their child attained 24 months of age, until the intended sample size was achieved.

The data and safety monitoring committee for this trial met in May 2021 after study enrollment had been completed. Based on clear evidence that the interventions yielded benefit for the primary growth-related outcomes at 24 months, the committee recommended halting further assessment of these outcomes. However, the committee recommended that interventions continue for children scheduled to undergo neurodevelopmental assessments at age 24 months; these were completed in early 2022.

Randomization and Masking

After providing written informed consent, eligible participants were randomized to receive either preconception interventions or routine care. Participants who became pregnant were randomized a second time either to pregnancy and early childhood interventions or to routine care (**Figure**). During both randomization phases, participants were allocated to groups in a 1:1 ratio using permuted block sizes of 8 and 16. There were 4 groups resulting from the 2-step randomization: preconception, pregnancy, and early childhood interventions (group A), preconception interventions only (group B), pregnancy and early childhood interventions only (group C), and no preconception interventions and routine pregnancy and early childhood care (group D).

Procedures

The preconception, pregnancy, and early childhood interventions have been described in detail elsewhere.[10,11]

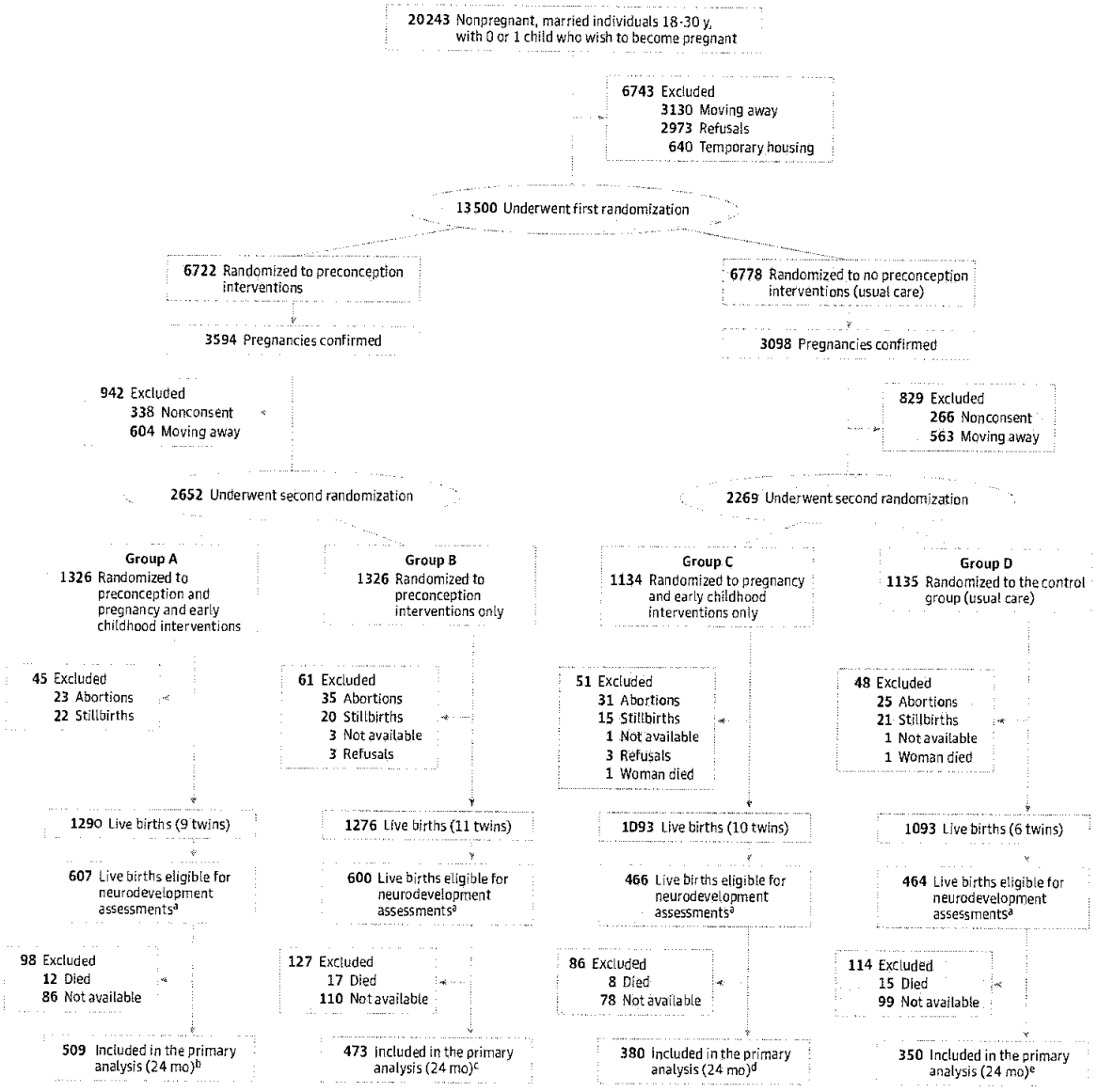
Preconception

Participants in the control group received preconception care available through a government program (eTable 1 in Supplement 2). Interventions in the preconception period (eTable 2 in Supplement 2) included screening and treatment of participants for infections, undernutrition, anemia, and medical illnesses (eg, thyroid disorders) using standard management protocols.[10,11] Participants received micronutrients, iron-folic acid along with dietary counseling, and counseling on

© 2024 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Universitetet i Bergen, Ranadip Chowdhury on 01/03/2024

Figure. Screening, Enrollment, Randomization, and Follow-Up of Participants in the WINGS Trial



[a] Neurodevelopment assessments done for a subsample of children born between November 1, 2018, and February 25, 2020, as the secondary outcome of the previously published WINGS trial.[11] All families were approached consecutively for assessment soon after their child attained 24 months of age, until the required sample size was achieved. There were no refusals; however, some children (and their families) had moved out of the study area at the time of their scheduled assessment (referred to as "not available").

[b] Two twins.

[c] Two twins.

[d] Three twins.

[e] Two twins.

menstrual and hand hygiene. Counseling on positive thinking and problem-solving skills was provided using an adaptation of the World Health Organization (WHO) *Thinking Healthy* manual.[12] The Patient Health Questionnaire (PHQ-9) presented in the local language (Hindi) was used to screen participants at 3-month intervals; those with a PHQ-9 score of 10 or higher received facilitated referral to a psychologist or psychiatrist.[11,13]

Pregnancy

Participants in the control group were advised to register at a health facility for antenatal care to ensure structured medical

© 2024 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Universitetet i Bergen, Ranadip Chowdhury on 01/03/2024

support, have at least 4 antenatal care checkups; maintain daily consumption of iron folic acid, calcium, and cholecalciferol (vitamin D) throughout pregnancy; obtain supplementary foods available through the Integrated Child Development Services scheme (https://wcd.nic.in/integrated-child-development-services-icds-scheme); and plan to deliver at a health care facility (eTable 1 in Supplement 2).

Participants in the intervention groups were encouraged and facilitated by the study team to register at a health care facility. Antenatal visits included weight measurement and screening for medical conditions. Micronutrient supplements, iron folic acid, calcium, and vitamin D were provided. Nutritional supplementation in the form of locally prepared snacks and milk were provided to all intervention participants. Other interventions included installation of water filters, provision of bottles for water storage, and setting up of handwashing stations with the provision of soap and disinfectants. Positive thinking and problem-solving skills were promoted, as well as screening for and management of depressive symptoms (eTable 2 in Supplement 2).

Postnatal Period

Participants in the control group were advised to arrange postnatal health checkups and to access services available through a government program (eTable 1 in Supplement 2). Postnatal visits for participants in the intervention group were facilitated by the study team (details in eTable 2 in Supplement 2). The participants were supplemented for 6 months with locally prepared snacks and milk that provided 600 kcal of energy and 20 g of protein. In addition, micronutrient supplements were given. Exclusive breastfeeding until 6 months was promoted with support from trained lactation counselors. Counseling on positive thinking and problem-solving skills and screening and management of depressive symptoms were continued. Counseling for complementary feeding in addition to breastmilk was started at 6 months of age. Infants were given a micronutrient-enriched milk-cereal mix to provide 40% to 60% of daily requirements, and iron supplements were recommended. The *Care for Child Development* participants manual, developed by the WHO and the United Nations Children's Fund (UNICEF) was adapted and used to promote child development.[14] Details about the early child play and stimulation interventions used in our study along with details on the training on the psychosocial interventions are presented in eTable 2 in Supplement 2. Adherence with interventions (health, nutrition, psychosocial support, and WASH) was assessed using key indicators by study workers either through observation and documented records or by interviewing the adult participants during home visits. The study observed high adherence with the interventions delivered.[10] Details on the adherence indicators are available at https://www.bmj.com/content/bmj/suppl/2022/10/26/bmj-2022-072046.DC1/tans072046.ww.pdf.

Outcomes

Neurodevelopmental outcomes at 12 and 24 months of age were prespecified secondary outcomes in this trial (Supplement 1) and were assessed by an independent team of trained personnel who were not aware of the group allocation using standardized measures. These outcomes were scores on the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) at 24 months of age.[15,16] (Composite scores for each domain range from 40-160 with a mean of 100 [SD, 15], higher scores indicate better development.) The BSID-III was adapted to make the items culturally relevant and to improve understanding of the language items. The assessment was conducted in a study clinic by trained and standardized psychologists. Cognitive, motor, language, and socioemotional performance was assessed at 24 months of age.[15,16] It was decided at the time of the sample size calculation that a change of approximately 2 points on BSID-III would qualify as a clinically significant difference. The Ages and Stages Questionnaire (ASQ-3) was used to assess 5 domains of development (ie, communication, gross motor, fine motor, problem solving, and personal social; range, 0-60; higher scores indicate better development).[17] The ASQ-3 is a parent-reported assessment and was conducted at each child's home at ages 12 and 24 months by trained and standardized study team workers.

The quality of stimulation, support, and opportunities for learning available for children at home was assessed using the Home Observation for Measurement of the Environment (HOME) inventory, a 45-item tool, a higher overall score indicates greater home stimulation.[18] Data were collected by trained independent outcome team members based on observation or caregiver interviews in home visits. An adapted version of the Observation of Mother Child Interaction (OMCI) tool developed by Rasheed and Yousafzai[19] was used to collect data on mother-child interaction at 6, 12, and 18 months of child age. The data collected were based on the observation of how the mother interacted with the child. Higher scores reflected more positive and responsive mother-child interactions.

Statistical Analysis

In the primary analysis, participants were counted with the group to which they were originally randomized. Three prespecified comparisons evaluated the effect of preconception interventions (groups A and B vs C and D), pregnancy and early childhood interventions (groups A and C vs B and D), and combined preconception, pregnancy and early childhood interventions (group A vs D). A 98.3% CI was used to account for multiple comparisons (3 comparisons) (significance level, .05/3 or .017). Interaction between preconception interventions and pregnancy and early childhood interventions was assessed.

Sample size was calculated for a power of 80% with a 2-sided α of .05, assuming that pregnancy and early childhood interventions (groups A and C) would lead to an increase in the SD of 0.15 (2.25 points) in BSID-III scores compared with routine care (groups B and D). Calculations also assumed that combined preconception, pregnancy and early childhood interventions (group A) would lead to an increase in the SD of 0.20 (3.0 points) in the neurodevelopment scores compared with the control group (group D). The final sample size was 1712 children, assuming approximately 10% refusals.

Generalized linear models were used to calculate the mean difference (MD) for continuous outcomes and incidence risk

© 2024 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Universitetet i Bergen, Ranadip Chowdhury on 01/03/2024

Table 1. Baseline Characteristics of Participants Whose Children Had Neurodevelopmental Assessments

Characteristics at enrollment	No. (%) of participants					
	First randomization preconception interventions		Second randomization			
	Yes (n = 982)	No (n = 730)	Preconception, pregnancy and early childhood interventions, group A (n = 509)	Preconception interventions only, group B (n = 473)	Pregnancy and early childhood interventions only, group C (n = 380)	Control, group D (n = 350)
Age, mean (SD), y	23.8 (3.0)	23.8 (3.1)	24.4 (3.5)	24.6 (3.0)	24.4 (3.2)	24.6 (3.0)
Height, mean (SD), cm	152.5 (5.8)	152.3 (5.5)	152.6 (6.0)	152.3 (5.7)	152.6 (5.6)	152 (5.3)
<150 cm	320 (32.6)	252 (34.5)	160 (31.4)	160 (33.8)	132 (34.7)	120 (34.3)
BMI						
≥25	224 (22.8)	168 (23.0)	117 (23.0)	114 (24.1)	85 (22.4)	87 (24.9)
18.5 to 24.99	591 (60.2)	445 (61.0)	306 (60.1)	297 (62.8)	235 (61.8)	208 (59.4)
<18.5	167 (17.0)	117 (16.0)	86 (16.9)	62 (13.1)	60 (15.8)	55 (15.7)
Joint or extended family[a]	686 (69.9)	502 (68.8)	353 (69.4)	333 (70.4)	264 (69.5)	238 (68.0)
Education ≥12 y						
Participant	475 (48.4)	355 (48.6)	241 (47.4)	234 (49.5)	189 (49.7)	166 (47.4)
Spouse	499 (50.8)	356 (48.8)	254 (49.9)	245 (51.8)	195 (51.3)	161 (46.0)
Homemaker	931 (94.8)	698 (95.6)	482 (94.7)	449 (94.9)	365 (96.1)	333 (95.1)
Annual family income, median (IQR), US$	3000 (1923-3590)	2307 (1692-3333)	3077 (1923-3589)	2821 (1923-3590)	2307 (1731-3589)	2307 (1692-3205)
Family below poverty line[b]	15 (1.5)	41 (5.6)	9 (1.8)	6 (1.3)	18 (4.7)	23 (6.6)
Family member covered by health insurance scheme	55 (5.6)	115 (15.8)	28 (5.5)	27 (5.7)	57 (15.0)	58 (16.6)
Place of birth						
Large hospitals			412 (81.0)	274 (57.9)	321 (84.5)	213 (60.8)
Small hospitals or birthing centers			86 (16.9)	162 (34.3)	47 (12.4)	107 (30.6)
Home birth			11 (2.1)	37 (7.8)	12 (3.1)	30 (8.6)

Abbreviation: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.

[a] Joint or extended family includes adult relatives other than the enrolled parents and siblings living together in a household.

[b] Families having an annual income of less than 24 000 Indian rupee (INR; US $360; 1 INR equivalent to US $0.015).

ratio (RR) for categorical outcomes. For moderate to severe neurodevelopmental impairment at 24 months of age, the absolute risk reduction was also reported. Moderate to severe neurodevelopmental impairment was defined as a composite score of less than 85 on the BSID-III.[20]

The baseline characteristics of the randomization groups were compared, and the analysis plan prespecified that characteristics with differences of more than 10% between groups would be adjusted in the final model.[11] This was important because not all enrolled and randomized participants became pregnant and had live births during the study period. The final models were adjusted for maternal height, maternal body mass index (BMI) at the time of pregnancy detection, paternal years of schooling, family income, below-poverty-line status, and place of birth and whether the birth was a twin or multiple. Analyses were conducted in Stata version 16.0 (StataCorp).

Results

The trial resulted in 2137 live births eligible for neurodevelopmental assessment (Figure). Of these, 1712 children (80%) were assessed at 24 months of age (509 in group A, 473 in group B, 380 in group C, and 350 in group D (Figure). The baseline characteristics of participants in these groups were similar except for maternal height and BMI at the time of pregnancy detection, father's years of schooling, annual family income, families with below-poverty-line status, and location of delivery (Table 1). Most characteristics of participants whose children had neurodevelopmental assessment were similar to those who did not (eTable 3 in Supplement 2).

Effect of the Interventions on Neurodevelopmental Outcomes

The interaction between preconception interventions and pregnancy and early childhood interventions for neurodevelopmental outcomes based on BSID-III and ASQ-3 at 24 months of age were assessed. There was no evidence of interaction, and the comparisons of individual groups have been presented (eTable 4 in Supplement 2). There were no evident harms or unintended effects due to the study interventions in any of the groups.

Preconception Interventions Alone

Compared with the control groups (C and D) at 24 months of age, children in the preconception intervention groups (A and B)

© 2024 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Universitetet i Bergen, Ranadip Chowdhury on 01/03/2024

Table 2. Effect on Neurodevelopment Outcomes Assessed at Age 24 Months

Outcomes	Group, mean (SD) score[a]				Mean difference (98.3% CI)[b]		
	A (n = 509)	B (n = 473)	C (n = 380)	D (n = 350)	Preconception intervention (A+B) vs none (C+D)	Pregnancy intervention (A+C) vs none (B+D)	Preconception and pregnancy intervention (A) vs none (D)
Bayley Scales of Infant and Toddler Development 3 composite score[c]							
Cognitive	95.0 (7.9)	93.7 (8.1)	93.9 (7.5)	92.4 (9.5)	1.16 (0.18 to 2.13)	1.48 (0.49 to 2.46)	2.60 (1.08 to 4.12)
Language	93.5 (9.8)	91.3 (10.1)	92.2 (9.7)	90.3 (11.7)	1.12 (−0.10 to 2.34)	2.29 (1.07 to 3.50)	3.46 (1.65 to 5.27)
Motor	97.4 (7.1)	95.9 (7.2)	96.4 (6.4)	95.2 (8.8)	0.87 (−0.01 to 1.75)	1.53 (0.65 to 2.42)	2.31 (0.93 to 3.69)
Socioemotional	117.0 (15.4)	113.3 (17.0)	115.9 (16.1)	111.5 (17.9)	1.50 (−0.45 to 3.45)	4.15 (2.18 to 6.13)	5.55 (2.66 to 8.43)
Ages and Stages Questionnaire 3 score[d]							
Communication	52.0 (10.3)	48.8 (13.3)	51.1 (11.5)	47.5 (13.8)	1.05 (−0.41 to 2.52)	3.43 (1.95 to 4.91)	4.66 (2.49 to 6.82)
Gross motor	52.8 (8.0)	51.3 (9.0)	52.6 (8.4)	50.8 (9.9)	0.25 (−0.80 to 1.30)	1.68 (0.63 to 2.74)	2.06 (0.47 to 3.65)
Fine motor	47.0 (9.1)	44.6 (10.4)	45.8 (9.2)	44.6 (10.3)	0.50 (−0.65 to 1.65)	1.93 (0.76 to 3.09)	2.44 (0.76 to 4.12)
Problem solving	52.0 (10.2)	49.4 (11.5)	50.6 (11.8)	49.2 (11.5)	0.71 (−0.64 to 2.05)	2.06 (0.72 to 3.40)	2.56 (0.66 to 4.47)
Personal social	49.2 (10.4)	47.2 (10.5)	48.8 (10.6)	46.3 (11.7)	0.57 (−0.71 to 1.86)	2.10 (0.81 to 3.38)	2.86 (0.94 to 4.79)

[a] The numbers denote children who were assessed for their neurodevelopment, the secondary outcome of the previously published WINGS trial,[11] at 24 months of age. Group A represents the preconception, pregnancy, and early childhood intervention; group B, only the preconception intervention; group C, only the pregnancy and early childhood intervention; and group D, control (usual care).

[b] Adjusted for clustering for twin birth, maternal height, maternal body mass index at the time of pregnancy detection, paternal years of schooling, family income, below-the-poverty-line status, and place of delivery.

[c] Composite scores for each domain range from 40 to 160 with a mean of 100 (SD, 15; higher scores indicate better development).

[d] Scores in each domain range from 0 to 60 (higher scores indicate better development).

Table 3. Neurodevelopmental Outcomes at 12 Months

Outcomes	Group, No. (%)[a]				Mean difference (98.3% CI)[b]		
	A (n = 403)	B (n = 380)	C (n = 323)	D (n = 320)	Preconception intervention (A+B) vs none (C+D)	Pregnancy intervention (A+C) vs none (B+D)	Preconception and pregnancy intervention (A) vs none (D)
Ages and Stages Questionnaire 3[c]							
Communication	51.1 (10.5)	48.5 (11.7)	50.8 (10.2)	48.2 (12.2)	0.20 (−1.22 to 1.62)	2.55 (1.08 to 4.02)	2.89 (0.77 to 5.02)
Gross motor	52.1 (10.8)	49.7 (12.1)	52.5 (10.3)	48.4 (15.2)	0.35 (−1.23 to 1.92)	3.46 (1.84 to 5.09)	3.98 (1.43 to 6.54)
Fine motor	47.6 (12.3)	44.9 (13.2)	48.1 (10.5)	42.8 (13.8)	0.83 (−0.80 to 2.45)	3.85 (2.22 to 5.49)	4.79 (2.39 to 7.19)
Problem solving	45.5 (12.2)	45.1 (12.9)	47.2 (11.5)	43.5 (13.3)	−0.19 (−1.79 to 1.42)	1.82 (0.14 to 3.50)	1.90 (0.51 to 4.31)
Personal social	42.7 (13.2)	40.7 (13.1)	42.2 (13.7)	39.8 (14.7)	0.73 (−1.04 to 2.50)	2.29 (0.48 to 4.09)	3.18 (0.59 to 5.77)
Observation of Mother-Child Interaction[d]							
At 6 mo	31.6 (4.9)	30.7 (4.5)	31.4 (4.7)	30.5 (4.3)	0.26 (−0.49 to 1.01)	0.84 (−0.08 to 1.60)	1.17 (−0.13 to 2.22)
At 12 mo	35.6 (6.5)	35.2 (6.2)	36.2 (6.0)	35.2 (6.5)	−0.29 (−1.13 to 0.55)	0.73 (−0.12 to 1.58)	0.34 (−0.93 to 1.60)
At 18 mo	38.0 (5.8)	38.2 (5.6)	38.6 (5.5)	37.6 (6.3)	−0.04 (−0.80 to 0.72)	0.33 (−0.44 to 1.10)	0.26 (−0.88 to 1.40)
Home Observation for Measurement of the Environment[e]							
24 mo	42.8 (3.5)	42.7 (3.4)	43.1 (3.5)	42.9 (3.3)	−0.23 (−0.75 to 0.30)	0.12 (−0.41 to 0.65)	−0.05 (−0.82 to 0.73)

Abbreviations: ASQ-3, Ages and Stages Questionnaire, Third Edition; HOME, Home Observation for Measurement of the Environment.

[a] Denotes the number (%) of children who were assessed for neurodevelopment, the secondary outcome of the previously published WINGS trial,[11] using ASQ-3 tool. See footnote *a* in Table 2 for the group definitions.

[b] Adjusted for clustering for twin births, maternal height, maternal body mass index at the time of pregnancy detection, paternal years of schooling, family income, below-the-poverty-line status, and place of delivery.

[c] Scores range from 0 to 60 (higher scores indicate better development).

[d] Assessments were conducted for a subsample of children: 6 months: 254 in group A, 223 in group B, 205 in group C, and 202 in group D; 12 months: 373 in group A, 348 in group B, 301 in group C, and 295 in group D; and 18 months: 398 in group A, 373 in group B, 313 in group C, and 313 in group D. The tool consists of a total of 19 items (score range, 0-3, with a maximum 57; higher scores indicate a more responsive interaction).

[e] HOME assessments were conducted in a subsample (296 in groups A and B each, 213 in group C, and 192 in group D). Consists of 45 items with responses coded at either 0 (not observed or reported during visit) and 1 (observed or reported during visit). The maximum score possible is 45. Higher scores indicate better stimulation and learning opportunities at home.

had higher BSID-III cognitive scores (MD, 1.16; 98.3% CI, 0.18 to 2.13) but similar language, motor and socioemotional scores (Table 2). On the ASQ-3 at 12 and 24 months of age, mean scores on communication, gross and fine motor, problem solving, and personal social domains did not differ between the preconception intervention and control groups (Table 2 and Table 3). The OMCI mother-child bonding score at 6, 12, and 18 months as well as the HOME score at 24 months did not differ between

© 2024 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Universitetet i Bergen, Ranadip Chowdhury on 01/03/2024

Table 4. Risk of Neurodevelopmental Delay Among Children Aged 24 Months

Outcomes	Group, No. (%)[a]				Preconception intervention, yes vs no, A+B vs C+D		Pregnancy intervention, yes vs no group, A+C vs B+D		Preconception and pregnancy intervention, yes vs no group, A vs D	
	A (n = 509)	B (n = 473)	C (n = 380)	D (n = 350)	IRR (98.3% CI)[b]	ARR (%) (98.3% CI)[b]	IRR (98.3% CI)[b]	ARR (%) (98.3% CI)[b]	IRR (98.3% CI)[b]	ARR (%) (98.3% CI)[b]
Cognitive	28 (5.5)	30 (6.3)	24 (6.3)	43 (12.3)	0.66 (0.44 to 1.01)	−3.0 (−6.0 to 0)	0.62 (0.40 to 0.96)	−3.0 (−7.0 to 0.00)	0.44 (0.24 to 0.80)	−7.0 (−12.0 to −2.0)
Language	78 (15.3)	106 (22.4)	69 (18.2)	84 (24.0)	0.90 (0.92 to 1.14)	−3.0 (−8.0 to 2.0)	0.73 (0.57 to 0.93)	−6.0 (−11.0 to −1.0)	0.65 (0.46 to 0.93)	−8.0 (−15.0 to −1.0)
Motor	16 (3.1)	21 (4.4)	13 (3.4)	22 (6.3)	0.78 (0.44 to 1.37)	−1.0 (−3.0 to 2.0)	0.65 (0.36 to 1.17)	−2.0 (−4.0 to 1.0)	0.52 (0.24 to 1.12)	−3.0 (−6.0 to 2.0)
Socioemotional	8 (1.6)	15 (3.2)	11 (2.9)	22 (6.3)	0.52 (0.28 to 0.98)	−2.0 (−4.0 to 0)	0.49 (0.24 to 0.97)	−2.0 (−4.0 to 0)	0.28 (0.10 to 0.79)	−4.0 (−8.0 to −1.0)

Abbreviations: ARR, absolute risk reduction; IRR, incidence rate ratio.

[a] Denotes the number (%) of children who were assessed for neurodevelopment, the secondary outcome of the previously published WINGS trial,[11] using the Bayley Scales of Infant and Toddler Development Third Edition assessment. See footnote a in Table 2 for the group definitions.

[b] Adjusted for clustering for twin birth, maternal height, maternal body mass index at the time of pregnancy detection, paternal years of schooling, family income, below-the-poverty-line status, and place of delivery. Neurodevelopmental delay was defined as composite score of less than 85 on Bayley Scales of Infant and Toddler Development, Third Edition, assessment.

the preconception intervention and routine care groups (Table 3). Except for the socioemotional domain with an incidence RR of 0.52 (98.3% CI, 0.28 to 0.98) and an absolute risk reduction of −2.0% (98.3% CI, −4.0% to 0%), the proportion of children with moderate to severe delay in all other domains considered (ie, cognition, language, and motor) were not different between the preconception intervention and control groups (Table 4).

Pregnancy and Early Childhood Interventions

Children in the pregnancy and early childhood intervention groups (A and C) had higher cognitive (MD, 1.48; 98.3% CI, 0.49-2.46), language (MD, 2.29; 98.3% CI, 1.07-3.50), motor (MD, 1.53; 98.3% CI, 0.65-2.42) and socioemotional scores (MD, 4.15; 98.3% CI, 2.18-6.13) than those in the control groups (B and D). Children in the pregnancy and early childhood intervention groups had higher mean scores on all ASQ-3 developmental domains compared with the control groups (Table 2 and Table 3).

The mother-child bonding score and the HOME score showed no significant differences between the pregnancy and early childhood intervention groups and the control groups (Table 3). The pregnancy and early childhood intervention groups compared with the control groups had a lower proportion with moderate to severe delay outcomes with incidence RRs of 0.62 (98.3% CI 0.40 to 0.96) for cognitive, 0.73 (98.3% CI, 0.57 to 0.93) for language, and 0.49 (98.3% CI, 0.24 to 0.97) for socioemotional domains. The absolute risk reductions were −3.0% (98.3% CI, −7.0% to 0.0%) for cognitive, −6.0%, (98.3% CI, −11.0% to −1.0%) for language, and −2.0% (98.3% CI, −4.0% to 0%) for socioemotional domains (Table 4).

Combined Preconception, Pregnancy, and Early Childhood Interventions

Children in the preconception, pregnancy, and early childhood intervention group (A) had significantly higher cognitive (MD, 2.60; 98.3% CI, 1.08 to 4.12), language (MD, 3.46; 98.3% CI, 1.65 to 5.27), motor (MD, 2.31; 98.3% CI, 0.93 to 3.69), and socioemotional scores (MD, 5.55; 98.3% CI, 2.66 to 8.43) than the control group (D; Table 2). On the ASQ-3 based assessments, children in the preconception, pregnancy, and early childhood intervention group had higher mean scores on all developmental domains compared with the control group (Tables 2 and 3). The mother-child bonding score and the HOME score were statistically similar between groups A and D (Table 3).

The preconception, pregnancy, and early childhood intervention group (A) compared with the control group (D) had a lower proportion of moderate to severe delay with incidence RRs of 0.44 (98.3% CI, 0.24 to 0.80) for cognitive; 0.65 (98.3% CI, 0.46 to 0.93) for language, and 0.28 (98.3% CI, 0.10 to 0.79) for socioemotional domains. The absolute risk reductions were −7.0% (98.3% CI, −12.0% to −2.0%) for cognitive, −8.0%, (98.3% CI, −15.0% to −1.0%) for language, and −4.0% (98.3% CI, −8.0% to −1.0%) for socioemotional domains (Table 4).

Interaction Between Interventions

The interaction between preconception interventions and pregnancy and early childhood interventions for neurodevelopmental outcomes based on BSID-III and ASQ-3 scores

© 2024 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Universitetet i Bergen, Ranadip Chowdhury on 01/03/2024

at 24 months of age was assessed. There was no evidence of interaction (eTable 4 in Supplement 2). No harms or unintended effects due to the study interventions were observed in any of the groups.

Discussion

A set of multidomain preconception, pregnancy, and early childhood interventions resulted in modest but significant improvements in cognitive, language, and socioemotional outcomes in children at 24 months of age compared with routine care. Interventions in pregnancy and early childhood alone also resulted in significant improvement, although the effects were smaller than combined preconception, pregnancy, and early childhood interventions. Preconception interventions alone did not have significant effect on neurodevelopmental outcomes except for small differences in the cognitive and socioemotional domains. Additional studies are required to better understand the intricate dynamics between various interventions and contextual elements and thereby provide granular insights on how best to optimize child neurodevelopmental outcomes.

This study was novel in several respects. First, the conventional approach of examining individual interventions was not adopted. Instead, an intervention package was rigorously tested. This package was thoughtfully curated, drawing from a systematic review of contemporary literature. Second, the study included the preconception period, a relatively understudied period in terms of understanding how interventions during this time influence birth outcomes, as well as growth and neurodevelopment outcomes at 24 months of age. Third, the question addressed was novel, evaluating the maximum impact on growth and neurodevelopment when interventions of known benefit were delivered together from preconception until the child was aged 24 months with high quality and rigor. The adoption of a factorial design enabled discernment of the distinct effects of (1) preconception interventions alone; (2) pregnancy and early childhood interventions alone; and (3) combined preconception, pregnancy, and early childhood interventions.

Other strengths include a robust study design with a large sample size, high adherence with the interventions, and the trial's setting in low- to middle-income populations, enhancing its generalizability to high-risk groups. Outcome assessments were conducted by a team of psychologists trained in standardized procedures. Another novel aspect is that the current study reported on the proportion of children in whom developmental delay was prevented, an outcome not addressed in previous studies. This study observed a 35% to 72% reduction in the risk of moderate to severe delay in cognitive, language, and socioemotional domains for children who received the package of interventions from preconception until 24 months of child age.

This trial found that integrated nutrition and stimulation interventions improved both growth and neurodevelopmental outcomes. A previous article from the current trial reported that the interventions in this study improved growth outcomes at birth and 24 months.[10] This trial's findings on growth contrast with previous trials that tested integrated interventions in children and documented improvements in child development outcomes but were unable to demonstrate impact on growth. A recent meta-analysis by Dulal et al[21] included 22 trials involving children younger than 5 years that had integrated interventions consisting of nutritional and child-stimulation components. The review found that the interventions did not improve growth but did improve developmental scores compared with either routine care or stand-alone nutritional interventions.

This study observed a larger effect on both growth and neurodevelopment than previous studies that only evaluated nutritional interventions, directed to either mother and/or child.[3,5,22-25] On the other hand, this study had somewhat smaller effects on neurodevelopment compared with studies focused on provision of learning opportunities in young children, positive parenting, and responsive care interventions alone. Such studies documented significantly higher effect sizes of approximately 0.30 to 0.60 SDs for cognitive, language, motor, and social-emotional development.[8,25,26] The higher effect sizes could reflect that such studies focused mostly on optimal delivery of the stimulation interventions through frequent contacts and more intensive delivery mechanisms that may not otherwise be possible with integrated interventions wherein focus tends to be shared among all individual components.

The specific mechanisms by which the current study's package of interventions led to improved neurodevelopment were not evaluated. However, interventions to improve nutritional status, manage medical morbidities, and enhance psychological health during preconception and pregnancy, along with improved breastfeeding, provision of high-quality complementary food, adequate management of infections, and optimal delivery of early child-stimulation interventions in the postnatal period could have played a critical role.

Limitations

This study had several limitations. First, because the interventions were delivered concurrently, it was not possible to discern the individual effects of the intervention components on child developmental outcomes. Second, complete blinding could not be established due to the nature of interventions. However, an independent team, not involved in the intervention delivery or aware of the group allocation, conducted the assessment of the study outcomes. Third, restrictions due to the COVID-19 pandemic had some effects on intervention delivery, and outcome assessment was delayed for some participants. Fourth, no universally accepted standard cutoff exists for defining moderate to severe neurodevelopmental delay using the BSID-III, and the choice of 85 was based on existing literature. Fifth, the raw scores for each domain in the BSID-III assessment were converted into a composite score based on US norms. When applied to children in India, the resulting scores might not have indicated their actual developmental function. However, this may not have biased the observed findings because of the study's design as a randomized clinical trial.

© 2024 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Universitetet i Bergen, Ranadip Chowdhury on 01/03/2024

Sixth, the study was conducted among low- to mid-socioeconomic populations of urban Delhi, but only 1% to 6% of the families were below the poverty line, a lower percentage than expected. Regardless of whether they were below the poverty line, the families within the study area exhibited similar access to health care facilities, nutritional practices, water and sanitation access, and cultural norms pertaining to childcare. Moreover, the health and nutrition indicators observed in the control group mirrored those found in many other regions across India.[10,27] Consequently, the findings can be extrapolated to a wide range of locations within the country, as well as to similar resource-limited settings globally.

Conclusion

Multidomain interventions during preconception, pregnancy, and early childhood led to modest improvements in child neurodevelopment at 24 months. Such interventions for enhancing children's development warrant further evaluation.

ARTICLE INFORMATION

Accepted for Publication: October 28, 2023.

Author Affiliations: Centre for Health Research and Development, Society for Applied Studies, New Delhi, India (Upadhyay, Taneja, Chowdhury, Dhabhai, Sapra, Mazumder, Sharma, Bhandari); Department of Psychology, Stellenbosch University, Cape Town, South Africa (Tomlinson); Department of Mental Health and Substance Use, World Health Organization, Geneva, Switzerland (Dua); Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India (Chellani, Dewan, Mittal); Knowledge Integration and Translational Platform (KnIT), Biotechnology Industry Research Assistance Council (BIRAC), Department of Biotechnology, Government of India, New Delhi, India (Bhan).

Author Contributions: Drs Upadhyay, Taneja, and Bhandari had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Upadhyay and Taneja contributed equally.
Concept and design: Upadhyay, Chowdhury, Tomlinson, Dua, Chellani, Dewan, Mittal, Bhandari.
Acquisition, analysis, or interpretation of data: Upadhyay, Taneja, Dhabhai, Sapra, Mazumder, Sharma, Bhandari.
Drafting of the manuscript: Upadhyay, Dewan, Bhandari.
Critical review of the manuscript for important intellectual content: Taneja, Chowdhury, Dhabhai, Sapra, Mazumder, Sharma, Tomlinson, Dua, Chellani, Mittal, Bhandari.
Statistical analysis: Upadhyay, Taneja, Chowdhury, Bhandari.
Obtained funding: Chowdhury, Bhandari.
Administrative, technical, or material support: Upadhyay, Taneja, Chowdhury, Dhabhai, Sapra, Sharma, Chellani, Dewan.
Supervision: Taneja, Mazumder, Sharma, Tomlinson, Dua, Chellani, Bhandari.
Other - Implementation of the study: Upadhyay.

Conflict of Interest Disclosures: None reported.

Funding/Support: The study was funded by grants GCI-ACT Ref No: BIRAC/GCI/0085/03/14-ACT from the Biotechnology Industry Research Assistance Council of the Department of Biotechnology, Government of India and ID OPP1191052 from the Bill & Melinda Gates Foundation.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The members of the Women and Infants Integrated Interventions for Growth Study (WINGS) Group appear in Supplement 4.

Data Sharing Statement: See Supplement 5.

Additional Contributions: We acknowledge the technical guidance for the study from Maharaj Kishan Bhan, MD, who died on January 26, 2020. We thank the participants and their families and community leaders for their cooperation; the members of the technical advisory group: Maharaj Kishan Bhan, MD, H. P. S. Sachdev, MD, Olufemi Oladapo, MD, MPH, Paul Hunter, MD, MBA, Reynaldo Martorell, PhD, Margaret Montgomery, PhD, Vibha Krishnamurthy, MD, Mark Tomlinson, PhD, Rajiv Bahl, MD, Nigel Rollins, MD, Jose Martines, PhD, Shirshendu Mukherjee, PhD, Parul Christian, PhD, Pratima Mittal, MD, and Gautam Bhan, PhD; the members of the data and safety monitoring committee: Anthony Costello, MD, chair, Ravindra Mohan Pandey, PhD, Satinder Aneja, MD, MPH, Pavitra Mohan MD, MPH, and Geeta Trilok Kumar, PhD, for providing independent safety review; Nigel Rollins, MD, for inputs during the design of the trial; Sachiyo Yoshida, PhD, for preparing the randomization list; Sasha Raikhy, MBBS, DNB, for psychiatric consultations; and Manju Bagdwal, for administrative support. We thank the Department of Maternal, Newborn, Child and Adolescent Health, WHO, and the Biotechnology Industry Research Assistance Council of the Department of Biotechnology, Government of India for providing technical oversight.

REFERENCES

1. Lu C, Black MM, Richter LM. Risk of poor development in young children in low-income and middle-income countries: an estimation and analysis at the global, regional, and country level. *Lancet Glob Health*. 2016;4(12):e916-e922. doi:10.1016/S2214-109X(16)30266-2

2. Fox SE, Levitt P, Nelson CA III. How the timing and quality of early experiences influence the development of brain architecture. *Child Dev*. 2010;81(1):28-40. doi:10.1111/j.1467-8624.2009.01380.x

3. Prado EL, Larson LM, Cox K, Bettencourt K, Kubes JN, Shankar AH. Do effects of early life interventions on linear growth correspond to effects on neurobehavioural development? a systematic review and meta-analysis. *Lancet Glob Health*. 2019;7(10):e1398-e1413. doi:10.1016/S2214-109X(19)30361-4

4. 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

5. Ip P, Ho FKW, Rao N, et al. Impact of nutritional supplements on cognitive development of children in developing countries: a meta-analysis. *Sci Rep*. 2017;7(1):10611. doi:10.1038/s41598-017-11023-4

6. Tumwine JK, Nankabirwa V, Diallo HA, et al. Exclusive breastfeeding promotion and neuropsychological outcomes in 5-8 year old children from Uganda and Burkina Faso: results from the PROMISE EBF cluster randomized trial. *PLoS One*. 2018;13(2):e0191001. doi:10.1371/journal.pone.0191001

7. Tofail F, Fernald LC, Das KK, et al. Effect of water quality, sanitation, hand washing, and nutritional interventions on child development in rural Bangladesh (WASH Benefits Bangladesh): a cluster-randomised controlled trial. *Lancet Child Adolesc Health*. 2018;2(4):255-268. doi:10.1016/52352-4642(18)30031-2

8. Jeong J, Franchett EE, Ramos de Oliveira CV, Rehmani K, Yousafzai AK. Parenting interventions to promote early child development in the first three years of life: a global systematic review and meta-analysis. *PLoS Med*. 2021;18(5):e1003602. doi:10.1371/journal.pmed.1003602

9. Yousafzai AK, Obradović J, Rasheed MA, et al. Effects of responsive stimulation and nutrition interventions on children's development and growth at age 4 years in a disadvantaged population in Pakistan: a longitudinal follow-up of a cluster-randomised factorial effectiveness trial. *Lancet Glob Health*. 2016;4(8):e548-e558. doi:10.1016/S2214-109X(16)30100-0

10. Taneja S, Chowdhury R, Dhabhai N, et al; WINGS Study Group. Impact of a package of health, nutrition, psychosocial support, and WaSH interventions delivered during preconception, pregnancy, and early childhood periods on birth outcomes and on linear growth at 24 months of age: factorial, individually randomised controlled trial. *BMJ*. 2022;379:e072046. doi:10.1136/bmj-2022-072046

11. Taneja S, Chowdhury R, Dhabhai N, et al; Women and Infants Integrated Growth Study (WINGS) Group. Impact of an integrated nutrition, health, water sanitation and hygiene, psychosocial care and support intervention package delivered during the pre- and peri-conception period and/or during pregnancy and early childhood on linear growth of infants in the first two years of life, birth outcomes and nutritional status of mothers: study protocol of a factorial, individually randomized controlled trial in India. *Trials*. 2020;21(1):127. doi:10.1186/s13063-020-4059-z

© 2024 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Universitetet i Bergen, Ranadip Chowdhury on 01/03/2024

12. World Health Organization. *Thinking Healthy: A Manual for Psychasocial Management of Perinatal Depression*. Version 1.0. 2015. World Health Organization. Accessed May 9, 2023. https://iris.who.int/handle/10665/15293

13. Patient health questionnaire (PHQ) screeners. Pfizer. Accessed May 18, 2023. https://www.phqscreeners.com/

14. United Nations Children's Fund. *Care for Child Development: Improving the Care for Young Children*. World Health Organization. 2012.

15. Bayley N. *Bayley Scales of Infant and Toddler Development: Technical Manual*. 3rd ed. Harcourt Assessment; 2006. https://journals.sagepub.com/doi/10.1177/0734282906297199

16. Bayley N. *Bayley Scales af Infant and Taddler Develapment: Administratian Manual*. 3rd ed. Harcourt Assessment; 2006.

17. Squire J, Twombly E, Bricker D, Potter L. *ASQ-3: User's Guide*. Paul H. Brookes Publishing Co; 2009.

18. Caldwell BM, Bradley RH. *Home Inventory: Administration Manual Camprehensive Edition*. University of Arkansas for Medical Sciences; 2003.

19. Rasheed MA, Yousafzai AK. The development and reliability of an observational tool for assessing mother-child interactions in field studies—experience from Pakistan. *Child Care Health Dev*. 2015;41(6):1161-1171. doi:10.1111/cch.12287

20. Johnson S, Moore T, Marlow N. Using the Bayley-III to assess neurodevelopmental delay: which cut-off should be used? *Pediatr Res*. 2014;75(5):670-674. doi:10.1038/pr.2014.10

21. Dulal S, Prost A, Karki S, Saville N, Merom D. Characteristics and effects of integrated nutrition and stimulation interventions to improve the nutritional status and development of children under 5 years of age: a systematic review and meta-analysis. *BMJ Glob Health*. 2021;6(7):e003872. doi:10.1136/bmjgh-2020-003872

22. Sudfeld CR, Bliznashka L, Salifou A, et al. Evaluation of multiple micronutrient supplementation and medium-quantity lipid-based nutrient supplementation in pregnancy on child development in rural Niger: a secondary analysis of a cluster randomized controlled trial. *PLoS Med*. 2022;19(5):e1003984. doi:10.1371/journal.pmed.1003984

23. Prado EL, Arnold CD, Wessells KR, et al. Small-quantity lipid-based nutrient supplements for children age 6-24 months: a systematic review and individual participant data meta-analysis of effects on developmental outcomes and effect modifiers. *Am J Clin Nutr*. 2021;114(suppl 1):43S-67S. doi:10.1093/ajcn/nqab277

24. Dewey KG, Wessells KR, Arnold CD, et al. Characteristics that modify the effect of small-quantity lipid-based nutrient supplementation on child growth: an individual participant data meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2021;114(suppl 1):15S-42S. doi:10.1093/ajcn/nqab278

25. Aboud FE, Yousafzai AK. Global health and development in early childhood. *Annu Rev Psychol*. 2015;66:433-457. doi:10.1146/annurev-psych-010814-015128

26. Yousafzai AK, Rasheed MA, Rizvi A, Armstrong R, Bhutta ZA. Effect of integrated responsive stimulation and nutrition interventions in the Lady Health Worker programme in Pakistan on child development, growth, and health outcomes: a cluster-randomised factorial effectiveness trial. *Lancet*. 2014;384(9950):1282-1293. doi:10.1016/S0140-6736(14)60455-4

27. International Institute for Population Sciences. *National Family Health Survey (NFHS-5), 2019-21: India*. Vol I. International Institute for Population Sciences. 2021. Accessed June 12, 2023. https://dhsprogram.com/pubs/pdf/FR375/FR375.pdf

© 2024 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by Universitetet i Bergen, Ranadip Chowdhury on 01/03/2024

Supplemental Online Content

Upadhyay RP, Taneja Sunita, Chowdhury R, et al. Child neurodevelopment after multidomain interventions from preconception through early childhood: the WINGS randomized clinical trial. *JAMA*. doi: 10.1001/jama.2023.23727

eTable 1. Control Group: National Programs for women of reproductive age, pregnant women and under-twos

eTable 2. Study interventions

eTable 3. Characteristics of participants whose children had neurodevelopmental evaluations, compared to those were not evaluated

eTable 4. Interaction between the groups that received preconception or pregnancy intervention compared to those who did not receive these interventions, for neurodevelopment outcomes at 24 months of age

This supplemental material has been provided by the authors to give readers additional information about their work.

© 2024 American Medical Association. All rights reserved.

eTable 1. Control Group: National Programs for women of reproductive age, pregnant women and under-twos

The control group had access to services provided by Accredited Social Health Activists (https://nhm.gov.in/index1.php?lang=1&level=1&sublinkid=150&lid=226), Integrated Child Development Services (http://www.wcddel.in/icds.html), Municipal Corporation of Delhi (MCD) Health Centers, hospitals and private health care practitioners in and around the study areas:

Interventions	National Programs	Access from
Preconception period		
Family planning services including promotion of spacing methods	Reproductive, Maternal, Newborn, Child, and Adolescent Health (https://nhm.gov.in/images/pdf/RMNCH+A/RMNCH+A_Strategy.pdf), Mission *Parivar Vikas* (https://main.mohfw.gov.in/sites/default/files/06Chapter.pdf)	Community health workers called Accredited Social Health Activists (ASHAs), Maternity & Child Welfare Centres, Family Planning Units in government and private health facilities
Weekly iron-folic acid supplementation	Anemia *Mukt Bharat* (https://anemiamuktbharat.info/wp-content/uploads/2019/09/Anemia-Mukt-Bharat-Brochure_English.pdf)	*Anganwadi* centres, government dispensaries
Pregnancy period		
Early registration of pregnancy, four antenatal care check-ups, institutional delivery	My Safe Motherhood (https://nhm.gov.in/images/pdf/programmes/maternal-health/guidelines/my_safe_motherhood_booklet_english.pdf)	Public and private helath facilities
Daily iron-folic acid supplementation for 180 days	Anemia *Mukt Bharat* (https://anemiamuktbharat.info/wp-content/uploads/2019/09/Anemia-Mukt-Bharat-Brochure_English.pdf)	*Anganwadi* centres, government dispensaries, government and private health facilities
Daily calcium and vitamin D supplementation for 180 days	National Guidelines for Calcium Supplementation During Pregnancy and Lactation (http://www.nrhmhp.gov.in/sites/default/files/files/NG_calcium.pdf)	*Anganwadi* centres, government dispensaries, government and private health facilities
Single dose of tablet Albendazole (400 mg) after 1st trimester		*Anganwadi* centres, government dispensaries, government and private health facilities
Supplementary food for mothers, either cooked food or take-home ration (600 calories, 18-20 g of protein)	Integrated Child Development Services (http://www.wcddel.in/icds.html)	*Anganwadi* centres
Postnatal period		
Supplementary food for mothers, either cooked food or take-home ration (600 calories, 18-20 g of protein)	Integrated Child Development Services (http://www.wcddel.in/icds.html)	*Anganwadi* centres
Daily iron-folic acid supplementation for 180 days	Anemia *Mukt Bharat* (https://anemiamuktbharat.info/wp-content/uploads/2019/09/Anemia-Mukt-Bharat-Brochure_English.pdf	*Anganwadi* centres, government dispensaries, government and private health facilities
Daily calcium and vitamin D supplementation for 180 days	National Guidelines for Calcium Supplementation During Pregnancy and Lactation	*Anganwadi* centres, government dispensaries, government and private health facilities

© 2024 American Medical Association. All rights reserved.

Interventions	National Programs	Access from
	(http://www.nrhmhp.gov.in/sites/default/files/files/NG_calcium.pdf)	
Postnatal health checkup	My Safe Motherhood (https://nhm.gov.in/images/pdf/programmes/maternal-health/guidelines/my_safe_motherhood_booklet_english.pdf)	Public and private health facilities where the woman has had her delivery
Postnatal period for children		
Promotion of optimal breastfeeding practices (early initiation of breastfeeding within one-hour, exclusive breastfeeding for the first six months, and continued breastfeeding for at least two years)	Mother's Absolute Affection –MAA (https://nhm.gov.in/MAA/Operational_Guidelines.pdf)	Home visits by ASHAs and *Anganwadi* workers
Home visits for newborn care (days 3, 7, 14, 21, 28 and 42; additionally, on day 1 for home births)	Home Based Newborn Care (http://www.nihfw.org/Doc/NCHRC-Publications/Operational%20Guidelines%20on%20Home%20Based%20Newborn%20Care%20%28HBNC%29.pdf)	ASHAs
Supplementary food (6 to 72 months of age): 500 calories, 12-15 g of protein. For children with severe acute malnutrition, supplementary food increased to 800 calories, 20-25 g of protein	Integrated Child Development Services (http://www.wcddel.in/icds.html)	*Anganwadi* centres
Immunization	Universal Immunization program (https://main.mohfw.gov.in/sites/default/files/5628564789562315.pdf) based on national immunization schedule (https://nhm.gov.in/New_Updates_2018/NHM_Components/Immunization/report/National_%20Immunization_Schedule.pdf)	Government dispensaries, public and private health facilities
IFA supplementation from 6 months to 24 months	Anemia *Mukt Bharat* (https://anemiamuktbharat.info/wp-content/uploads/2019/09/Anemia-Mukt-Bharat-Brochure_English.pdf)	*Anganwadi* centres, government dispensaries, private practitioners, public and private health facilities
Care for pneumonia and diarrhea among children Integrated Action Plan for Pneumonia and Diarrhea	SAANS initiative (https://nhm.gov.in/index1.php?lang=1&level=4&sublinkid=1336&lid=716)	Government dispensaries, public and private health facilities

© 2024 American Medical Association. All rights reserved.

eTable 2. Study Interventions

PRECONCEPTION PERIOD

Intervention	Control [d]
HEALTH Screen and treat medical conditions known to affect fetal and infant growth i.e. reproductive tract infections, syndromic approach (RTI), symptoms of tuberculosis (TB), hypertension, diabetes (HbA1c ≥6.5%) and pre-diabetes (HbA1c 5.7%-6.4%), hypo-thyroidism (thyroid-stimulating hormone (TSH) >5.5 mIU/ml or TSH 4.01 to 5.5 mIU/l and anti-TPO Ab positive) and hyper-thyroidism (<0.4 mIU/ml) Provision of contraception to women living with husband for <1 year, having a child aged <1 year, severe malnutrition, moderate to severe anemia, hypothyroidism, RTI/STI and diabetes, hypertension Bi-annual deworming (Albendazole 400 mg)	Weekly IFA supplementation as part of the National Iron plus Initiative Program
NUTRITION Weekly iron-folic acid (IFA) supplementation (300 mg ferrous fumerate, 1.5 mg folic acid, 15 mcg cyanocobalamin) Multiple micronutrients thrice weekly [a] Screening for malnutrition and anemia Management of undernutrition - BMI <16 kg/m^2: Refer to hospital, locally-prepared snacks and egg or milk[b] (1000 kcal/day and 20-22 g protein/day) - BMI 16 to 18.49 kg/m^2: Snacks and egg or milk[b] (500 kcal/day and 12-14 g protein/day) - BMI <18.5 to 20.99 kg/m^2: Egg or milk[b] (70 kcal, 6 g protein) 6 days a week Monthly weight assessment for those with BMI <18.5 kg/m^2: nutrition counselling and management of infections for those with inadequate weight gain (IWG, weight gain <500 g per month) Anemia - Severe anemia (hemoglobin <8 g/dL): Refer to hospital for treatment - Mild to moderate anemia (hemoglobin 8 to 11.99 g/dL): treatment with IFA (300 mg ferrous fumerate, 1.5 mg folic acid, 15 mcg cyanocobalamin)	
WaSH Promotion of personal, menstrual and hand hygiene	
PSYCHOSOCIAL SUPPORT [c] Screen for depressive symptoms (using PHQ-9). Counselling by study psychologist if PHQ score ≥10. Referral to psychiatrist if PHQ-9 score ≥15 and/or presence of suicidal ideation. Promotion of positive thinking and problem-solving skills Screen for substance abuse and exposure to second-hand smoke and alcohol use in husbands and counsel	

[a]Composition given at the end

[b] Observed intake

Monitor above interventions every three months until corrected or pregnancy reported., Repeat investigations done at baseline and for those non-pregnant 12 months post-enrollment.

Electronic monitoring system for tracking women with problems to support them for achieving intervention compliance across all domains.

[d] National Programs for women of reproductive age, pregnant women and undertwos (eTable 1)

© 2024 American Medical Association. All rights reserved.

PREGNANCY

Intervention Group	Control Group[d]
HEALTH At least eight antenatal care (ANC) contacts according to WHO ANC guidelines, registration for institutional delivery In addition to hospital-based ANC clinics, increase coverage through free-of-cost, high-quality, study outpatient clinic services within community including laboratory services. **Screening and treatment for medical conditions**: HIV, VDRL, syndromic RTI, syndromic TB, Hepatitis B (HbsAg), hypo- and hyper-thyroidism (TSH) assessment at first contact Urine routine and microscopic examination and asymptomatic bacteriuria by urine culture four times Gestational diabetes by oral glucose tolerance test thrice Pregnancy induced hypertension (blood pressure) at every visit Anemia (hemoglobin) four times Tetanus toxoid immunization Calcium (1000 mg) and vitamin D (400 IU) supplementation daily starting from second trimester throughout pregnancy Anti-helminthics (Albendazole 400 mg) at 20 weeks	Routine antenatal care
NUTRITION Counselling IFA (100 mg iron, 500 µg folic acid) supplementation daily throughout pregnancy from second trimester Multiple micronutrients [a] daily throughout pregnancy Food Supplements BMI <25 kg/m^2 - Second trimester: Food supplements (210 kcal, 2 g protein) in the form of a choice of snacks prepared locally and milk (70 Kcal, 6 g protein)[b] - Third trimester: Food supplements (400 kcal, 21 g protein) in the form of a choice of snacks prepared locally and milk (70 Kcal, 6 g protein)[b] Extra snacks (500 kcal, 20 g protein) throughout pregnancy, to women with BMI <18.5 kg/m^2 BMI 25 to <30 kg/m^2 - Milk (70 kcal, 6 g protein) 6 days a week [b] No food supplements to overweight and obese women (BMI ≥25 kg/m^2) Anemia - Severe anemia (hemoglobin <7 g/dL): Refer to hospital for treatment - Mild to moderate anemia (hemoglobin 7 to 10.99 g/dL): treatment with IFA (100 mg iron, 500 µg folic acid) twice daily Gestational weight gain Weight monitoring every month; identification of inadequate weight gain (IWG) according to Institute of Medicine's guidelines Management of inadequate weight gain (IWG): - Nutritional Counselling - Hot meal (500 Kcal, 20 g protein) 6 days a week till delivery - Screening and treatment of infections (UTI, RTI, TB)	

© 2024 American Medical Association. All rights reserved.

Intervention Group	Control Group
WaSH Provision of water filters, hand washing stations, water storage bottles, soap and disinfectants and counselling	
PSYCHOSOCIAL SUPPORT [c] Screen for depressive symptoms using PHQ-9 questionnaire Counselling by study psychologist if PHQ score ≥10. Refer to psychiatrist if PHQ-9 score ≥15 and/or suicidal ideation. Promotion of positive thinking and problem-solving skills Screen for substance abuse and exposure to second-hand smoke and alcohol use in husbands and counsel	

[a] Composition given at the end

[b] Observed intake

Electronic monitoring system for tracking women with problems to support them for achieving intervention compliance across all domains.

[d] National Programs for women of reproductive age, pregnant women and undertwos (eTable 1)

© 2024 American Medical Association. All rights reserved.

EARLY CHILDHOOD

0-6 months: Mothers

Intervention group	Control Group [d]
HEALTH Facilitate hospital visit at 6 weeks postpartum and encourage compliance to supplements.	Routine postnatal and early childhood care
NUTRITION Locally-prepared snacks daily and milk[b] 6 days a week (600 kcal, 20 g protein). IFA (100 mg iron, 500 µg folic acid), Calcium (1000 mg) and vitamin D (400 IU) supplementation daily Multiple micronutrients daily [a]	
WaSH Continuation of all the WaSH interventions provided during pregnancy (water filters, water storage bottles, hand washing station, soap and disinfectants) and counselling on handwashing and hygiene practices (bathing the infant regularly, keeping the infant's surroundings clean, safe disposal of infant's feces, and handwashing before handling the baby).	
PSYCHOSOCIAL CARE [c] Promotion of positive thinking and problem-solving skills Screening mothers for depressive symptoms and management as required Counselling by study psychologist if PHQ score ≥10. Referral to psychiatrist if PHQ-9 score ≥15 and/or suicidal ideation.	

[a]Composition given at the end

[b]Observed intake

Electronic monitoring system for tracking women with problems to support them for achieving intervention compliance across all domains.

[d]National Programs for women of reproductive age, pregnant women and undertwos (eTable 1)

© 2024 American Medical Association. All rights reserved.

0-6 months: Infants

Intervention group	Control Group [d]
NUTRITION Initiation of breastfeeding (BF) within the first hour of birth. Early lactation counselling for all mothers to prevent BF problems, resolution anytime during the first 6 months. Counsel on exclusive BF till 6 months of age emphasizing exclusivity of BF from 3 up to 6 months of age. Growth monitoring and management of IWG Weight measurement on day 14 and thereafter monthly to identify IWG (<15th centile as per WHO Growth Velocity Standards, i.e. weight gain <20 g/day between ages day 14 to month 2; <15 g/d for months 3 and 4; <10 g/d for months 5 to 6) for all term infants. Management through: lactation counselling, screening and treatment of infections, facility based management of IWG by senior paediatrician at Safdarjung Hospital after 15 days of continued efforts of lactation support and no medical cause is identified Additional support for LBW babies and preterm babies (even if not LBW). BF support by lactation counselling through home visits in the first three months (biweekly in first month, weekly in second and third month, monthly from fourth to sixth month). Offer expressed breastmilk feeding for preterm babies only after a breastfeed. Extended support for preterms (through assessment of feeding, growth and investigations within 4-6 weeks after birth) after discharge and ensuring that the advice given at the hospital is followed at home. Support kangaroo mother care at home Vitamin D 400 IU daily for all infants up to 6 months Iron supplementation up to 6 months: VLBW from 2 weeks, LBW from 6 weeks	Routine postnatal and early childhood care
HEALTH Educating mother and other family members to identify danger signs and in early care seeking for illness. Facilitating referral to health facility for infants with any danger signs or illness requiring facility-based management. Counselling on timely immunisation	
PSYCHOSOCIAL CARE [c] Counselling, demonstration and practice sessions for mothers at each home visit on early child play and responsive care. [e] Identification of delayed development and timely referral for further management	

Electronic monitoring system for tracking infants with problems to support them for achieving intervention compliance across all domains.

[d] National Programs for women of reproductive age, pregnant women and undertwos (eTable 1)

© 2024 American Medical Association. All rights reserved.

6-24 months: Children

Intervention group	Control [d]
NUTRITION Effective counselling on initiation of complementary feeding by preparing the mother and family 1-2 weeks prior to 6 months of infant's age Initiation of complementary feeding at 6 months of age and teaching the mother by demonstrations on how to prepare foods at home which can be fed easily to the child 6 months onwards. Provision of daily food supplement with 125 kcal, 2.5 g protein up to 12 months and 250 kcal energy and 5 g protein from 12 to 24 months that includes 80 to 100% RDA of micronutrients Counselling for intake of home-based food Counselling and demonstration of responsive feeding to mother and family members IFA (10 mg iron and 100 mcg folic acid) supplementation daily up to 24 months Lactation counselling for supporting continued BF till 24 months of age Growth monitoring (weight and length monthly); management of IWG (<25th centile as per WHO Growth Velocity Standards) by providing additional food supplements in form of snacks (125 kcal and 2.5 g protein up to 12 months, and 250 kcal energy and 5 g protein from 12 to 24 months) till child has adequate weight gain for 2 consecutive months; nutritional counselling; screening and treatment of infections Home based management of moderate acute malnutrition through counselling, on preparation of augmented home-based foods. Facilitating facility-based management of severe acute malnutrition.	Routine early childhood care
HEALTH Educating mother and other family members to identify danger signs, and in early care seeking. Facilitating medical management. Counselling on feeding the child during and after illness. Counselling on timely immunization Provision of Albendazole (200 mg) for deworming starting 12 months of age and then 6 monthly	
WaSH Continuation of all the WaSH interventions provided during pregnancy (water filters, water storage bottles, hand washing stations, soap, disinfectants) and counselling on hygiene practices (safe preparation of food, storage and feeding of the child utilizing clean utensils and clean water for cooking and drinking). Clean play area for children; provide play mat. Safe disposal of child's faeces; provide potty.	
PSYCHOSOCIAL SUPPORT [c] **CHILDREN** Counselling on early child development. Demonstration and practice session for mother at each home visit on early child play and responsive care. [e] Identification of delayed development three-monthly or as response to parental concerns and timely referral to developmental psychologist. **MOTHERS** Promotion of positive thinking and problem-solving skills. Screening mothers for depressive symptoms. Counselling by study psychologist if PHQ score ≥10. Referral to psychiatrist if PHQ-9 score ≥15 and/or suicidal ideation.	

© 2024 American Medical Association. All rights reserved.

Electronic monitoring system for tracking children and mothers with problems to support them for achieving intervention compliance across all domains.

[d]National Programs for women of reproductive age, pregnant women and undertwos (eTable 1)

[c]Training information for the psychosocial care interventions: We adapted the WHO Thinking Healthy Module for delivering psychosocial care interventions to the mother. The "Care for Child Development, Participants Manual" developed by World Health Organization and UNICEF was adapted for early child development related interventions. The adaptations were done under the guidance of Child development experts (Dr. Tarun Dua, WHO Geneva and Dr. Mark Tomlinson, Stellenbosch University, South Africa). Both the documents were pilot tested before using it in the study. To ensure the successful implementation of these interventions, a senior psychologist played a pivotal role in training our study team members. Initially, during the early phase of the study, these training sessions were conducted weekly. However, as the study progressed and stabilized, they transitioned to a bi-weekly schedule (once every two weeks). The primary objective of these training sessions was to impart a comprehensive understanding of the significance of these interventions and to equip our team with the skills and strategies necessary for effective engagement with families and caregivers. To further guarantee the quality of our interventions, regular supervision visits were conducted by both the study coordinator and the senior psychologist. During these visits, the delivery of interventions in the field was observed, and detailed observations were recorded. Subsequently, these observations were discussed individually with the specific team members after each home visit and collectively during the fortnightly training and review sessions. This feedback loop proved invaluable in refining the delivery of psychosocial care and early child development interventions. Additionally, competency checklists were meticulously maintained by the senior psychologist for each study team member involved in the delivery of psychosocial care and ECD interventions. The checklist comprised of important attributes relevant for the effective engagement with the family and delivery of the interventions. For instance- Is the team member effectively establishing a friendly and relaxed rapport with the caregiver? Does she regularly confirm the caregiver's comprehension of the information conveyed? Is she maintaining an appropriate and balanced pace during the intervention, avoiding both excessive haste and overly slow delivery? Is her approach with the caregiver more interactive and engaging, or does she primarily deliver the intervention in a didactic manner? Is she actively demonstrating the activities that the mother is expected to perform?

In cases where significant deficiencies or gaps in competency were identified, team members underwent re-training sessions to ensure that they were fully equipped to provide the necessary support to families and caregivers. For each psychosocial and ECD-related visit, specific checklists were prepared to outline the key intervention points that the study team members were expected to address during that visit. This systematic approach was designed to prevent the omission of important messages and to maintain consistency in the delivery of interventions. Overall, rigorous training, meticulous supervision, and evaluation mechanisms were integral to the delivery of psychosocial care interventions with quality and rigor.

[e]Details about the early child play and stimulation interventions: The strategies employed for early child development were adapted from the Care for Child Development Manual, which was developed collaboratively by UNICEF and WHO. Mothers and other caregivers in the family were introduced to the concept of age-appropriate child play, responsive care and feeding, communication and stimulation right from the birth of their child. They were encouraged to engage with the child using home-based, easily available materials such as rattles or putting chickpeas/lentils in plastic bottles for making sounds. Particular attention was dedicated to making the most of breastfeeding time, encouraging mothers to forge a strong bond with their child by engaging in activities such as singing, gentle touching and caressing, as well as making eye contact with their child while sharing warm smiles. Emphasis was placed on informing the caregivers about identifying infant hunger cues. During each home visit, skilled study workers provided demonstrations to caregivers on effective ways to interact with the child and assisted them in practicing these techniques. These visits lasted for approximately an hour. The team member, during these home visits, also focused on assessing whether the mother was actively engaging with the child. Any identified barriers were discussed, and possible solutions were offered to ensure the mother had the time and resources to interact with the child. Age-appropriate activities were introduced and demonstrated to the mother during these visits. The visit schedule was designed with more frequent visits in the first few months after birth, gradually reducing to once a month and becoming less frequent as the child grew older. The visit intervals were as follows: visits at birth, 7 days, 14 days, 21 days, 28 days, and 42 days; followed by monthly visits from 2 to 12 months of age, and then at 15, 18, and 21 months of age. If family members or mothers requested assistance related to child development at any point in between, the team would make

© 2024 American Medical Association. All rights reserved.

additional visits to address specific issues. At specific ages i.e., 6, 9, 12, and 18 months of age, the team assessed key developmental milestones. Infants and young children who were unable to achieve age-appropriate milestones were referred to trained psychologists and/or pediatricians for further evaluation and support. The team also inquired if the parent(s) had any concerns related to the development of their child and if reported, the child was referred to a child psychologist who was a part of the study team. Furthermore, the counselling efforts also aimed to emphasize the importance of creating a safe and nurturing home environment for the child. This included guidance on refraining from shouting, resorting to spanking, engaging in parental conflicts, and avoiding the child's exposure to screen time.

© 2024 American Medical Association. All rights reserved.

Composition of multiple micronutrient tablet

Micronutrient	per tablet	Micronutrient	per tablet
Vitamin A (mcg)	750	Zinc (mg)	15
Vitamin D (mcg)	5	Iodine (mcg)	150
Vitamin K (mcg)	10	Selenium (mcg)	25
Vitamin C (mg)	50	Magnesium (mg)	100
Vitamin E (mg a-TE)	10	Copper (mg)	2
Thiamine (mg)	2	Manganese (mg)	2.5
Riboflavin (mg)	3	Phosphorus (mg)	125
Niacin (mg)	26	Potassium (mg)	40
Pyridoxine (mg)	1.5	Phosphorus (mg)	125
Pantothenate (mg)	5	Chloride (mg)	36.3
Folate (mcg)	300	Chromium (mcg)	25
Vitamin B12 (mcg)	1	Molybdenum (mcg)	25
Biotin (mcg)	30	Nickel (mcg)	5
Iron (mg)	9	Silicon (mcg)	10
Calcium (mg)	162	Vanadium (mcg)	10

© 2024 American Medical Association. All rights reserved.

eTable 3. Characteristics of participants whose children had neurodevelopmental evaluations, compared to those were not evaluated

Characteristics at enrolment	Assessed (n=1712)	Not assessed (n=1046)
Mean (SD) age of participants – yr	24.5 (3.1)	24.2 (3.0)
Mean (SD) Height of participants – cm	152.4 (5.7)	152.1 (5.7)
Height <150 cm – n (%)	572 (33.4)	369 (35.3)
BMI category (kg/m^2) – n (%)		
≥25	403 (23.5)	244 (23.3)
18.5 to 24.99	1046 (61.1)	644 (61.6)
<18.5	263 (15.4)	158 (15.1)
Joint or extended family [a,b] – n (%)	1188 (69.4)	673 (64.3)
Participant's schooling ≥12 yr – n (%)	830 (48.5)	490 (46.9)
Father schooling ≥12 yr – n (%)	855 (50.0)	515 (49.2)
Homemaker – n (%)	1629 (95.2)	997 (95.3)
Family below poverty line (BPL) – n (%)	56 (3.3)	45 (4.3)
Family member covered by health insurance scheme– n (%) [b]	170 (9.9)	138 (13.2)
Place of birth – n (%) Institutional birth	1622 (94.7)	986 (94.3)

[a] Joint or extended family: Adult relatives other than the enrolled woman's husband and children living together in a household; [b] statistically significant difference at P<0.05

© 2024 American Medical Association. All rights reserved.

eTable 4. Interaction between the groups that received preconception or pregnancy intervention compared to those who did not receive these interventions, for neurodevelopment outcomes at 24 months of age

OUTCOME	No preconception intervention		Preconception intervention		Measure of interaction (95% CI)
	Mean (SD)	MD (95% CI)	Mean (SD)	MD (95% CI)	
BSID-III assessment					
Cognitive composite score					
No pregnancy intervention	92.4 (9.5)	0.00	93.7 (8.1)	1.08 (-0.15, 2.31); p=0.086	-0.10 (-1.70, 1.50); p=0.901
Pregnancy intervention	93.9 (7.5)	1.50 (0.22, 2.78); p=0.022	95.0 (7.9)	2.60 (1.35, 3.85); p<0.001	
Language composite score					
No pregnancy intervention	90.3 (11.7)	0.00	91.3 (10.1)	0.86 (-0.65, 2.38); p=0.264	0.40 (-1.59, 2.39); p=0.695
Pregnancy intervention	92.2 (9.7)	1.93 (0.40, 3.47); p=0.013	93.5 (9.8)	3.46 (1.97, 4.94); p<0.001	
Motor composite score					
No pregnancy intervention	95.2 (8.8)	0.00	95.9 (7.2)	0.55 (-0.59, 1.68); p=0.345	0.45 (-0.98, 1.88); p=0.539
Pregnancy intervention	96.4 (6.4)	1.09 (-0.05, 2.24); p=0.061	97.4 (7.1)	2.31 (1.17, 3.44); p<0.001	
Socio-emotional composite score					
No pregnancy intervention	111.5 (17.9)	0.00	113.3 (17.0)	1.69 (-0.72, 4.10); p=0.169	-0.47 (-3.65, 2.70); p=0.770
Pregnancy intervention	115.9 (16.1)	4.29 (1.80, 6.77); p=0.001	117.0 (15.4)	5.55 (3.18, 7.92); p<0.001	
ASQ-3 assessment					
Communication					
No pregnancy intervention	47.5 (13.8)	0.00	48.8 (13.3)	1.20 (-0.70, 3.10); p=0.215	-0.28 (-2.67, 2.10); p=0.815
Pregnancy intervention	51.1 (11.5)	3.71 (1.81, 5.62); p<0.001	52.0 (10.3)	4.66 (2.88, 6.43); p<0.001	
Gross motor					
No pregnancy intervention	50.8 (9.9)	0.00	51.3 (9.0)	0.44 (-0.90, 1.78); p=0.521	-0.37 (-2.08, 1.35); p=0.676
Pregnancy intervention	52.6 (8.4)	1.89 (0.52, 3.27); p=0.007	52.8 (8.0)	2.06 (0.75, 3.37); p=0.002	
Fine motor					
No pregnancy intervention	44.6 (10.3)	0.00	44.6 (10.4)	-0.17 (-1.61, 1.27); p=0.821	1.23 (-0.64, 3.10); p=0.197
Pregnancy intervention	45.8 (9.2)	1.14 (-0.30, 2.57); p=0.120	47.0 (9.1)	2.44 (1.06, 3.82); p=0.001	
Problem solving					
No pregnancy intervention	49.2 (11.5)	0.00	49.4 (11.5)	0.03 (-1.59, 1.64); p=0.976	1.32 (-0.84, 3.49); p=0.231
Pregnancy intervention	50.6 (11.8)	1.41 (-0.29, 3.11); p=0.104	52.0 (10.2)	2.56 (0.99, 4.13); p=0.001	
Personal social					
No pregnancy intervention	46.3 (11.7)	0.00	47.2 (10.5)	0.86 (-0.71, 2.43); p=0.283	-0.44 (-2.54, 1.65); p=0.678
Pregnancy intervention	48.8 (10.6)	2.67 (1.00, 4.33); p=0.002	49.2 (10.4)	2.86 (1.28, 4.44); p<0.001	

MD: Mean difference; BSID-III- Bayley Scales of Infant and Toddler Development, 3rd Edition; ASQ-3: Ages and Stages Questionnaire, 3rd edition; models adjusted for clustering for twin birth, maternal height, maternal body mass index (BMI) at the time of pregnancy detection, paternal years of schooling, family income, below poverty line (BPL) status and place of delivery

© 2024 American Medical Association. All rights reserved.