Improving Linear Growth of Children in Low Resource Settings through Integrated Nutrition, Health, WASH, Psychosocial Care and Support Interventions during the Pre- and Peri-conceptional Period, Pregnancy and Early Childhood - A Randomized Controlled Trial

Women and Infants Integrated Interventions for Growth Study (WINGS)

Final Statistical Analysis Plan

August 2022

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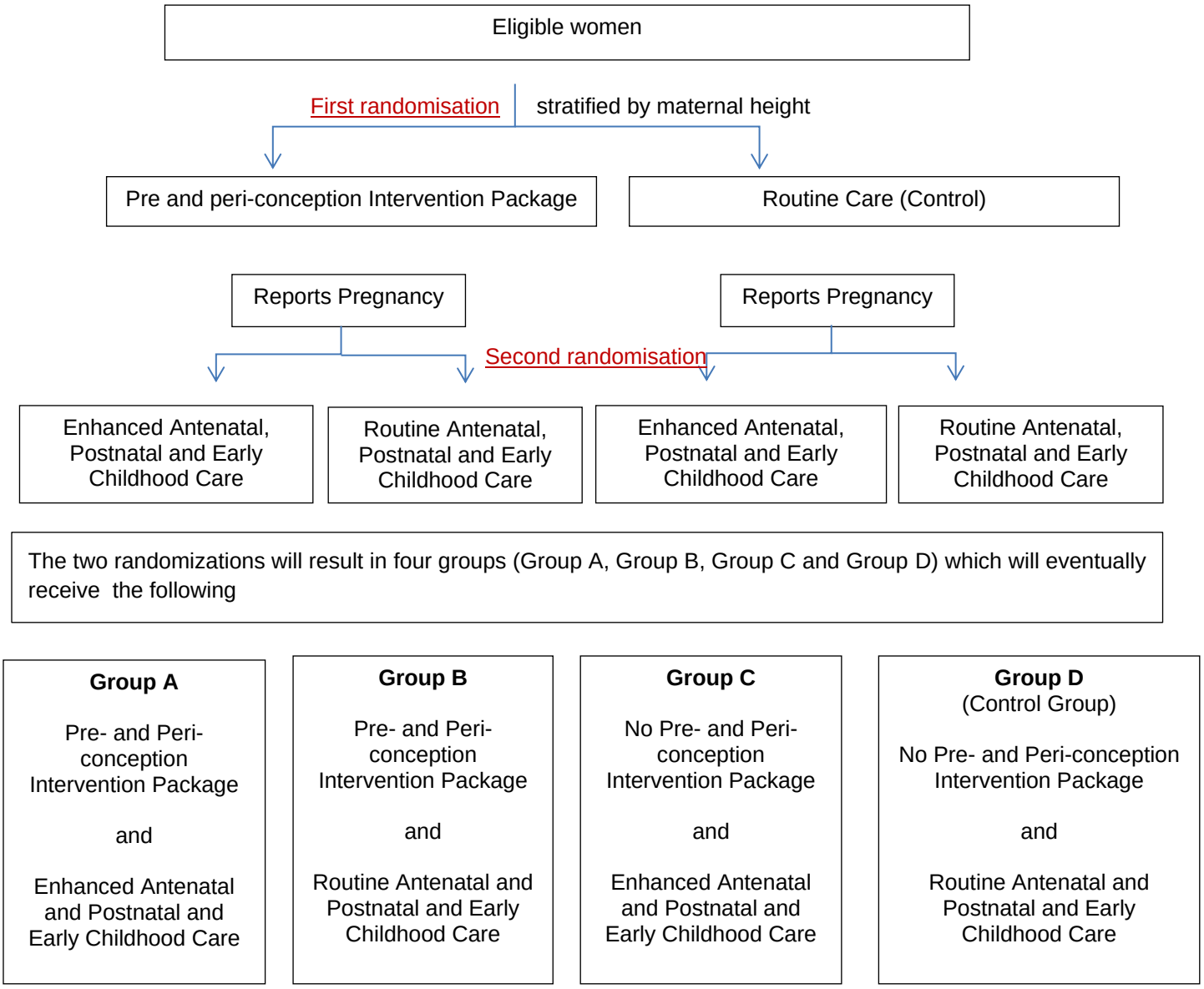
SECTION 1: STUDY DESCRIPTION AND METHODS

Summary

This is an individually randomized study with a factorial design, being conducted among married women aged 18-30 years living in urban and peri-urban low-mid socioeconomic neighbourhoods in South Delhi.

Study design and objectives



Briefly eligible women are identified through a door-to-door survey. Those who consent for participation are enrolled (first randomization) and followed up until they are confirmed to be pregnant or have completed 18 months of follow up post-enrolment. Once pregnancy is confirmed, consent is taken (second randomization) from the women for her and her infant's participation in the trial.

Inclusion criteria

Women aged 18–30 years, married and living with their husband, with no or one child and wish to have a child, and consent for participation in the study.

Exclusion criteria

Families who plan to move out of the study area or live in temporary housing (households without concrete roof, toilet, water connection and legal electricity) are excluded as they are likely to be relocated by the goverment in the near future.

Objectives

Primary Objectives

To determine the effect of integrated and concurrent delivery of interventions to improve health, nutrition, WASH and psychosocial status:

- during pre- and peri-conception period alone (**pre- and peri-conception intervention package**)
- during pregnancy and early childhood (**enhanced antenatal, postnatal and early childhood care**) and
- throughout pre- and peri-conception period, pregnancy and early childhood (**pre- and peri-conception intervention package and enhanced antenatal, postnatal and early childhood care**)

at birth on low birth weight (LBW), preterm birth, small for gestational age (SGA), birth weight and length, and at 24 months on length for age z scores (LAZ) and stunting, compared to routine care.

To assess whether the effect of these interventions differs by maternal stature (<150 cm or ≥150 cm)

Secondary Objectives

To determine the effect of the package on nutritional status, morbidity and neurodevelopment in children

To determine the effect of the package on nutritional status and morbidity in the pre- and peri-conception, pregnancy and postpartum periods in women.

Outcomes

The preconception outcomes will be measured at the end of 18 months of follow up of preconception period or when the women will get pregnant. Outcomes in the pregnancy period will be measured at 26-28 and 35-37 weeks of gestation. Outcomes of children will be measured at birth or day 7 of life, 1,3,5,6,9,12,15,18,21 and 24 months of age.

The primary outcomes at birth are proportion LBW (birth weight <2500 g); preterm birth (ultrasound-confirmed gestational age at birth < 37 completed weeks); SGA (birth weight centile <10^{th} using INTERGROWTH-21st standards); mean birth weight and length At 24 months age, these are mean length-for-age z scores (LAZ) and proportion stunted.

The list of secondary outcomes along with the timing of measurements during the pre- and peri-conception, pregnancy and postnatal periods are provided below (Table 1 and 2).

The key secondary outcomes for children are proportion stunted at 6 and 12 months, wasted and underweight at 6, 12 and 24 months, weight, and length trajectories from birth to 24 months, body composition (in a subsample) at 1 month of age and neurodevelopment at 6, 12, 18 and 24 months (in a subsample), micronutrients and anemia status at 24 months, morbidity and hospitalization from birth to 24 months The key secondary outcomes for women are micronutrient and anemia status, depressive symptoms and infections at the end of pre- and peri-conception, during pregnancy and postpartum period.

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Table 1. Secondary outcomes in women and timing of measurement

	Time Points						
	End of pre-conception period or reporting of pregnancy	**Gestational age 26-28 weeks**	**Gestational age 35-36 weeks**	**At birth or day 7**	**Month 2**	**Month 6**	**Month 12**
Birth interval	✓						
Body mass index	✓					✓	✓
Weight Gain		✓	✓				
Symptoms of reproductive tract infections	✓		✓				
Depressive symptoms	✓				✓		✓
Inflammatory markers (C-reactive protein, Alpha-acid glycoprotein) in a subsample	✓		✓			✓	
Micronutrient status (vitamin A, D, B12, zinc, iron, folate and selenium) in a subsample	✓		✓			✓	
Anemia status	✓		✓			✓	
Thyroid status	✓						
Diabetes status	✓						
Postpartum morbidity				✓			
Pregnancy outcomes, still birth				✓			

Table 2. Secondary outcomes in children and timing of measurement

	Time points										
	At birth or day 7		Month 3	Month 5	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
Attained length (length-for- age z score)					✓		✓				
Attained weight (weight-for-age z score)					✓		✓				✓
Stunted (length-for- age <-2 SD of the WHO Child Growth Standards)					✓		✓				
Underweight (weight-for-age z score <−2 SD of the WHO Child Growth Standards)					✓		✓				✓
Wasted (weight-for-height z score <−2 SD of the WHO Child Growth Standards)					✓		✓				✓
Weight and length trajectories	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Head circumference	✓						✓				✓
Mid-upper arm circumference					✓		✓				✓
Body composition in a sub sample		✓									
Caregiver reported development outcomes in a sub sample							✓				✓
Cognitive, language and motor scores in a sub sample											✓
Mother-infant bonding in a sub sample					✓		✓		✓		
Micronutrient status (vitamin A, D, B12, zinc, iron, folate and selenium) in a subsample											✓
Anemia status											✓
Inflammatory markers: C-reactive protein, Alpha acid glycoprotein in a sub sample											✓
Morbidity: Severe infection in neonatal period, 2 weeks prevalence of diarrhea, pneumonia, dysentery		✓	✓		✓		✓		✓		✓
Hospitalizations		✓	✓		✓		✓		✓		✓
Early initiation of breastfeeding	✓										
Exclusive breastfeeding		✓		✓							
Continued breastfeeding							✓		✓		✓
Complementary feeding: 24 dietary recalls in a sub sample						✓	✓		✓		✓

Adverse events

Adverse events to supplements will be documented. The adverse events for this study are severe allergic reactions to supplements, and deaths due to any cause which will be presented by study groups.

Sample size

Assumptions

- All sample size calculations are based on 90% power and 95% confidence level except for prematurity for which the power is 80%.
- The assumed effect sizes are larger for the combined effect of preconception, pregnancy and early childhood interventions because of delivery of multiple interventions in which the individual interventions have shown some evidence of impact.
- Available literature suggests that the largest impact of a single intervention during pregnancy on mean difference in birth weight was ~50 g (0.1 SD), and reduction of LBW was~15% (1, 2). The largest impact of a single intervention during pregnancy and/or post-natal period on mean difference in attained length ~ 0.4 cm (0.1 SD) and reduction in stunting at 24 months of age ~15% (3). We assumed at least 1.5 times higher effect size for the impact of either preconception or pregnancy and early childhood interventions compared with control. We assumed at least 2 times higher effect size for combined effect of preconception, pregnancy and early childhood interventions compared to control.

Table 3: Sample size matrix for effect of preconception interventions alone (A+B vs C+D) or pregnancy and early childhood interventions alone (A+C vs B+D)

	Main effect size	**Sample size per two groups**
Linear growth at 24 months - Mean LAZ - Proportion stunted (30%)	 0.15 SD (Absolute value 0.65 cm at 24 months) 25% relative reduction	 935 772
Birth weight/birth length Proportion LBW (25%)	0.15 SD (Absolute value 75 g birth weight and 0.35 cm birth length) 25% relative reduction	935 918
Preterm birth (12%)	25% relative reduction	**2193**
SGA at birth (36%)	25% relative reduction	558

Table 4: Sample size matrix for combined effect of preconception, pregnancy and early childhood interventions (A vs D)

	Main effect size	**Sample size per group**
Linear growth at 24 months - Mean LAZ - Proportion stunted (30%)	 0.20 SD (Absolute value 0.80 cm at 24 months) 30% relative reduction	 527 491
Birth weight/birth length Proportion LBW (25%)	0.20 SD (Absolute value 100 g birth weight and 0.45 cm birth length) 30% relative reduction	527 624
Preterm birth (12%)	30% relative reduction	**1100**
SGA at birth (36%)	30% relative reduction	381

We aim to get 1100 live births and 600 children in each group in each group (groups A, B, C, D)

The sample size of 2400 (600 children in each group) at 24 months will allow us to detect an interaction odds ratio (lOR) of ≥1.70 to 1.85 in proportion of stunted children among short mothers (height <150 cm) and proportion of stunted children among tall mothers (≥height 150 cm) between control (Routine care) and the full package intervention group with 80% power and 95% confidence.

We propose to enroll and randomize a total of 13500 eligible women (6750 in preconception group and 6750 in routine care group). Assuming 45% of women will get pregnant and randomized post pregnancy and ~30% loss prior to second randomisation and 5% between pregnancy and live birth (moving away, refusals, abortions, stillbirths, maternal deaths), we will have 1100 live births in each of the four groups at birth. During the 2 years follow up, we are assuming a 20% loss (non-availability, child deaths, refusals) and this will give us at least 600 children per group at 24 months.

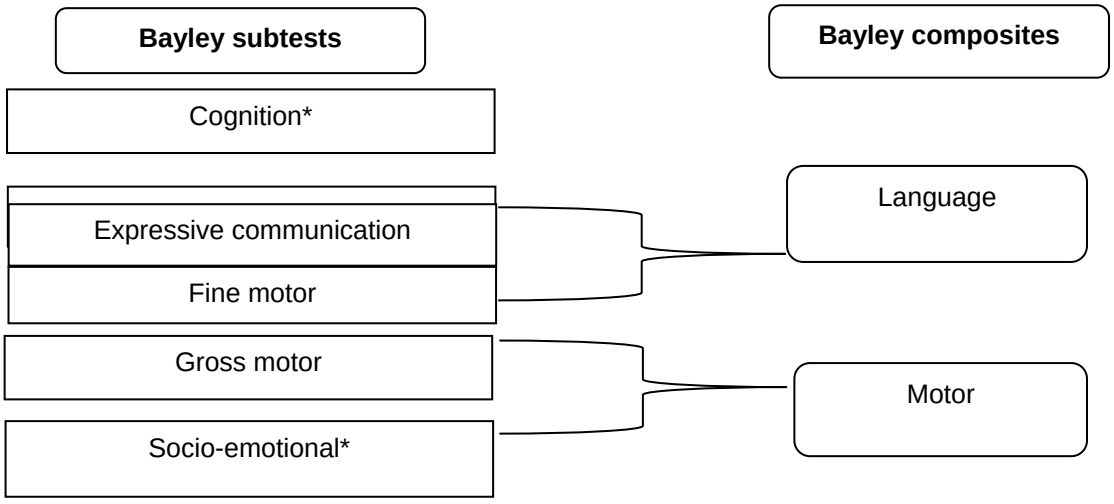
Sample size for neurodevelopment

We calculated the sample size based on the assumption that pregnancy and early childhood interventions (Group A+C) will lead to a 0.15 SD (2.25 points) increase in the neurodevelopment scores assessed by BSID-III, compared to standard/no pregnancy and early childhood interventions (B+D). We further assumed that combined preconception, pregnancy and early childhood interventions (Group A) will lead to 0.20 SD (3.0 points) increase in the neurodevelopment scores compared to control (Group D). All calculations done assuming ~10% refusals, power of 80% and two-sided alpha of 0.05. We propose to conduct neurodevelopment assessments in the sample of 1712 children.

Note on the neurodevelopment tools proposed to be used

Bayley Scales of Infant and Toddler Development (BSID), 3rd edition: This is a comprehensive assessment tool of developmental functioning in infants and toddlers aged 1-42 months. The tool is directly administered to the child to assess cognitive, language and motor development whereas socioemotional and adaptive behaviour is assessed using parent/caregiver completed rating scale. The scores are reported either as scaled scores (mean 10, SD 3; range 1 to 19) or as composite scores (mean 100, SD 15; range 40 to 160). The figure below shows the structure of the Bayley-III tool.

Figure 1. Bayley-III Structure



*Composite score equivalents available

Adaptation

We have previously done adaptations, prior to using BSID-III, in similar study settings. For the adaptation, the test items were reviewed by the team of psychologists with respect to their cultural relevance. Subsequently, necessary modifications were identified, discussed and incorporated. While conducting the adaptations, care was taken to match the style of the original item. For items that required translation in the local language i.e., Hindi, the translation was done by psychologists fluent in the local language and with a thorough understanding of the cultural context. An individual that was not a part of the study team, performed the back-translation. The adapted materials were piloted on approximately 15–20 infants and children. Standardization exercises were conducted and the inter-rater agreement was excellent (Intraclass correlation, ICC ranged between 0.92-0.99).

Ages and stages questionnaire (ASQ-3): The Ages and Stages Questionnaire (ASQ-3) is a comprehensive parent-reported assessment tool that evaluates five key domains of child development: communication, gross motor, fine motor, problem-solving, and personal-social skills. This questionnaire is specifically designed to monitor and track developmental progress in children from birth up to 5 years of age. In the study, ASQ-3 assessments were conducted at the children's homes by a team of trained and standardized researchers. The assessment took place at two specific points in the child's life: once at 12 months and again at 24 months of age. The questionnaire contains age-appropriate questions tailored to each developmental domain, allowing parents to report on their child's skills and behaviors in communication, gross motor skills, fine motor skills, problem-solving abilities, and personal-social interactions. Each of the 5 domains has 6 questions where the mother is expected to answer “Yes”, “No” or “Not Yet”. 10 Points are given for “Yes”; 5 points for “No” and 0 points for “Not Yet”. The score obtained within each domain can range from 0 to 60.

Mother-child bonding assessment: Adapted version of the Observation of Mother Child Interaction (OMCI) tool developed by Rasheed and Yousafzai has been used to collect data on mother child interaction at 6, 12 and 18 months of child age. The tool consisted of questions pertaining to maternal and child behaviours. During the home visit for observing the interaction, the trained and standardized outcome team members counted each behaviour and then coded that behaviour as either 0: never occurred, 1: occurred infrequently (1–2 times), 2: sometimes occurred (3–4 times), or 3: occurred frequently (5+ times). A separate maternal and child score was calculated based on the responses for the items. The negative items were reverse coded so that higher scores reflected more positive and responsive mother-child interactions. Child and maternal scores were also combined to create a total score.

Home Observation for Measurement of the Environment (HOME) inventory tool: The quality of stimulation, support and opportunities for learning available for children at home was assessed through Home Observation for Measurement of the Environment (HOME) inventory tool. It has a set of 45 items, responses for which are either marked through observation or through interview with the

caregivers. The responses are coded as either 0 (not observed/reported during visit) and 1 (observed/reported during visit). A higher attained overall score reflects better stimulation at home. Data collection is to be done by trained independent outcome team members through home visits.

SECTION 2: STATISTICAL PRINCIPLES

Trial population

Married women aged 18-30 years fulfilling the eligibility criteria and when they will become pregnant and are randomized again and their babies.

Recruitment

A CONSORT flow diagram will be used to summarise the following:

- Number of women screened
- Ineligible at screening with reasons
- Eligible and randomised
- Eligible but not randomised with reasons
- Lost to follow-up

The numbers (with reasons) of losses to follow-up (drop-outs and withdrawals) over the course of the trial will be summarised by randomization group.

Analysis population

The primary analysis will be performed according to the intent-to-treat principle. The intention-to-treat population will include all randomised participants according to the intervention they were randomised to receive.

Primary comparisons

We will conduct three pre-specified comparisons for all primary and secondary outcomes;

1. Effect of preconception interventions: groups that received preconception interventions (A+B) compared to the groups that did not receive preconception interventions (C+D)

2. Effect of pregnancy and early childhood interventions: groups that received pregnancy and early childhood interventions (A+C) compared to the groups that did not receive pregnancy and early childhood interventions (B+D)

3. Effect of combined preconception, pregnancy and early childhood interventions: group that received interventions during preconception, pregnancy and early childhood (A) compared to the control group (D)

Interaction assessment for factorial design

We will examine for interaction between the intervention package delivered during preconception and during pregnancy and early childhood periods on primary outcomes at birth and 24 months. We will create two dummy variables for receiving preconception interventions (0=No, 1=Yes) and pregnancy and early childhood interventions (0=No, 1=Yes). We will include a multiplicative interaction term of these two variables in the generalized linear model to assess the interaction between two intervention groups. Interaction will be significant if the p value of interaction term will be <0.05.

Comparability of participants across the groups

We will compare means, and proportions by different groups to check whether the randomization schemes resulted in comparability of different groups. Characteristics both at first and second randomization will be compared to check imbalances across the groups. We will present mean age of women, mean height of women, proportion of women with height <150 cm, women education, women occupation, religion, wealth index of the household, women BMI, family having BPL card, family having health insurance, and place of birth. As per the Consolidated Standards of Reporting Trials (CONSORT) guidelines, we will not perform significance tests to compare baseline characteristics among the intervention groups. Characteristics with a 20-25% relative difference between groups will be adjusted in the final model.

Main effects

We will use generalized linear models of the Poisson family with a log-link function for binary outcomes to calculate incidence rate ratio (IRR). Generalized linear models of gaussian family with an identity-link function will be used for continuous outcomes to calculate mean difference (MD). The final models will be adjusted for potential confounders.

We will also display comparisons of individual groups and assess interaction between preconception interventions and pregnancy and early childhood interventions for all primary outcomes.

LAZ and WAZ scores from birth to 24 months will be created using Kernel weighted local polynomial smoothing technique (a natural extension of the local mean smoothing of Nadaraya–Watson, local polynomial regression involves fitting the response to a polynomial form of the regressor via locally weighted least squares) for all three comparisons.

We will also estimate absolute risk reduction and their 98.3% confidence intervals for categorical primary and secondary outcomes at birth and at 24 months.

Adjustment for multiplicity

We will use 98.3% confidence intervals of effect sizes for all primary and secondary outcomes to adjust for the three primary comparisons (significance level 0.05/3 or 0.017).

The study has multiple primary outcomes related to low birthweight (proportion LBW, SGA and preterm, and mean birth weight and length) and stunting (proportion stunted and mean length for age z-score at 24 months of age). Our *a priori* decision is not to adjust for multiple primary outcomes because the primary outcomes are likely to be correlated, we are not addressing a universal null hypothesis, and that formal adjustments for multiplicity are unlikely to enhance interpretation (4).

However, we will conduct a *post-hoc* sensitivity analysis where we will adjust p values for multiple primary outcomes using the Holm-Bonferroni method (5). In this sensitivity analysis, we will adjust for a total of 21 comparisons; seven primary outcomes (five at birth and two at 24 months) and three two-group comparisons.

All summary statistics will be rounded presented to one decimal precision of the raw values, except for the minimum and maximum values. These values will be presented with the same decimal precision as the raw values and SD will be presented to 2 but if too small then to 3 decimal precisions than the raw value. P-values will be presented to 3 decimal precisions.

Missing Data

We will include all subjects in the analysis irrespective of duration or compliance to intervention, provided the outcome data are available for primary outcomes. No imputation will be made for the primary outcomes.

Adherence

Compliance will be assessed for all interventions periodically during all periods; preconception, pregnancy , postnatal and childhood . Compliance to nutritional interventions will be assessed based

on the percent days the intervention i.e., Iron folic acid tablets, multiple micronutrients, snacks, milk or egg was consumed. It will be defined as:

% compliance = (number of IFA tablets taken / number of IFA tablets supposed to have been taken) *100%.

The number of IFA tablets supposed to have been taken will be calculated for the duration of intervention (end of study intervention – start of study intervention).

It will be summarised as descriptive statistics median, IQR) or mean (SD)

The compliance to health, psychosocial intervention will be presented as proportion screened and proportion treated.

Definitions used for analysis

Outcome	Definition
Birth weight	Weight measured by study team on day 7 (up to + 6 days)
Birth length	Length measured by study team on days 1-7 (up to + 6 days)
Low birth weight	Birth weight <2500g
Preterm birth	Ultrasound confirmed gestational age at birth <37 weeks
Small for gestational age	Birth weight <10th centile according to intergrowth standards-21
Length-for-age z score	Calculated based on length measured on days 1-7 (up to + 6 days) and at 6,12,24 months (up to 12 weeks)
Stunted	Length for age z score <-2SD by WHO Child Growth Standards
Gestational age	Calculated using crown to rump length (CRL) measured according to intergrowth standards if CRL is >15mm and <95mm. If CRL >95mm then head circumference and femur length will be used.
Spontaneous preterm	Spontaneous onset of labour before 37 completed weeks of gestation with intact membranes, without intervention from the caregiver.
Head circumference	Head circumference measured by study team on day 7 (up to + 6 days) and at 6,12, 24 months (up to 12 weeks)
Stillbirth	A baby who dies after 28 weeks of gestation, but before or during birth.
Weight-for-length z score	Calculated based on weight and length measured at 6,12, 24 months (up to 12 weeks)
Weight-for-age z score	Calculated based on weight measured at 6,12, 24 months (up to 12 weeks)
Wasted	Weight-for-length z score <-2SD by WHO Child Growth Standards
Underweight	Weight-for-age z score <-2SD by WHO Child Growth Standards
Mid-upper arm circumference	Mid-upper arm circumference measured by study team at 6,12, 24 months (up to 12 weeks)
Gestational weight gain	Weight gain from second randomization (pregnancy confirmation) to 26-28 weeks and 35-37 weeks of gestation
Exclusive breastfeeding	No other food or drink, not even water, except breast milk (including milk expressed or from a wet nurse), but allows the infant to receive ORS, drops and syrups (vitamins, minerals and medicines) in last 24 hours
Continued breastfeeding	Breastfeeding continued till 12 months of age
Possible serious bacterial infection	Reported one of the following – not able to breastfeed or feed, fever, cold to touch, lethargy or unconscious or convulsions or fast or difficult breathing or pneumonia (local term)
Local infection	Presence of skin infection or discharge from eyes or ears
Diarrhea	Reported by mother or caregiver Symptoms of dehydration and dysentery: Not able to drink, lethargy or unconsciousness, restlessness or irritability and sunken eyes; dysentery: blood in stool
Pneumonia	History of cough reported by the mother or difficult breathing or chest indrawing
Severe pneumonia	Pneumonia with one or more of the following danger signs – not able to

Outcome	Definition
	breastfeed or feed, fever, cold to touch, lethargy or unconsciousness or convulsions or stridor
Reproductive tract infection	Any symptoms of vaginal discharge, itching, burning, swelling, ulcer in genital region, swelling and pain lower abdomen
Hypothyroidism	Preconception: TSH >5.5 mIU/ml; Pregnancy: TSH ≥4.0 mIU/ml
Pre-diabetes or diabetes	HbA1c >5.7%
Hypertension	systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg
Anemia	Preconception: Mild anemia: Hb 10 to 11.99 g/dL, Moderate anemia: Hb 8 to 9.99 g/dL, Severe anemia: Hb <8g/dL Pregnancy: Mild Anemia: hemoglobin 10-10.99 g/dL, Moderate Anemia: hemoglobin 7-9.99 g/dL, Severe Anemia: hemoglobin <7 g/dL Postnatal mother: Mild anemia: Hb 10 to 11.99 g/dL, Moderate anemia: Hb 8 to 9.99 g/dL, Severe anemia: Hb <8g/dL Children: Mild Anemia: hemoglobin 10-10.99 g/dL, Moderate Anemia: hemoglobin 7-9.99 g/dL, Severe Anemia: hemoglobin <7 g/dL
Months between previous birth to pregnancy	Interval (in months) between previous birth to current pregnancy
Months between marriage to pregnancy	Interval (in months) between marriage to current pregnancy
Depressive symptoms	PHQ-9 score ≥10 or suicidal ideation
Moderate to severe neurodevelopmental delay	Composite score of less than 85 on BSID-III assessment- for each of the domains i.e., cognition, motor, language and socio-emotional
Antepartum hemorrhage	Reported excessive bleeding from vagina occurring any time during pregnancy, before delivery that wet her clothes
Preeclampsia/ Eclampsia	Preeclampsia: Measured diastolic blood pressure ≥90 mmHg and/or systolic blood pressure ≥140 mmHg and proteinuria (by dipstick1-4+), Eclampsia: Preclampsia with convulsions before, during or after pregnancy
Postpartum hemorrhage	Reported excessive bleeding after delivery, with or without loss of consciousness

Subgroup Analysis

We will conduct pre-specified sub-group analysis according to women's height (< 150 cm and ≥ 150 cm), BMI status at enrolment and at the time of pregnancy confirmation (<18.5, 18.5 to 24.99 and ≥25 to 29.99 and ≥30 kg/m^2 (based on WHO classification of BMI), years of education (1-5, 6-11, 12-14, ≥15 years), high risk pregnancy and wealth quintile of the household. The relative measures of effect within each of these subgroups will be presented as forest plots for three pre-specified primary comparisons for primary outcomes at birth and 24 months. High risk pregnancy will be defined if a woman has any of the following condition at the time of confirmation of pregnancy; moderate or severe anemia or symptoms of reproductive tract infections or hypertension, or hypothyroidism or diabetes or moderate to severe depressive symptoms (PHQ-9 score ≥10 or suicidal ideation) or history of previous preterm birth, intrauterine deaths, lower segment caesarean section. We will use generalized linear models as used for primary outcomes to assess the intervention effect.

All analysis will be conducted using STATA, version 16.

Data Safety Monitoring Committee (DSMC)

The Data Safety Monitoring Committee (DSMC) will be a technical body constituted by the WHO with members who have expertise in epidemiology, paediatrics, nutrition, community health and statistics. DSMC will be responsible for safeguarding the interests of study participants, investigators and funders, assessing the safety and early efficacy of study interventions according to data available at a

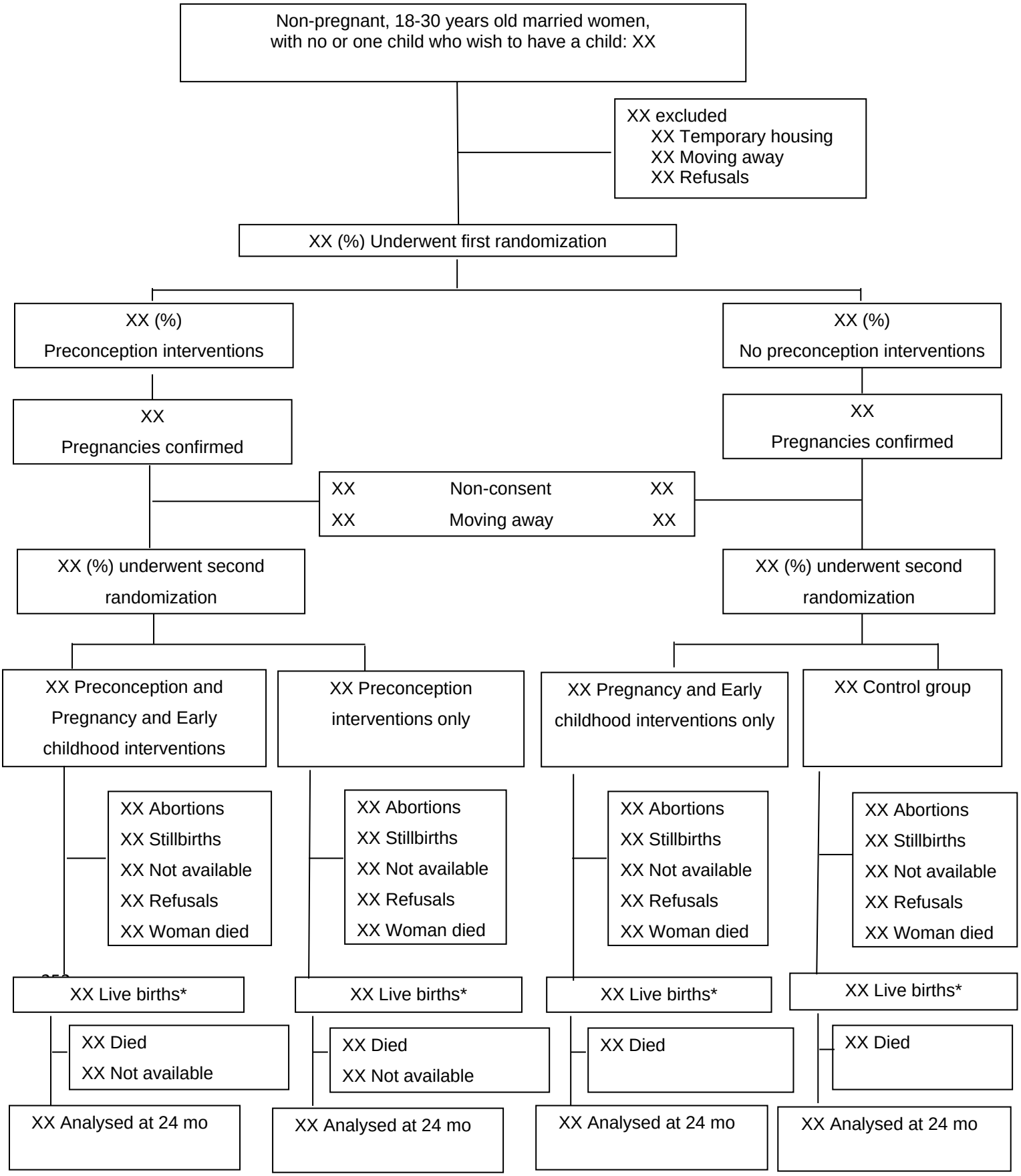
predefined schedule, monitoring the study overall conduct and quality and protecting its validity and credibility and making recommendations concerning continuation/terminate of study.

The DSMC will conduct one interim analysis when 50% of sample size for primary outcomes will be achieved. The two sets of primary outcomes will be assessed at different time points, at birth and at 24 months. The DSMC will use prespecified conservative O'Brien-Fleming stopping rule (P<0.001) for early efficacy to have minimum impact on type 1 error in the final analysis (6).

Dummy figures and tables

The dummy figures and tables of CONSORT flow diagram, baseline characteristics of enrolled women at first and second randomization, pre-specified comparisons of primary and secondary outcomes at birth and 24 months, and compliance to interventions during preconception, pregnancy, post-natal and early childhood periods are given below. Other secondary outcomes will be presented in similar way.

Figure X. Screening, enrollment, randomization and follow up



*X twins

Table X. Baseline characteristics of enrolled women at first and second randomization

Characteristics at enrolment	First randomization		Second randomization			
	Preconception interventions N=	No Preconception interventions N=	Preconception, pregnancy and early childhood interventions Group A N=	Preconception interventions only Group B N=	Pregnancy and early childhood interventions only Group C N=	Control group Group D N=
Mean (SD) Age of women – yr						
Mean (SD) Height of women – cm						
Height <150 cm – n (%)						
BMI category (kg/m^2) – n (%)						
≥25						
18.5 to 24.99						
<18.5						
Joint or extended family* – n (%)						
Women schooling ≥12 yr – n (%)						
Homemaker – n (%)						
Family has below poverty line card – n (%)						
Family covered by health insurance scheme – n (%)						
Place of births‡ – n (%)						
Large hospitals						
Small hospitals or birthing centres						
Home births						
Twins – n (%)						

* Joint or extended family: Adult relatives other than the enrolled woman's husband and children living together in a household

Table X. Pre-specified comparisons of primary and secondary outcomes at birth

Outcomes	Group A n=1290	Group B n=1276	Group C n=1093	Group D n=1093	Preconception intervention groups vs no preconception intervention groups A+B vs C+D		Pregnancy intervention groups vs no pregnancy intervention group A+C vs B+D		Preconception and pregnancy intervention groups vs no preconception and pregnancy intervention group A vs D	
					IRR (98.3%)	ARR (%) or MD (98.3%)	IRR (98.3%)	ARR (%) or MD (98.3%)	IRR (98.3%)	ARR (%) or MD 98.3%
Primary										
LBW*†										
Preterm†										
SGA†										
Birth weight, g‡										
Birth length, cm§‡										
Secondary										
Spontaneous preterm†										
Stunting†										
Head circumference, cm‡										
Stillbirths†										

†Adjusted incidence rate ratio (IRR), §Adjusted mean difference or absolute risk reduction adjusted for potential confounders

Group A: Preconception, pregnancy and early childhood intervention; **Group B**: Only preconception intervention; **Group C**: Only pregnancy and early childhood intervention; **Group D**: Control

Group A+B vs Group C+D: Effect of preconception interventions: women who received interventions compared with those who did not receive preconception interventions; **Group A+C vs Group B+D**: Effect of pregnancy and early childhood interventions: women who received these interventions compared with those who did not receive these interventions; **Group A vs Group D:** Effect of preconception, pregnancy and early childhood interventions: women who received interventions in these periods compared with those who received routine care

Table X. Primary and secondary anthropometry outcomes at 24 months of age

Outcomes	Group A n=453	Group B n=439	Group C n=293	Group D n=271	Preconception intervention groups vs no preconception intervention groups A+B vs C+D		Pregnancy intervention groups vs no pregnancy intervention group A+C vs B+D		Preconception and pregnancy intervention groups vs no preconception and pregnancy intervention group A vs D	
					IRR (98.3%)	ARR (%) or MD (98.3%)	IRR (98.3%)	ARR (%) or MD (98.3%)	IRR (98.3%)	ARR (%) or MD (98.3%)
Primary outcomes										
Mean (SD) length-for-age z score*										
Stunted – n (%)†										
Secondary outcomes										
Mean (SD) weight-for-length z score*										
Wasted – n (%)†										
Mean (SD) weight-for-age z score*										
Underweight – n (%)†										
Mean (SD) mid-upper arm circumference – cm*										
Mean (SD) head circumference – cm*										

*Adjusted mean difference (MD), Absolute risk reduction (ARR). †Adjusted Incidence rate ratio (IRR), adjusted for potential confounders

Group A: Preconception, pregnancy and early childhood intervention; **Group B**: Only preconception intervention; **Group C**: Only pregnancy and early childhood intervention; **Group D**: Control

Group A+B vs Group C+D: Effect of preconception interventions: women who received interventions compared with those who did not receive preconception interventions; **Group A+C vs Group B+D**: Effect of pregnancy and early childhood interventions: women who received these interventions compared with those who did not receive these interventions; **Group A vs Group D:** Effect of preconception, pregnancy and early childhood interventions: women who received interventions in these periods compared with those who received routine care

Table X . Neurodevelopment outcomes assessed by BSID-III and ASQ-3 at 24 months of age

Outcomes	Group A (n=)	Group B (n=)	Group C (n=)	Group D (n=)	Preconception intervention groups vs no preconception intervention groups A+B vs C+D	Pregnancy intervention groups vs no pregnancy intervention group A+C vs B+D	Preconception and pregnancy intervention groups vs no preconception and pregnancy intervention group A vs D
					MD (98.3% CI) †	MD (98.3% CI) †	MD (98.3% CI) †
BSID-III composite score							
Cognitive							
Language							
Motor							
Socio-emotional							
ASQ-3 score							
Communication							
Gross motor							
Fine motor							
Problem solving							
Personal social							

BSID-III: Bayley Scales of Infant and Toddler Development, 3rd edition; ASQ-3: Ages and Stages Questionnaire, 3rd edition; †Adjusted mean difference (MD) (98.3% CI), adjusted for potential confounders

Group A: Preconception, pregnancy and early childhood intervention; **Group B**: Only preconception intervention; **Group C**: Only pregnancy and early childhood intervention; **Group D**: Control

Group A+B vs Group C+D: Effect of preconception interventions: women who received interventions compared with those who did not receive preconception interventions; **Group A+C vs Group B+D**: Effect of pregnancy and early childhood interventions: women who received these interventions compared with those who did not receive these interventions; **Group A vs Group D:** Effect of preconception, pregnancy and early childhood interventions: women who received interventions in these periods compared with those who received routine care

Table X. Neurodevelopment outcomes at 12 months assessed by ASQ-3, mother child bonding and child stimulation scores

Outcomes	Group A (n=)	Group B (n=)	Group C (n=)	Group D (n=)	Preconception intervention groups vs no preconception intervention groups A+B vs C+D	Pregnancy intervention groups vs no pregnancy intervention group A+C vs B+D	Preconception and pregnancy intervention groups vs no preconception and pregnancy intervention group A vs D
					MD (98.3% CI)‡	MD (98.3% CI)‡	MD (98.3% CI)‡
ASQ-3 score							
Communication							
Gross motor							
Fine motor							
Problem solving							
Personal social							
Mother child bonding score (OMCI)							
At 6 months							
At 12 months							
At 18 months							
HOME score at 24 mo							

ASQ-3: Ages and Stages Questionnaire, 3rd edition;
‡Model adjusted for potential confounders; OMCI - observation of mother-child interaction tool
Group A: Preconception, pregnancy and early childhood intervention; **Group B**: Only preconception intervention; **Group C**: Only pregnancy and early childhood intervention; **Group D**: Control
Group A+B vs Group C+D: Effect of preconception interventions: women who received interventions compared with those who did not receive preconception interventions; **Group A+C vs Group B+D**: Effect of pregnancy and early childhood interventions: women who received these interventions compared with those who did not receive these interventions; **Group A vs Group D:** Effect of preconception, pregnancy and early childhood interventions: women who received interventions in these periods compared with those who received routine care

Table X. Risk of neurodevelopmental delay in children aged 24 months of age across the study groups

Outcomes	Group A (n=)	Group B (n=)	Group C (n=)	Group D (n=)	Preconception intervention groups vs no preconception intervention groups A+B vs C+D		Pregnancy intervention groups vs no pregnancy intervention group A+C vs B+D		Preconception and pregnancy intervention groups vs no preconception and pregnancy intervention group A vs D	
					IRR (98.3% CI) †	ARR (%) (98.3% CI) †	IRR (98.3% CI) †	ARR (%) (98.3% CI) †	IRR (98.3% CI) †	ARR (%) (98.3% CI) †
Cognitive										
Language										
Motor										
Socio-emotional										

BSID-III- Bayley Scales of Infant and Toddler Development, 3rd Edition; † adjusted for potential confounders; IRR-Incidence Rate Ratio; ARR- Absolute Risk Reduction; neurodevelopmental delay defined as composite score of less than 85 on BSID-III assessment

Group A: Preconception, pregnancy and early childhood intervention; **Group B**: Only preconception intervention; **Group C**: Only pregnancy and early childhood intervention; **Group D**: Control

Group A+B vs Group C+D: Effect of preconception interventions: women who received interventions compared with those who did not receive preconception interventions; **Group A+C vs Group B+D**: Effect of pregnancy and early childhood interventions: women who received these interventions compared with those who did not receive these interventions; **Group A vs Group D:** Effect of preconception, pregnancy and early childhood interventions: women who received interventions in these periods compared with those who received routine care

Table X. Compliance to interventions during the preconception period

	At Enrollment		At 12 month
SCREENING AND TREATMENT			
HEALTH			
Hypothyroidism			
Proportion screened (TSH), – n/total (%)			
Proportion with hypothyroidism prescribed treatment – n/total (%)			
Pre-diabetes or diabetes			
Proportion screened (HbA1c) – n/total (%)			
Proportion with pre-diabetes or diabetes prescribed treatment – n/total (%)			
Hypertension			
Proportion screened (blood pressure) – n/total (%)			
Proportion with hypertension prescribed treatment – n/total (%)			
Reproductive tract infection (RTI)			
Proportion screened (symptoms) – n/total (%)			
Proportion with RTI treated by physician – n/total (%)			
NUTRITION			
Anemia			
Proportion screened – n/total (%)			
Median (IQR) percent days iron consumed by anemic women, n=			
PREVENTIVE AND PROMOTIVE INTERVENTIONS	**Enrollment to 6 months**	**6 to 12 months**	**12 to 18 months**
NUTRITION			
Median (IQR) percent weeks ferrous fumarate plus folic acid consumed by women (anemia prophylaxis),n=			
Median (IQR) percent days multiple micronutrient consumed, n=			
Median (IQR) percent days egg or milk consumed by women with BMI <21 kg/m^2, n=			
Median (IQR) percent days snacks consumed by women with BMI <18.5 kg/$m^{2,}$ n=			
PSYCHOSOCIAL INTERVENTION			
Proportion screened for depressive symptoms (PHQ-9)			
Proportion with depressive symptoms (PHQ-9 ≥10 or suicidal ideation) initiated treatment			
Proportion counselled for positive thinking and problem solving skills			
WATER, SANITATION AND HYGIENE (WaSH)			
Proportion of women received WaSH counselling			

Anemia: Hb <12 g/dL, Hypothyroidism: TSH levels were >5.5 mIU/L or if TSH levels were between 4.0 and 5.5 mIU/L and Anti-TPO Ab positive, Prediabetes: HbA1c between 5.7% and 6.4%, Hypertension: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, Reproductive tract infection: Any symptoms of vaginal discharge, itching, burning, swelling, ulcer in genital region, swelling and pain lower abdomen

Table X. Compliance to interventions during pregnancy

HEALTH
Anemia
Proportion screened – n/total (%)
Proportion received treatment – n/total (%)
Urinary tract infections
Proportion screened – n/total (%)
Proportion provided treatment – n/total (%)
Reproductive tract infections
Proportion screened (symptoms) – n/total (%)
Proportion treated by physician – n/total (%)
Gestational Diabetes Mellitus
Proportion screened – n/total (%)
Proportion provided treatment – n/total (%)
Hypothyroidism
Proportion screened – n/total (%)
Proportion prescribed treatment – n/total (%)
Hypertension
Proportion screened (blood pressure) – n/total (%)
Proportion prescribed treatment – n/total (%)
NUTRITION
Median (IQR) percent days micronutrient supplement consumed, n=
Median (IQR) percent days iron-folic acid consumed n=
Median (IQR) percent days calcium and Vitamin D supplement consumed, n=
Median (IQR) percent days snacks consumed by women with BMI <25 kg/m^2, n=
Median (IQR) percent days egg or milk consumed by women with BMI <30 kg/m^2, n=
PSYCHOSOCIAL INTERVENTION
Proportion screened for depressive symptoms (PHQ-9) – n/total (%)
Proportion women received counselling on positive thinking and problem solving skills – n/total (%)
WATER, SANITATION AND HYGIENE (WaSH)
Proportion women who provided water filter – n/total (%)
Proportion homes where hand washing stations were installed – n/total (%)

Anemia: Hb <11 g/dL, Urinary tract infection: Urine culture microbial growth of 10^5 CFU/ml, Reproductive tract infection: Any symptoms of vaginal discharge, itching, burning, swelling, ulcer in genital region, swelling and pain lower abdomen, Gestational Diabetes mellitus: 2 hr blood sugar ≥140 mg/dL in Oral Glucose Tolerance Test, Hypothyroidism: TSH levels were >2.6 mIU/L, Hypertension: Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg

Table X. Compliance to interventions in mothers during the postnatal period

INTERVENTION	
NUTRITION	n=
Median (IQR) percent days micronutrient supplements consumed	
Median (IQR) percent days iron-folic acid consumed	
Median (IQR) percent days calcium and vitamin D supplement consumed	
Median (IQR) percent snacks consumed	
Median (IQR) percent days milk consumed	
PSYCHOSOCIAL	
Women screened for depressive symptoms (PHQ-9), n (%)	
Women who received counselling on positive thinking and problem-solving skills, n (%)	

Table X. Compliance to interventions in children from birth to 24 months

Received counselling for danger signs – n/total (%)
Birth to 6 months
Received lactation counselling
Median (IQR) percent days vitamin D consumed, n=
Median (IQR) days Iron consumed (for low birth weight), n=
6 to 24 months
Median (IQR) days iron consumed, n=
Median (IQR) days milk cereal mix consumed, n=
Received early child play and responsive care – n/total (%)
Received play mats – n/total (%)
Received potty – n/total (%)

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