BMJ Open

Protocol for a cluster randomised trial evaluating a multifaceted intervention starting preconceptionally—Early Interventions to Support Trajectories for Healthy Life in India (EINSTEIN): a Healthy Life Trajectories Initiative (HeLTI) Study

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To cite: Kumaran K, KrishnaveniGV,SuryanarayanaKG, *et al*. Protocol for a cluster randomised trial evaluating a multifaceted intervention starting preconceptionally—Early Interventions to Support Trajectories for Healthy Life in India (EINSTEIN): a Healthy Life Trajectories Initiative (HeLTI) Study. *BMJ Open* 2021;**11**:e045862. doi:10.1136/bmjopen-2020-045862

► Prepublication history and additional material for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-045862).

Received 15 October 2020
Revised 11 December 2020
Accepted 18 December 2020

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ABSTRACT

Introduction The Healthy Life Trajectories Initiative is an international consortium comprising four harmonised but independently powered trials to evaluate whether an integrated intervention starting preconceptionally will reduce non-communicable disease risk in their children. This paper describes the protocol of the India study.

Methods and analysis The study set in rural Mysore will recruit ~6000 married women over the age of 18 years. The village-based cluster randomised design has three arms (preconception, pregnancy and control; 35 villages per arm). The longitudinal multifaceted intervention package will be delivered by community health workers and comprise: (1) measures to optimise nutrition; (2) a group parenting programme integrated with cognitive–behavioral therapy; (3) a lifestyle behaviour change intervention to support women to achieve a diverse diet, exclusive breast feeding for the first 6 months, timely introduction of diverse and nutritious infant weaning foods, and adopt appropriate hygiene measures; and (4) the reduction of environmental pollution focusing on indoor air pollution and toxin avoidance.
The primary outcome is adiposity in children at age 5 years, measured by fat mass index. We will report on a host of intermediate and process outcomes. We will collect a range of biospecimens including blood, urine, stool and saliva from the mothers, as well as umbilical cord blood, placenta and specimens from the offspring.

An intention-to-treat analysis will be adopted to assess the effect of interventions on outcomes. We will also undertake process and economic evaluations to determine scalability and public health translation.

Ethics and dissemination The study has been approved by the institutional ethics committee of the lead institute.

Strengths and limitations of this study

- The study will evaluate, for the first time in India, whether a multifaceted intervention starting preconceptionally and continuing through pregnancy, infancy and early childhood reduces risk factors for non-communicable disease in the offspring.
- The study builds on 35 years of local work which has resulted in strong community engagement and rapport.
- The process and economic evaluations will help in scalability while the use of local community workers will aid translation.
- Given the long-term nature of the study, unblinding of selected outcomes will occur at the end of each phase to enable interim mechanistic analyses and thereby maximise the study potential.
- Due to the study design, effectiveness of individual components of the intervention cannot be evaluated.

Findings will be published in peer-reviewed journals. We will interact with policy makers at local, national and international agencies to enable translation. We will also share the findings with the participants and local community through community meetings, newsletters and local radio.
Trial registration number ISRCTN20161479, CTRI/2020/12/030134; Pre-results.

INTRODUCTION

Non-communicable diseases (NCDs) are major causes of death and disability globally[1 2] and are rising rapidly in low/middle-income countries (LMICs).[1–3] The rising burden of cardiometabolic disease in LMICs is accompanied by a growing recognition of the burden of mental health disorders. Depression is the leading neuropsychiatric cause of disease burden globally and in LMICs,[4] and is projected to be the second leading cause of disease burden by 2020.[5]

In India, an estimated 65 million people have diabetes and a further 77 million are pre-diabetic.[6 7] Unchecked, the population with diabetes is expected to reach 109 million by 2035.[6] A review showed that 13% of young people aged 1–16 years in India experience mental health disorders.[8] In later life, ~3.7 million people over 60 years of age have dementia; this number is expected to double by 2030 and triple by 2050.[9] These diseases have significant economic implications; the treatment and related costs amount to INR 19 914 (US$398) and INR 43 285 ($865) per person per year for diabetes[10] and dementia,[11] respectively.

The developmental origins of health and disease (DOHaD) hypothesis suggests that adversity during early life influences adult NCD risk.[12 13] DOHaD research suggests that NCD risk is influenced not only by exposure to the well-known 'load' factors such as adult obesity and physical inactivity, but also by the 'capacity' of key metabolic tissues, which is acquired during early development.[14] It is now well established that low birth weight (LBW), poor infant nutrition, and rapid childhood weight gain and obesity are risk factors for poor health trajectories and development of NCDs in later life.[15 16]

Undernutrition (including widespread micronutrient deficiencies) remains a significant problem in India. In children under 5, the prevalence of stunting is ~35%; wasting ~17%; underweight ~33% and anaemia ~41%.[17] In women aged 15–49 years, 23% are underweight (body mass index (BMI) <18.5 kg/m^2) while ~53% are anaemic.[18] These factors are reflected in a high prevalence of LBW (<2500 g) in ~21% of the 26 million babies born in India each year.[19] Rates of obesity are also increasing; it is estimated that ~12% of children and ~21% of women of reproductive age are overweight or obese (adult BMI>25 kg/m^2).[18]

Application of DOHaD principles offers a novel approach to tackling NCDs by delivering interventions in an integrated manner across the lifecourse: in adolescent or young women to ensure they approach pregnancy in optimum health; in pregnant women to ensure a healthy pregnancy and safe delivery; and in infancy and childhood to prevent excessive childhood adiposity and promote child development.

The Healthy Life Trajectories Initiative

In this context, the Healthy Life Trajectories Initiative (HeLTI) was launched as a joint initiative between the Canadian Institute of Health Research, the Department of Biotechnology of India, the South African Medical Research Council, the National Science Foundation of China and the WHO. This programme follows a DOHaD approach, focusing on reducing the long-term risk of NCDs through interventions that target the interaction between environmental factors and genes during preconception, conception, fetal life, infancy and early childhood. The HeLTI programme comprises four separate but harmonised randomised controlled trials in India, China, South Africa and Canada. The HeLTI interventions are multifaceted; the rationale is that previous single intervention trials (eg, multiple micronutrient supplementation) have shown only modest benefits for pregnancy and child outcomes and that multiple interventions are needed to create impact in populations with multiple environmental and social disadvantages. Previous trials have usually started after confirmation of pregnancy and have therefore missed the important periconceptional and early pregnancy processes of epigenetic change, placentation and organogenesis; starting preconceptionally will address these issues.

The HeLTI consortium has a collective governance structure for the management of the trials. The two colead PIs of each of the four HeLTI trials form an overarching Research Committee (RC), with rotating chairpersons, responsible for overall project management and oversight, liaising with working groups and reporting to the HeLTI Council (comprising representatives from all the funders and a WHO secretariat). Working groups, including investigators from all countries chaired by one of the lead PIs, develop harmonised protocols, covering biospecimens, data collection, interventions, cohort management and retention, and data management. Each country project team has a steering committee, comprising the two PIs and selected co-PIs, which deals with day-to-day operations and reports to the RC, as well as liaising with participating institutions and community representatives. The four HeLTI trials have a common data monitoring and safety committee comprising independent international experts, with representation from the four countries involved. The WHO will monitor the trial conduct.

The India study

We report the protocol for the Indian study, Early Interventions to Support Trajectories for Healthy Life in India in this paper. Research by our group has shown that part of the increased NCD risk in Indians comes from changes in fetal body composition. The undernourished Indian newborn is typically light and thin (average birth weight 2.7 kg) and has a low lean body mass, but is

disproportionately adipose (the 'thin-fat' Indian).[20 21] This phenotype persists through childhood and into adult life, and is associated with diabetes and CVD at relatively low levels of obesity. The effects of early life undernutrition are exacerbated by poor weight gain in infancy and rapid childhood weight gain even in the absence of obesity.[22]

We have specifically chosen a rural population where obesity is currently uncommon, but undernutrition is common. This population is representative of a large section of the Indian population where economic transition has started and is likely to benefit most from interventions to improve early development (capacity) as well as those that reduce the postnatal obesogenic effects of transition (load).

METHODS AND ANALYSIS

Our overarching aim is to investigate whether an integrated intervention starting preconceptionally and continuing at appropriate points across the lifecourse (pregnancy, infancy and childhood) will reduce childhood adiposity and the risk for NCDs as well as improve measures of child neurodevelopment.

Patient and public involvement

Community participation is key to the success of our programme and we have engaged with the local community including community leaders, village women, village elders and local groups, particularly women's self-help groups. We held engagement meetings at village level to explain the study and clarify any queries people may have. We undertook extensive formative work over a period of ~18 months which included face-to-face meetings and focus group discussions. This work helped to finalise our intervention package and delivery methods, and dissemination plans.

Subjects

Our proposed study will be set in rural Mysore, in HD Kote and Saragur Taluks about 50 km from Mysore city in southern India. The population is characterised by subsistence farming, poor nutritional status, low levels of literacy particularly among women, and limited access to specialist health services. Approximately 25% of women are underweight, 19% are overweight and 45% are anaemic.[23] Less than 60% of infants are exclusively breast fed for 6 months.[24] Over 60% of children under 5 are anaemic and less than two-thirds are fully immunised.[23 24] The prevalence of both stunting and underweight in children under 5 is ~38%.[24] Sanitation and hygiene facilities are limited and toilets are mostly shared. The local area receives potable water from taps, most commonly from shared taps situated in streets. Borewells are also a common source of water. The population is relatively stable, minimising loss to follow-up. Signs of transition are evident; village shops sell high-energy, high-salt, high-sugar snacks and drinks which are mainly consumed by children and young people. Better transport links have increased access to nearby towns and cities, allowing people to seek employment in small/cottage industries.

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 will allocate 35 villages to each group, using a standard computerised randomisation programme. We will include women who are over the age of 18, married, have no children or one child and are planning to have a child within the next 2 years. We will particularly focus on newly married women, who have a high likelihood of pregnancy within a year.

Study design

The study is a community-based, cluster-randomised intervention with three arms (preconception, pregnancy and control), with individual villages forming the basis for the cluster. Women in all three arms will be recruited together, preconceptionally for baseline measurements. The longitudinal multifaceted intervention will be delivered by trained community health workers (CHWs), which will allow future scalability.

All participants will receive iron and folic acid tablets during pregnancy as per Indian guidelines. Calcium is routinely prescribed in pregnancy by many obstetricians. We will not interfere with routine care provided by the women's obstetricians. We will liaise with local doctors to ensure that they are aware of the study and the supplements their patients are taking, so that the women do not receive 'excess' micronutrients. All women will also receive menstrual hygiene advice and will be provided with a supply of menstrual pads to promote appropriate hygiene practices.

Intervention details

Group 1 (preconception arm)

Micronutrient supplementation: women will receive daily micronutrient supplement tablets from recruitment preconceptionally, throughout pregnancy and during breast feeding. Given the high likelihood of multiple deficiencies, the composition will be based on the WHO/UNICEF/UNU international multiple micronutrient preparation.

Lifestyle behaviour change support: women will receive support from CHWs trained in Healthy Conversation Skills (HCS), in group settings. The details of the group work are in online supplemental appendix 1. HCS is a communication technique developed at the University of Southampton by our wider team for use by health workers to support behaviour change in socioeconomically disadvantaged women.[25] This technique has been translated to LMIC settings; in a recent feasibility study involving our group in South Africa, CHWs have been successfully trained in HCS to support young women to improve their diets and lifestyles. The group work emphasises the role of increasing self-efficacy in promoting behaviour change. It is based on the understanding that providing participants with knowledge alone is not sufficient to

change their behaviour unless they are also motivated and empowered to change. The aim will be to promote a diverse diet, achieve a normal body weight, and achieve an adequate intake of micronutrients before and during pregnancy, and while breast feeding. CHWs will provide support postnatally to encourage exclusive breast feeding for the first 6 months and the timely introduction of diverse and nutritious infant weaning foods. Women will be educated about the importance of using safe water for feeding their infants after 6 months, and advised to use boiled and cooled water. They will receive support to ensure that their infants are fully vaccinated, and that they adopt appropriate hygiene measures, particularly hand washing after using the toilet, changing 'nappies' and before preparing food, eating and feeding their infants. During the preconception stage, the group work will be held at approximately monthly intervals. There will be six modules, with the first module serving as an introductory and general health module. This will be delivered first to all women in the arm. The other five modules will be delivered cyclically and address diet, physical activity and sleep, environmental exposure and hygiene, mental health and preparing for pregnancy.

Group parenting and cognitive behaviour intervention (Learning Through Play Plus (LTP Plus)): LTP Plus is a group parenting programme, integrated with a cognitive–behavioural therapy intervention (Thinking Healthy Programme) designed to address perinatal depression and improve child development in LMIC settings.[26 27] It is a manual assisted, low-literacy, potentially sustainable programme whose activities enhance children's development. It simultaneously promotes attachment security through building parents' ability to be sensitive to their children's cues, and be actively involved in their children's development. These sessions will be delivered in phases which will not only match the woman's pace, but also the gestational period antenatally and the infant's developmental stages postnatally. This two-pronged psychosocial participatory group intervention will help mothers to cope with stress, reduce depression and provide information and strategies that they need to nurture their children's health and development. This will consist of a total of 10 sessions, 3 during pregnancy and 7 postnatally. LTP Plus uses a standardised manual and the material will be delivered by CHWs.

Avoiding environmental pollution: we will provide advice and information on avoidance of environmental pollutants particularly indoor smoke (cooking and smoking). We will facilitate liquefied petroleum gas (LPG) connections actively through a recently introduced government scheme which provides subsidised stoves and fuel. We will also address exposure to, and safe handling of pesticides.

Group 2 (pregnancy arm)

Women in this group will receive the same package of interventions described above, but starting only after they become pregnant, which, in practice, will mean late in the first trimester. Last menstrual period dates will be monitored monthly and women will be offered a urine pregnancy test when they report missing two consecutive periods.

Group 3 (control arm)

Women in this group will receive an enhanced standard of care. In addition to encouraging vaccinations (two doses of tetanus toxoid) during pregnancy, provision of 100 tablets of iron and folate, and promoting institutional delivery, they will have a similar number of contact sessions with CHWs untrained in our behaviour change and parenting interventions. They will receive standard advice on healthy lifestyle during pregnancy and postnatally, supported by information leaflets (mainly pictorial and using simple language); these will include advice on breast feeding, immunisations and infant weaning foods.

Outcomes and assessments

The primary outcome at age 5 years in the children (across all HeLTI cohorts) is adiposity as measured by fat mass index (fat mass/height^2), using dual X-ray absorptiometry (DXA)). 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 modified Kaufman battery, validated for Indian settings.

Baseline data on all participants as well as data throughout the study at intervals will be collected (table 1). Additional phenotypic data will be collected in a subset (ranging between 50 and 200 individuals per arm, depending on the assessment).

Sample size and power

All the HeLTI studies have calculated their sample size using a minimum power of 80% at 5% significance level to detect a 0.25 SD difference in offspring fat mass index at 5 years of age between intervention and control groups. We intend to recruit ~6000 initially at baseline. We anticipate 50% will become pregnant within 2 years (based on data from our formative work). Allowing a 5% pregnancy loss and 20% drop out/loss to follow-up rate, we will have ~750 children in each arm available for follow-up to assess our primary outcome (~22 per per village). Assuming an intracluster correlation of 0.03, this gives ~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. If pregnancy rates are lower than expected, we will undertake a second round of recruitment at the end of the first year.

Data analysis

As the main outcomes for the study are fat mass index, OWO rate, resting blood pressure, fasting glucose and neurodevelopmental outcomes at age 5 years, and as

Table 1 List of assessments to be carried out at various time points

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 hours 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 hours 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; OGTT; blood samples
Biospecimen	Blood: plasma, serum, DNA, RNA (subset), OGTT
Questionnaires	FFQ; 24 hours 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 hours 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 DXA, cord blood; placenta; umbilical cord; meconium
	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 (heel prick at 24 months and venous sample at 60 months): plasma, serum, DNA, RNA, glycaemia feeding history; sleep questionnaire; ages and stages questionnaire; neurocognitive developmental tools: Developmental Assessment *Scale* for Indian Infants (DASII) at 24 months; modified Kaufmann Battery at 60 months; executive function assessment tools; physical activity (questionnaire and accelerometry); screen time questionnaire; general health assessment; vaccination history; medical/treatment/drug history

most children will achieve these ages only in cycle 2 (5–10 years of project), analyses at the end of cycle 1 (0–5 years of project) will explore the effects of the intervention on child anthropometric measures (at birth and serially) and neurodevelopmental outcomes. We will also assess effects on maternal anthropometry, mental health, behavioural risk factors for adiposity/obesity and glycaemia. Process indicators including recruitment, retention and indicators of programme delivery in the intervention group/s will also be determined.

An intention-to-treat analysis will be used for the key outcomes, based on all viable pregnancies. Analysts will be blinded to the study groups. Unblinding will occur after analysis or on the advice of the independent data monitoring committee. We will use mixed models with a cluster-specific approach and robust error estimators adjusted for prespecified potential risk factors related to individual clusters and subjects (such as locality and level of care, maternal age, parity, pregnancy complications, smoking and socioeconomic status). First, standard data screening/cleaning procedures will be conducted including the extent and pattern of missing data. We will assess the comparability at randomisation of the treatment groups using descriptive analyses. The distribution of modifiable risk factors for childhood obesity, poor cardiometabolic and neurodevelopmental outcomes at baseline, and their changes over time will be assessed according to study group. For women in the intervention groups, we will evaluate the number of scheduled intervention visits, and compliance with micronutrient supplements and attendance at group sessions.

At the end of the first cycle of the project, we expect the youngest children to be 1 year of age. We will evaluate the impact of the intervention on all indicators of potential risk factors including weight for length at 1 year, birth weight and proportions of SGA/LGA, head and abdominal circumferences at birth and 1 year of age, as well as on indicators of perinatal morbidity/mortality. 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 OWO, BMI and centiles and adiposity (skinfold thickness, arm circumference). We will also assess the effect of the intervention on glucose metabolism, blood pressure and neurodevelopmental outcomes.

Mixed models with random intercept/slope effects and fixed effects (for the intervention) will be used to estimate the intervention effect. Due to possible heterogeneity of effects for key outcomes according to the time of initiation of the intervention (eg, preconception vs pregnancy), we will conduct a subgroup analysis stratifying by this variable, testing for heterogeneity. For a 'per-protocol' analysis, we will categorise clusters as high or low according to the compliance with implementation of the intervention. Sensitivity analyses will be performed to assess the influence of losses to follow-up. We will use data on all participants (ie, with viable pregnancies at inclusion) through multiple imputation.

Economic evaluation: we will undertake cost-effectiveness analysis, from a healthcare payer perspective. We will collect data related to healthcare resource use during the study, including costs of the intervention, CHWs' time, and healthcare use during pregnancy, delivery and infant/child care. Unit costs will be estimated using the activity-based costing method. Our measure of effectiveness will be based on our primary outcome; we will estimate the relative cost effectiveness of the preconception strategy, pregnancy strategy and standard care; an incremental analysis will be conducted comparing the three strategies.

Process evaluation: evaluation will focus on implementation, mechanisms of impact and context. Assessment of implementation will focus on determining what is delivered and how delivery is achieved. We will measure fidelity of intervention delivery by observing CHWs in their contacts with intervention group participants, focusing on their use of HCS and LTP Plus and the competencies they demonstrate. We will also observe the contact between CHWs and control participants to record the nature of interactions. We will monitor intervention dose by recording the frequency and duration of contact between participants and CHWs. To understand the mechanisms through which the intervention brings about change in our specified outcomes, we will assess the acceptability of the intervention, and women's experiences of contact with CHWs using interviews and focus groups. In assessing context, we will aim to identify any factor that might act as a barrier or facilitator to intervention implementation or effects. This will include local and national policy, local service configuration and provision, sociodemographic and environmental factors within the villages taking part in the trial, and consultation with key stakeholders. We will also survey non-respondents and those who drop out to gain an understanding of why they did not consent to take part in the study or dropped out during the course of the trial.

Expected outcomes

The study will provide robust evidence whether an integrated multifaceted intervention starting preconceptionally and continuing through pregnancy and postnatally reduces risk factors for NCD in the offspring. The use of culturally appropriate interventions will allow scalability if successful. The process and economic evaluations will aid in assessment of translation potential. We will also be able to assess the relative costs and benefits of starting interventions preconceptionally versus starting in pregnancy. The study will generate extensive data and build a biorepository which can be used by other researchers within India and elsewhere.

ETHICS AND DISSEMINATION

Ethics approval

The study has been approved by the CSI Holdsworth Memorial Hospital Ethics Committee (Ref CSIHMH/ERU2019/1). Any protocol modifications will be reported to the committee and approval will be sought for any significant amendments. Informed consent will be obtained from all participants. The families will be given verbal information initially followed by written information in Kannada (local language). The participants will be encouraged to ask questions before obtaining written consent. It will be made clear that they are free to withdraw at any time from the study.

Anonymity and/or confidentiality

Every precaution will be taken to respect the privacy of the women and the confidentiality of their information. We follow research governance practice in accordance with Indian and international guidelines. All data are coded and anonymised before analysis. Strict confidentiality is maintained throughout; hard copy data are stored in locked filing cabinets and in locked rooms, with limited access. Digital data are stored on password-protected encrypted computers, with access only by authorised members of the research team. Biological samples are stored in locked freezers in a secure facility.

Potential risks/harm to participants in the study

None of the interventions or investigations present risks to the participants. Micronutrient supplements have been previously used in community trials and are recommended in the Lancet series on Maternal and Child Nutrition[28] and in the 2015 Cochrane Review on micronutrient supplementation in pregnancy.[29] While we do not expect any adverse effects due to the supplements, the participants will be monitored for adverse events. The LTP Plus programme has been used previously in various LMIC settings and has been shown to reduce maternal depression; there have been no reported adverse outcomes. HCS have also been used previously in community settings without any adverse outcomes. Serious adverse events will be investigated by a medical doctor and reported to the PI and local Co-PIs. Reports will also be submitted to the local institutional ethics committee and the sponsor. Data on adverse events will also be submitted to the independent data monitoring committee. All tests are done under medical supervision and appropriate referral arrangements are in place for issues requiring medical attention.

Dissemination

Participants will receive reports of the relevant physical and biological measurements. If there are any abnormal results, participants will be referred to appropriate medical specialists in VMH for further management and advice.

To maximise the scientific impact, we will engage with the scientific community by presenting our work at major national and international conferences, and by publishing in high-quality peer-reviewed journals, ensuring open access. We will engage with other research groups working on maternal and child health, and develop collaborative opportunities even beyond the duration of the project. Our data will be available to the scientific community after we publish our main findings.

We also will interact with policy-makers at local, national and international health agencies, and governments to enable translation of our findings into policy. Members of our collaborative group are linked into national and international policy advisory groups including local, state and national governmental committees in India and Canada, the WHO and UNICEF, and we will ensure relevant findings are disseminated through these groups to influence policy. We have met with local health and government officials in the district councils to discuss the public health importance of our study. Their support will be invaluable in future translation. Research findings will be translated into project summaries and policy briefs that capture the major findings and suggest practical policy changes, based on the evidence provided by the project. Recommendations to policy-makers will also focus on cost effectiveness. These documents will be published in English as well as local languages.

The results have implications for all mothers and children, and we will engage with our communities, the wider public, and the mass media. VMH runs a radio station and we will use broadcasts to engage with the local community and provide information and updates. VMH is also actively engaged with local women's self-help groups; we will interact with them throughout the project to not only provide updates of the project, but also to incorporate their feedback into the conduct of the study. We will explain the relevance of our research to our participants and feedback important results to them through 6 monthly newsletters and also by community meetings on an annual basis. We will also publicise the study on our institutional websites and use mass media to ensure that our research findings reach a wide public audience.

In summary, our study will determine whether a longitudinal integrated intervention starting preconceptionally improves cardiometabolic and neurodevelopmental outcomes in the next generation. The results will have significant public health implications which can be generalised to other similar settings. The range of biospecimens being collected will allow us to understand causal mechanisms.

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Acknowledgements The authors are grateful to their funders and the HeLTI Council for their support. They are indebted to the local community for their participation in the study. They acknowledge the role of the WHO in supporting the HeLTI collaboration and providing quality assurance support. They also thank the HeLTI PI Research Committee and HeLTI Research Office for the mutual support, intellectual contributions and administrative support. Elena M. Comelli holds the Lawson Family Chair in Microbiome Nutrition Research at the University of Toronto.

Contributors All authors contributed to the conception of the study, study design and development of the protocol. KK, GVK, KGS, MP, DS, CF, PSS and SGM wrote the first draft of the manuscript. BA, SA, RB, RB, ZB, GC, EMC, STD, CD, GLH, PJ, KSJ, SJ, MK, KL, SL, PM, PAN, VP, SP, HS, SAS, NS, JT, CY, JB, MB, M-CM and NH critically reviewed the manuscript and contributed to subsequent drafts. All authors approved the final version.

Funding This work is supported by the Department of Biotechnology, Government of India (BT/MED/WHO-CIHR/2014) and the Canadian Institutes of Health Research (NDN-151554). The lead institutes are the CSI Holdsworth Memorial Hospital, Mysore, India and the University of Toronto, Canada.

Disclaimer The funders and sponsors have no direct involvement in the design and conduct of the study.

Competing interests None of the authors declare any conflict of interest. The HeLTI Council of funders and WHO have required all Principal Investigators to complete annual Declarations of Interest and to commit to having no direct or indirect relations with the tobacco, arms and infant food industries during the course of the study.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

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