Healthy Life Trajectories Initiative (HeLTI): Early Interventions to Support Trajectories for Healthy Life in India (EINSTEIN).

A cluster randomised trial evaluating a multi-faceted intervention starting preconceptionally

Statistical analysis plan

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SECTION 1: STUDY DESCRIPTION AND METHODS

Background

The Healthy Life Trajectories Initiative (HeLTI) is an international consortium that comprises four separate but harmonised intervention studies in India, South Africa, China and Canada. All projects are based on developmental origins of health and disease (DOHaD) concepts and will test evidence-based interventions spanning from preconception into the postnatal period, to improve maternal health and reduce non-communicable disease (NCD) risk in their children. The HeLTI interventions are multi-faceted and comprise: (i) optimising nutrition, physical health and mental well-being of women pre-conceptionally, during pregnancy, and postnatally; (ii) optimising infant and childhood growth, and development; and (iii) delivery of the intervention through either community health workers (India and South Africa) or professional health providers (China and Canada), using a similar approach grounded in empowerment to achieve behavioural change. The studies have adopted a longer-term view with the primary outcome being adiposity at 5 years of age in the children. Other major outcomes include child neurodevelopment, systolic blood pressure and blood glucose.

Study design

The Indian arm of the study, Early Interventions to Support Trajectories for Healthy Life in India (EINSTEIN), is set in the rural taluks (sub-districts) of HD Kote and Saragur, about 50 km from the city of Mysore in southern India. The study is a cluster randomised design with three arms (pre-conception, pregnancy and control). The HeLTI India study is unique in having three arms (two intervention and one control). We specifically added an additional arm where the interventions commence once pregnancy is established; this will allow us to compare the relative benefits and costs of initiating an intervention preconceptionally versus in pregnancy only. We have selected 105 villages based on population size (from ~250 in the area) around our main field site, Vivekananda Memorial Hospital (VMH) in Saragur, and allocated 35 villages to each arm, using a standard computerised randomisation programme. The study will recruit ~6000 married women over the age of 18 years who intend to have a child within the next two years, with a particular focus on women on newly married women. Women in all three arms will be recruited together, pre-conceptionally for baseline measurements. The longitudinal multi-faceted intervention will be delivered by trained community health workers (CHWs), which will allow future scalability.

Objectives

The overarching aim of HeLTI is to generate evidence to inform national and international policy and decision-making for the improvement of health and the prevention of NCDs.

Specific objectives:
1. To assess the effectiveness of an integrated longitudinal package of interventions delivered pre-conceptionally, during pregnancy and infancy on potential risk factors for NCD in the offspring.
2. To undertake process evaluation of the intervention package
3. To undertake an economic evaluation of the intervention package
4. To build up a diverse biorepository of samples
5. To undertake preliminary analysis on biospecimens

Outcomes

The primary outcome at age 5 years in the children is adiposity as measured by fat mass index (fat mass/height^2), using DXA (dual x-ray absorptiometry) at 5 years of age in the children. Other key outcomes at 5 years in the children include:

- Overweight and obesity (OWO) as assessed by BMI and indicators of body composition and distribution (waist circumference, skinfold thickness)
- Glucose metabolism as measured by fasting venous plasma glucose concentration
- Resting systolic blood pressure
- Child development as assessed using a cognitive battery, validated for Indian settings.

Data on all participants will be collected throughout the study at baseline and at specific intervals (Table below).

Mothers	**Baseline**
Physical health	Anthropometry: weight, height; Body composition: Bioimpedance, skinfolds (subset), DXA (subset), stable isotope (subset); Blood pressure: Digital sphygmomanometer
Biospecimen	Blood sample: Plasma, serum, DNA, RNA (subset)
Questionnaires	Diet: Food frequency questionnaire (FFQ), 24-hour food recall, diet diversity and food security questionnaires; Physical activity: Global Physical Activity Questionnaire (GPAQ); Sleep: Pittsburgh Sleep Quality Index (PSQI); General Self Efficacy Scale (GSES); Generalised Anxiety Disorder-7 (GAD-7); Patient Health Questionnaire -9 (PHQ-9); Adverse Childhood Experience (ACE) questionnaire Sociodemography; Socioeconomic status (Standard of Living Index; SLI); Medical/ treatment/drug history; Smoking and alcohol history
	Pregnancy
Physical health	Anthropometry: weight; Body composition: Bioimpedance, stable isotope (subset); Blood pressure: Digital sphygmomanometer
Biospecimen	Blood: Oral glucose tolerance test (OGTT), plasma, serum, DNA, RNA (subset); Urine; Saliva (subset)
Questionnaires	FFQ, 24-hour food recall, diet diversity and food security; GPAQ; PSQI; GSES; GAD-7; Edinburgh Postnatal Depression Scale (EPDS); Social Provision Scale; Breast-feeding Self-efficacy Scale; Perceived Stress Scale Sociodemography; Socioeconomic status (SLI); Medical/ treatment/drug history; Smoking and alcohol history
	Delivery
	Weight; Stool/rectal swab (subset); Delivery details
	Serial postnatal follow-up (up to 60 months)
Physical health	Anthropometry: Weight; Body composition: DXA (subset), stable isotope (subset); Blood pressure: Digital sphygmomanometer
Biospecimen	Blood: Plasma, serum, DNA, RNA (subset), oral glucose tolerance test (OGTT)
Questionnaires	FFQ; 24-hour food recall, diet diversity and food security; GPAQ; PSQI; GSES; GAD-7; EPDS; PHQ-9; Social Provision Scale; Breast-feeding Self efficacy Scale; Perceived Stress Scale; Parenting Stress Index; Sociodemography; Socioeconomic status (SLI); Medical/ treatment/drug history; Smoking and alcohol history
Fathers	**Index pregnancy**
	Anthropometry: Weight, height; Body composition: Bioimpedance, DXA (subset); Blood pressure: Digital sphygmomanometer Blood: Plasma, serum, DNA, RNA (subset), saliva (subset) FFQ; 24-hour food recall, diet diversity and food security; GPAQ; PSQI; PHQ-9 Sociodemography, Socioeconomic status (SLI); Medical/ treatment/drug history; Smoking and alcohol history
Child	**Birth**
	Anthropometry: Weight, length, head/arm/abdomen/chest circumference, skinfolds; Body composition: DXA Cord blood; Placenta; Umbilical cord; Meconium (subset)

	Birth to 12 months
	Anthropometry: Weight, length, circumferences; Body composition: DXA, stable isotope (subset) Feeding history; Vaccination history; Medical/treatment/drug history Stool
	Serial postnatal follow-up (major follow-up at 24 and 60 months)
	Anthropometry: Weight, length/height, circumferences; Body composition: DXA, Blood pressure; Blood samples (blood spot in infancy and venous sample at 60 months): Plasma, serum, DNA, RNA, glycaemia Feeding history; Sleep questionnaire; Ages and stages questionnaire; Neuro-cognitive developmental tools at major follow-up periods of 24 and 60 months; Executive function assessment tools; Physical activity (questionnaire and accelerometry); Screen time questionnaire; General health assessment; Vaccination history; Medical/treatment/drug history

Adverse events

Adverse events will be documented and reported to the local ethics committees at timely intervals as appropriate, and to the HeLTI Data Monitoring Committee (DMC) as regular reports.

Severe adverse events to be reported are deaths (maternal, child), stillbirths, any persistent/significant disability, any life threatening event requiring ICU admission and congenital anomalies.

Other reportable adverse events are incidents requiring child protection service involvement, hospitalization of more than 24 hours (mother, child), suicidal behavior and physical/sexual assault incidents.

SECTION 2: STATISTICAL PRINCIPLES

Sample size

Our study has been powered to detect a 0.25 standard deviation (SD) difference in offspring fat mass index at 5 years of age between intervention and control groups. Our recruitment strategy is based on having ~2100 children at age 5 for the measurement of the primary outcome. We intend to recruit ~6000 initially at baseline. We anticipate 50% will become pregnant within two years (based on data from our formative work). Allowing a 5% pregnancy loss and 20% drop out/loss to follow-up rate, we expect to have ~750 children in each arm available for follow up to assess our primary outcome; this allows us a buffer. Assuming an intra-cluster correlation of 0.03, this gives over 95% power to detect a 0.25 SD difference in fat mass between the intervention and control groups and ~80% power to detect sex differences. Our median time to pregnancy is ~7 months currently and pregnancy rates are higher than expected.

Recruitment and retention

As per the Consolidated Standards of Reporting Trials (CONSORT) guidelines, a flow diagram will be used to summarise the following:

- Number of women screened
- Eligible
- Randomised (by group)
- Pregnancies (by group)
- Deliveries (by group)
- Lost to follow-up/drop-outs (by group, at each stage)

Primary analysis

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

Comparability of participants across the groups

We will compare means, and proportions by different groups to check whether the randomisation process resulted in comparable groups. Characteristics at baseline will be compared to check imbalances across the groups.

Baseline characteristics of the women
Number of women enrolled in the study
Baseline questionnaire data collected
Age
Mean (SD)
Maternal BMI (kg/m^2)
Mean (SD)
Maternal underweight (%)
Maternal Overweight (%)
Maternal Obese (%)
Employment Status (%)
Smoking status
Education Level
Education completed years Mean (SD)

Highest level of education (Masters) n (%)

As per the CONSORT guidelines, we will not perform significance tests to compare baseline characteristics among the intervention groups. Where there are considerable differences in characteristics, we will undertake analyses with and without adjustment for such characteristics to assess their potential for confounding.

Unblinding

The HeLTI Research Committee (RC) sought feedback from external experts in clinical trials, epidemiology, statistics, ethics and DOHaD science about the unblinding of results to investigate interim analyses. After consideration of this feedback and extensive further discussion, the HeLTI RC had resolved to unblind at different times of the trials, to investigate interim analyses at the end of each of the four phases (preconception; pregnancy; infancy (0-2 years); and early childhood (3-5 years)).

Main comparisons

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

1. Effect of interventions in the preconception group versus the control group
2. Effect of interventions in the pregnancy group versus the control group
3. Effect of interventions in the preconception group versus the pregnancy group.

We will use generalised linear models (Gaussian and Poisson) for continuous and binary outcomes to calculate mean difference and incidence rates. We will also estimate absolute risk reduction and confidence intervals for categorical primary and secondary outcomes. We will use models with random intercept/slope effects to estimate the intervention effect. We will adjust for potential confounders in the final models including the baseline characteristics outlined.

We will evaluate the impact of the intervention on birth size (weight, length and head circumference), weight and length/height at the end of 1, 2 and 5 years, proportions of SGA/LGA at birth, as well as on indicators of perinatal morbidity/mortality including gestational diabetes mellitus and preeclampsia. We will also assess the impact of the intervention on maternal gestational weight gain, the proportion meeting international gestational weight gain guidelines, breastfeeding status as well as on maternal diet and physical activity in the preconception and pregnancy periods.

At 5 years of age in the children, we will assess the effect of the intervention on fat mass index (the primary outcome). Other anthropometric outcomes to be assessed at this time include weight/BMI/height and overweight/obesity/underweight/stunting. We will also assess the effect of the intervention on glucose metabolism and blood pressure. In addition, neurodevelopmental outcomes will also be assessed longitudinally.

We will also assess a host of process outcomes and other secondary outcomes outlined in the table of data collection.

Adjustment for multiplicity

As we have decided on a single primary outcome, our a priori decision is not to adjust for multiple secondary outcomes. We will undertake analyses on multiple secondary outcomes provided the data are available for such outcomes; outcomes will not be imputed.

Missing data

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

Adherence

Compliance will be assessed for all interventions during all periods: preconception, pregnancy and postnatal. Compliance to micronutrient supplements will be assessed based on pill counts. It will be defined as:
% compliance = (number of MMN tablets taken / number of MMN tablets supposed to have been taken)*100%.
The number of MMN tablets supposed to have been taken will be calculated for the duration of intervention (end of study intervention – start of study intervention).

The compliance to the behavioural / health / psychosocial interventions will be presented as the number (and proportion of expected) sessions attended, duration of sessions and number of repeat sessions attended.

Subgroup analysis

Due to possible heterogeneity of effects for key outcomes according to the time and duration of initiation of the intervention, we will conduct a subgroup analysis stratifying by this variable, testing for heterogeneity. Sensitivity analyses will be performed to assess the influence of losses to follow-up and compliance to intervention.

Data Monitoring Committee

The Data Monitoring Committee (DMC) is a technical body constituted for all four HeLTI trials with members who have expertise in epidemiology, paediatrics, obstetrics, public health, statistics and trial methodology. The DMC is 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 overall study overall conduct and quality, and making recommendations for continuing or stopping the study.