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Protocol for a randomised trial evaluating a preconception-early childhood telephone-based intervention with tailored e-health resources for women and their partners to optimise growth and development among children in Canada: A Healthy Life Trajectory Initiative (HeLTI Canada)

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ABSTRACT

Introduction: The "Developmental Origins of Health and Disease (DOHaD)" hypothesis suggests that a healthy trajectory of growth and development in pregnancy and early childhood is necessary for optimal health, development, and lifetime wellbeing. The purpose of this paper is to present the protocol for a randomized controlled trial evaluating a preconception-early childhood telephone-based intervention with tailored e-health resources for women and their partners to optimise growth and development among children in Canada: A Healthy Life Trajectory Initiative (HeLTI Canada). The primary objective of HeLTI Canada is to determine whether a 4-phase "preconception to early childhood" lifecourse intervention can reduce the rate of child overweight and obesity. Secondary objectives include improved child: (1) growth trajectories; (2) cardiometabolic risk factors; (3) health behaviours including nutrition, physical activity, sedentary behaviour, and sleep; and (4) development and school readiness at age 5 years.

Method and analysis: A randomized controlled multicenter trial will be conducted in two of Canada's highly populous provinces – Alberta and Ontario – with 786 nulliparous (15%) and 4444 primiparous (85%) women, their partners, and, when possible, the first "sibling child." The intervention is telephone-based collaborative care delivered by experienced public health nurses trained in healthy conversation skills that includes detailed risk assessments, individualized structured management plans, scheduled follow-up calls, and access to a web-based app with individualized, evidence-based resources. An "index child" conceived after randomization will be followed until age 5 years and assessed for the primary and secondary outcomes. Pregnancy, infancy (age 2 years), and parental outcomes across time will also be assessed.

Ethics and dissemination: The study has received approval from Clinical Trials Ontario (CTO 1776). The findings will be published in peer-reviewed journals and disseminated to policymakers at local, national and international agencies. Findings will also be shared with study participants and their communities.

Trial registration: ISRCTN13308752

Keywords: Non-communicable disease; Developmental Origins of Health and Disease, preconception care, childhood obesity, child development, Healthy Life Trajectory Initiative

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The HeLTI Canada study will be the first trial to determine whether a public health nurse facilitated telephone-based

intervention with e-health resources, from preconception through early childhood, compared to a standard care control group, will reduce child obesity and adiposity while improving BMI trajectories, cardiometabolic risk factors, health behaviours and child development at age 5 years.

- The HeLTI Canada study will examine outcomes of the whole family, including the mother, father, the index child, and any sibling child who will be 3-12 months old at trial enrollment.
- Harmonization of core study measures and outcomes with the four HeLTI studies (Canada, China, India, and South Africa) will enable pooled analyses of outcomes and direct comparisons.
- Participation level of fathers is unknown and may require different approaches and incentives.
- Detailed measures of body composition, such as air displacement plethysmography, are not feasibly measured in HeLTI Canada and more practical measures of anthropometry including BMI will be used.

BACKGROUND

Non-communicable diseases (NCDs), including cardiovascular disease, type 2 diabetes mellitus and mental illness, are major global contributors to premature death and disability[1,2]. In Canada, NCDs account for an estimated 89% of all mortality of which cardiovascular disease accounts for 33% of all deaths[3]. Cardiometabolic disease -- hypertension, coronary artery disease, and diabetes -- has risen in prevalence globally in parallel with economic development, urbanization, an obesogenic lifestyle, and obesity[4-6]. In Canada, 60% of men and 50% of women are overweight or obese[7], forecasting serious economic, societal, and individual health consequences[8]. Today, 27% of children in Canada are overweight or obese with rates steadily increasing[9]. Accelerated growth in infancy and early childhood is a strong risk factor for obesity in older children. A higher body mass index (BMI) in the preschool-aged child is associated with subclinical atherosclerosis in adulthood[10]. Childhood overweight and obesity can also impact child development[11-13], with negative effects found related to cognitive function[14], social achievement, and emotional wellbeing [15-18]. This is important given that as 1 in 5 Canadian children has a mental health problem[19].

Intrauterine and early infancy exposures appear to influence a person's risk of adult-onset chronic diseases[20] – the core idea of the "Developmental Origins of Health and Disease" (DOHaD hypothesis[21]. Sub-optimal maternal nutrition in pregnancy can lead to fetal growth restriction, and a sequence of over-compensatory responses that predispose to cardiometabolic disease in adulthood[22]. Low birth weight and *in utero* exposure to maternal diabetes, hypertension, and obesity are each associated with elevated blood pressure, plasma glucose, insulin, and lipid concentrations in children at age 5 years[23-25]. These childhood risk markers at age 5 years and beyond further predict cardiometabolic disease in adulthood[26-31]. A similar sequence has been described with a well-studied list of exposures in pregnancy or early infancy: (1) maternal obesity[27,28,32]; (2) gestational diabetes (associated with fetal hyper-insulinemia and excess fetal

adiposity)[23–25,33]; (3) maternal smoking[34,35]; (4) formula feeding in infancy[36]; and (5) fetal/infant exposure to stress or parental depression[37–39].

The preconception period represents an important life stage when exposures can damage germline DNA and epigenetically alter gene expression, subsequently impacting offspring outcomes[40–43]. A narrative review of preconception interventions to prevent obesity and NCD in children found that no study reported directly on obesity and NCD in children but rather research to date has focussed mainly on pregnancy outcomes and birthweight[44]. Existing approaches tend to focus solely on the mother. Increasingly, scientific evidence shows that the preconception health of the future father is also important[49], representing an unrealized, under-developed, and under-studied opportunity.

A meta-analysis of 38 studies found a consistent relationship between maternal pre-pregnancy weight and child obesity[45]. Maternal pre-pregnancy obesity is also linked to the hypertensive disorders of pregnancy, gestational diabetes, high infant birthweight, and shorter breastfeeding duration[49–57,121]. A meta-analysis of 23 trials[58] found that preconception interventions can positively modify maternal health behaviours, including calorie restriction with increased physical activity, that when reinforced by a support system and monitoring can be sustained over longer time periods[59]. Importantly, growing evidence suggests that health behaviour interventions, even those producing a modest change, can successfully and efficiently reduce metabolic disease risk in pregnancy[60–62]. A meta-analysis of 23 studies found maternal exposure to smoking in pregnancy was associated with increased risk of child obesity[45]. Fetal exposure to maternal smoking impacts prematurity, low birthweight, congenital malformations, and sudden infant death syndrome[63–68] suggesting psychosocial smoking cessation programs[69] are warranted *before* conception. Paternal smoking is also associated with childhood cancer, cardiovascular disease, and obesity, not only in the child but grandchildren as well possibly through epigenetic mechanisms[70,71]. Mental illness is common in women and men of reproductive age of which a substantial proportion go untreated, especially during pregnancy and postpartum. Parental mental illness negatively affects the entire family and increases a child's risk for poor cognitive, behavioural, and emotional developmental trajectories. The recognized association between mental illness and obesity supports evaluation of whether treating the former preconceptionally can reduce the latter[72]. Accordingly, we will deliver evidence-based preconception interventions targeting both a woman and her partner, that align with current evidence suggesting that parental BMI, diet, lifestyle, and mental health might alter pregnancy and child health outcomes.

The Healthy Life Trajectories Initiative (HeLTI) was developed in partnership with research teams from Canada, China, India, and South Africa and in collaboration with the World Health Organization to address the increasing burden of NCDs around the world. Four separate randomized controlled trials implemented in Soweto (South Africa), Mysore (India), Shanghai (China), and the provinces of Ontario and

Alberta (Canada) have been harmonized. All trials are focused on developing evidence-based interventions that span from preconception across pregnancy and into the postnatal period with the primary goal of reducing child obesity and improving maternal, paternal, and child health and wellbeing. The protocol described here is for HeLTI Canada, one of the four trials in the HeLTI Initiative.

Consistent with the international HeLTI studies, our main objectives are to determine whether the complete 4-phase (preconception, pregnancy, infancy, and early childhood) intervention, compared to standard care, can among index children at age 5 years: (1) reduce overweight and obese status; (2) reduce zBMI and improve zBMI trajectories; (3) reduce adiposity; (4) improve cardiometabolic risk factors; (5) enhance development and school readiness; and (6) improve health behaviours including nutrition, physical activity, screen time, and sleep. We will also examine the impact of the intervention on parental outcomes across time. We will determine the 'cumulative-impact' of the 4-phase intervention, including the effect of the ***preconception phase*** on parental outcomes at the time of conception; the effect of the ***preconception + pregnancy phases*** on pregnancy outcomes; and the effect of the ***preconception + pregnancy + infancy phases*** on child outcomes at age 2 years. Our unique study design also provides an opportunity to understand the effect of the ***infancy + early childhood phases*** of the intervention on "sibling child" outcomes at age 5 years. The Glass and McAtee[73] childhood obesity model provides a general overarching conceptual framework modified based on meta-analytic data on child obesity risk factors[45]. Our study will target modifiable risk factors for childhood obesity during the 4 phases of the intervention.

METHODS/DESIGN

STUDY DESIGN

A randomized controlled multicenter trial will be conducted in Canada with **5230** women who are planning to be pregnant within the next 3 years. We will recruit up to **786** nulliparous (15%) and at least **4444** primiparous (85%) women, their partners, and, when possible, the first "sibling child." These women will be randomly allocated in a 1:1 ratio to the 4-phase preconception-early childhood intervention or to usual care, using individual, web-based, central randomization. An "index child" conceived after randomization (n = 3660; 70%) will be followed until age 5 years and assessed for the primary and secondary outcomes. Pregnancy, infancy (at age 2 years), and parental outcomes will also be assessed. In addition, among the 4444 primiparous women planning their second pregnancy, their preceding first child (called the "sibling child"), eligible range 3 to 12 months when the mother is randomized, will also be followed until age 5 years. This concurrent randomized trial will compare those intervention phases specific to infancy and early childhood vs. usual care in these "sibling" children. This added component will allow us to estimate the additional effectiveness of the ***preconception + pregnancy phases*** of the intervention (which are only received by the index child), beyond that of the ***infancy + early childhood phases*** of the intervention (which are also received by the sibling child), while fully preserving

randomization. Couples who do not conceive will complete an exit assessment 3 years post-randomization.

SETTING

The trial will be conducted in two of Canada's high populous provinces, Alberta (4.4 million) and Ontario (14.6 million), from three main recruitment settings: (1) public health regions; (2) obstetric and postpartum clinics; and (3) primary care practices and community healthcare centres that provide postpartum and well-child care in Alberta and Ontario. The selected public health regions are strategically located in Edmonton and across Ontario, including rural regions to promote participant diversity. In total, five public health regions have agreed to participate of which four are in Southern Ontario (Toronto, York, Peel, and Niagara) and one is in Alberta (Edmonton). In Edmonton, the Healthy Living, Population, Public and Indigenous Health team in Alberta Health Services will participate. The obstetric clinics that will participate include those at Mount Sinai Hospital, Sunnybrook Hospital, and North York General Hospital. The selected primary care practices are all affiliated with *TARGetKids* in the Greater Toronto Area, where healthy children and their parents are enrolled in a prospective cohort with embedded studies at their primary care practices and followed at their well-child visits. We will also recruit participants via postpartum health centres (Monarch centres) in Ottawa and social media.

INCLUSION / EXCLUSION CRITERIA

The target population consists of non-pregnant women who meet the following entry criteria: (1) nulliparous (no children), or primiparous (one child) between 3-12 months postpartum; (2) planning a pregnancy in the next 3 years; and (3) understands spoken and written English. Excluded are women with (1) type 1 diabetes; (2) parity ≥ 2; and (3) residence outside of the five participating health regions or Ottawa area. If a woman has a twin birth, the first child born will be the index child. Single women and those with same-sex partners will be included.

STUDY DESIGN OVERVIEW

Our intervention will take a 'cumulative-impact' approach designed to improve health behaviours (e.g., nutrition, physical activity, screen time, and sleep) and reduce modifiable risk factors that influence child obesity. The intervention will start prior to conception and continue through to early childhood. It will be evidence-based, professionally-facilitated, proactive, individualized, multifaceted, and sex- and gender-specific. It will build on existing research and clinical resources while recognizing the growing trend of e-Health[74]. Local stakeholders, such as public health nurses/family physicians, will participate in providing services and referrals to ensure the intervention is tailored to local circumstances. Our intervention will target not only women but also their partners and other key individuals in the child's environment who can influence child health such as grandparents, if appropriate. Among primiparous women, we will also provide information and support to promote healthy growth and development with the sibling child with the goal of taking a family-approach to care. Our intervention, with its foundation on

public health and primary care platforms and e-Health technologies, is structured to facilitate scalability across Canada, if effective.

PRECONCEPTION-EARLY CHILDHOOD INTERVENTION

The intervention will be provided in 4 phases: (1) preconception, (2) pregnancy, (3) infancy [0-2 years], and (4) early childhood [3-5 years]. Each phase has time-sensitive goals based on child obesity risk factor meta-analyses[45]. To achieve these goals, two core strategies will be used throughout the 4 phases: (1) public health nurse collaborative care and (2) an individualized webpage as part of the responsive HeLTI Canada app that will include expert-selected ehealth resources. Systematic reviews for each of these intervention strategies have demonstrated their growing effectiveness in improving health behaviours and clinical outcomes[75–79]. We will combine these two different strategies which will allow us to: (1) reach participants, including those in rural/remote locations or those with transportation limitations; (2) provide support that is convenient and accessible 24-hours per day; (3) offer multiple options for peer/professional support; and (4) deliver care at a low cost[81].

A. Public Health Nurse Collaborative Care. Women allocated to the intervention group will be assigned an experienced public health nurse (HeLTI nurse) hired and trained by the team to provide telephone-based collaborative care starting within a week of randomization. The HeLTI nurses are trained in Healthy Conversation Skills, an evidence-based client-centered program developed by UK researchers at Southampton University, designed to support health behaviour change[80]. The activities provided will include the standard criteria for collaborative care: (1) individual assessment; (2) structured management plan; and (3) scheduled follow-up. ***Part I: Telephone Assessment***. At the beginning of each of the 4 intervention phases, the assigned HeLTI nurse will telephone the woman, complete an assessment based on phase goals, and identify potential risks. ***Part II: Structured Management Plan***. The HeLTI nurses' role will be to: (1) educate the woman and her partner (if applicable) about identified risks and management options; (2) assess management barriers and preferences; and (3) coordinate a management plan with appropriate public health, primary care, and community services. ***Part III: Scheduled Follow-Up***. The HeLTI nurse will telephone participants every 2 weeks to follow-up on management plans and track targeted behaviours. Based on behaviour modification and reduced risk, the participant will move from the 'active phase' of the intervention to the 'continuation phase'. During this phase, participants will receive telephone follow-up every 2 months until completion of the phase. All participants have the option to proactively call their HeLTI nurse as needed. All intervention activities will be documented.

B. Responsive HeLTI App. A responsive HeLTI Canada app will be developed with easy access functionality. Each woman and her partner will be provided with their own secure login to a site that includes personalized web-based educational materials and apps based on the needs identified by their HeLTI nurse. Our expert-recommended e-health resources and apps will be easily accessible on a mobile device, tablet, or computer and will enable us to provide innovative and engaging support to participants with diverse health issues.

C. Usual Care – Control Group. Women allocated to the control group will have access to standard care provided to all women from preconception to early childhood (child age 5) but they will not receive the preconception-early childhood intervention. However, as a retention strategy they will also have access to their own individualized webpage with secure log-in to receive injury prevention and child safety eHealth resources based on recommendations from experts from York University and the University of British Columbia[82]. Focus groups with parents suggested this would be useful information and the content will not be related to the trial primary and secondary outcomes.

OUTCOMES AND FREQUENCY OF FOLLOW-UP

All participants will be asked to complete online questionnaires via REDCap[83], a secure encrypted web based electronic data capturing system, at baseline and at scheduled intervals during preconception (12, 24 and 36 months post-randomization or until conception), pregnancy (24-28 weeks' gestation), infancy (3, 6, 12 and 24 months following delivery) and early childhood (36, 48 and 60 months following delivery) phases of the trial (Figure 1). Specific outcomes measures are presented in Table 1. Participants who do not complete any follow-up questionnaires within 2 weeks will be telephoned by a trained research assistant blinded to group allocation to provide a reminder and the REDCap questionnaire link will be resent via email. All women and their partners who complete a questionnaire will be provided with a $15 (CAD) gift card. Participants will also be asked to provide clinical data (height, weight, arm and waist circumference, and blood pressure[46-48,.85,98]) via a scheduled visit to designated community-based clinics or by home visits, if requested by the participant. Biospecimen data (e.g., blood) will also be collected from a voluntary sub-sample of participants (N=1000) who live in the Greater Toronto Area. We will link health card numbers of consenting mothers, partners, and children to provincial health administrative data that will allow for long-term follow-up for inpatient and outpatient physician diagnoses and procedures, including emergency department and hospitalization data, and Early Development Instrument (EDI) data for children. In Ontario, this includes linkage to BORN Ontario[84], a clinical registry with detailed obstetrical and neonatal data for all Ontario in-hospital and out-of-hospital births. Relevant to the current study, this clinical registry will be used to collect data on birth outcomes including infant birthweight and gestational age. In Alberta, we will use the Alberta Perinatal Health Program, which captures information about all births (and pregnancies).

Biospecimen Collection and Management. It is anticipated that future sub-studies may require additional biospecimens and supplementary external funding. At baseline, biospecimens will be collected, processed, and aliquoted by trained technicians at a province-wide professional lab (LifeLabs) using established standard operating procedures (SOPs) aligned with those outlined at the Global Alliance to Prevent Prematurity and Stillbirth (GAPPS) Repository. Biospecimens will be stored at Lunenfeld-Tanenbaum Research Institute's established biorepository. The laboratory fully complies with the Canadian laboratory accreditation program.

SAMPLE SIZE

Current estimates in Canada suggest that ~25% of children at age 5 years are overweight or obese, defined as greater than the 85th percentile for age and sex standardized BMI[142]. A reduction of overweight and obesity rates of 20% is aligned with the goals of the *National Framework for Action to Promote Healthy Weights*[143] and provincial recommendations including the Ontario Ministry of Health. At age 5 years, 1464 children per group (2928 in total) are required to detect a clinically meaningful 20% relative reduction, corresponding to an absolute reduction of 5% with 90% power at a two-sided alpha of 0.05 for the primary randomized comparison of the preconception-lifecourse intervention versus control. Allowing for 20% attrition from conception to age 5 years, 3660 viable conceptions are required. We expect that an average of 70% of women will conceive within 3 years of recruitment and subsequently give birth. This estimate is conservative: The 2013 guidelines on assessing and treating fertility problems of the UK National Institute of Health and Care Excellence (NICE) estimate the cumulative probability to conceive a viable pregnancy after 2 years (24 cycles) among women without contraception to be 98% for age 19 to 26 to 90% for age 35 to 39 years[144] based on data from a contemporaneous cohort of 782 women from Western European centers[145]. Estimates in a frequently cited article by Heffner[146] are somewhat lower, but these are 1-year estimates based on historical cohorts of women[147] and are still compatible with our assumptions, with an estimated probability of conception of 86% in women aged 20 to 24 to 70% in women aged 35 to 39 years after 3 years (36 cycles). Therefore, 5230 women will need to be recruited[145,148]. The sample size for this trial will also yield more than 95% power to detect a minimal clinically important difference in age- and sex-standardized BMI z-score of 0.25 between groups[149,150]. Our sample size will yield more than 95% power to detect the minimally clinically important difference of 0.25 standard deviation units between groups. The study design will also allow for evaluation of the infancy to early childhood phase of the intervention for the sibling child: Assuming that 85% of women will be primiparous and be randomised when their first, sibling child is aged 6 months (eligible range 3 to 12 months), 4444 children will be included in a concurrent, powered second randomized comparison of the lifecourse intervention received during infancy to early childhood phase versus control. This sample size provides more than 95% power for the same outcome and treatment effect as above after accounting for 20% attrition.

PATIENT AND PUBLIC INVOLVEMENT

Formative work with over 1300 Canadian families was completed to understand preconception needs, prevalence of preconception risk factors, trial recruitment strategies, intervention preferences and key strategies for disseminating trial results.

PLANNED ANALYSES

Primary and concurrent secondary randomized comparisons will be analyzed independently and hypothesis testing will use a two-sided 0.05 significance level for both comparisons. Since outcomes are identical in the two concurrent comparisons, the same methods will be

used. Primary outcome and binary secondary outcomes will be compared by means of a Chi-square test and treatment effects will be expressed as absolute risk differences with 95% CI. Continuous secondary outcomes will be compared by an independent t-test and treatment effect will be expressed as the mean difference with 95% CI. Additional analyses of pregnancy and parental outcomes will be done using the same approaches. If baseline values are available for continuous parental outcomes, however, we will use analysis of covariance adjusted for baseline values for these outcomes. As secondary outcomes are considered exploratory in nature, we will not adjust for multiple comparisons.

All outcome data will be analysed according to the intention-to-treat principle, analysing all individuals in the group they were originally allocated to. The primary approach for these analyses will be a complete case analysis, including all individuals with available data. Two types of sensitivity analyses will be performed to account for missing outcome data, using multiple imputation[151] and inverse-probability weighting[152]. Results from these sensitivity analyses will be reported along with the primary analyses. For multiple imputation, we will use baseline characteristics of mothers and outcomes of children in the imputation model to create 20 imputed datasets. Standard errors will be calculated using Rubin's rules[153], taking the variability in results between the imputed datasets into account. For inverse-probability weighting, we will calculate the probability of having complete outcome data for each individual using logistic regression; observations will then be weighted by the inverse of these probabilities and outcome models will be built to approximate results of a trial with no missing information[152]. To determine the relative effectiveness of the preconception intervention as compared with the infancy intervention, we will do indirect comparisons that fully preserve randomization[154]. As up to two children per mother can be included in these analyses, we will use mixed maximum-likelihood logistic and linear regression models, which allow for the correlation of children within families. Pre-specified subgroup analyses will be performed by sex and by number of children in the family (one versus two) and accompanied by tests for interaction between treatment effect and subgroup.

DATA MANAGEMENT AND OVERSIGHT

We will work with the international HeLTI research teams to establish a detailed collaborative plan and governance/management structure to ensure that the HeLTI initiative objectives are met. A Data Monitoring Committee (DMC) has been established. The DMC is independent of sponsors and competing interests. The Principal Investigators (PIs; Dennis and Birken) of the Canadian team will sit on the international HeLTI Research Committee, while Canadian workgroup leads will contribute to the international HeLTI working groups. At the HeLTI Canada Office, an experienced research manager will oversee the whole HeLTI Canada study while a trial coordinator will be responsible for the day-to-day trial management. Research assistants will be hired to perform recruitment activities (detailed explanation about the study, consent form, and eligibility screening) while others, blinded to group allocation, will complete follow-up data collection activities

for non-responders and gift card management; they will also receive extensive training and will be able to collect all REDCap outcome data via telephone if necessary. HeLTI nurses will be hired and extensively trained to deliver and document the intervention. Women and their partners in both groups will have access to usual standard care across all intervention phases. During depression screens, any participant who has a positive response on the EPDS self-harm ideation item will be further assessed by trained research staff[104]. In addition, for ethical reasons, local public health nurses will be notified of all participants scoring very high (>20) on any EPDS or PHQ-9 assessment. We will follow a protocol for infant/child harm if we suspect any potential child abuse/neglect. All these safety strategies have been effectively used previously by Dennis [lead PI][132-136]. Negative intervention effects will be assessed through participant evaluations. All data will be managed through REDCap, which is fully configurable and incorporates validation rules to ensure high quality data. It allows for remote web-based data entry directly from the participating sites. REDCap will be managed by the Applied Health Research Centre (AHRC) at the Li Ka Shing Knowledge Institute, St. Michael's Hospital (Toronto).

Nearly 1 in 3 Canadian children are overweight or obese, and interventions to prevent obesity have been largely unsuccessful. This randomized controlled trial, conducted with pregnancy planning women and their partners, will evaluate whether an intervention starting in the preconception period and continued to early childhood can reduce child overweight and obesity and improve developmental trajectories and mental health, compared to usual standard care. The harmonization of the intervention and outcomes across the four HeLTI studies (Canada, India, China, and South Africa) will enable pooled analysis and direct comparisons. If effective, this telephone-based intervention with e-health resources may be scalable to other sites and settings.

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PROTOCOL REGISTRATION
This study is registered with ISRCTN, ID ISRCTN13308752, and has received the approval from Clinical Trials Ontario (CTO1776) on January 14, 2020.

FUNDING STATEMENT
This work was supported by Canadian Institutes of Health Research (CIHR), grant number HLC-154502.

ETHICS AND DISSEMINATION
The study has received the approval from Clinical Trials Ontario (CTO 1776). All other participating sites ceded review to the CTO. The study has received approval from Clinical Trials Ontario (CTO 1776).

The findings will be published in peer-reviewed journals and disseminated to policymakers at local, national and international agencies. Findings will also be shared with study participants and their communities.

DATA SHARING STATEMENT

The final trial dataset will be available to study investigators, Steering Committee members and the Research Ethic Boards at all participating sites.

AUTHOR'S CONTRIBUTION: Drs. Dennis and Birken are co-Principal Investigators for HeLTI Canada. Drs. Dennis, Birken and Marini wrote the initial protocol draft. Drs. Abbass-Dick, Atkinson, Barrett, Bell, Bérard, Berger, Brown, Constantin, Da Costa, Feller, Guttmann, Janus, Joseph, Juni, Kimmins, Letourneau, Li, Lye, Maguire, Matthews, Millar, Misita, Murphy, Nuyt, O'Connor, Parekh, Paterson, Puts, Ray, Roumeliotis, Scherer, Sellen, Semenic, Shah, Smith, Stremler, Szatmari, Telner, Thorpe, Tremblay, Vigod and Walker read and contributed to the final version.

COMPETING INTERESTS' STATEMENT: None declared.

PATIENT CONSENT FOR PUBLICATION: Not required.

WORD COUNT: 3989 words.

Table 1 – HeLTI Canada Outcome Measures

Primary Outcome		
Outcome (At Age 5 Years)		**Outcome Measure**
Child Overweight and Obesity Prevalence		BMI >85th percentile[85]
Secondary Outcomes		
Child Outcomes(At Ages 2 And 5 Years)		**Outcome Measure**
Child Anthropometry and Adiposity	BMI (Age- and sex-standardize)	zBMI[87]
	BMI Growth Trajectories	zBMI growth rates[86,87]
	Waist circumference	WHO reference ranges[85,87]
	Mid-upper arm circumference	WHO reference ranges[85,87]
	Head Circumference	WHO reference ranges[85,87]
	Adiposity	Bioelectrical Impendence Analysis (BIA)[88,89]
Child Cardiometabolic Risk	Blood Pressure	Systolic and Diastolic Blood Pressure[91]
	Biomarkers	Total cholesterol; HDL-cholesterol; Triglycerides; Non-HDL cholesterol; LDL-cholesterol (friedewald equation); Insulin, glucose, hsCRP[91]
	Insulin Sensitivity and Beta-cell function	HOMA-IS; HOMA B-cell function[91]
	Cardiometabolic Risk Score	CMR score = z-WC + z-TRG + z- HDL(*-1) + z-glucose + z-SBP[90]
Child Health Behaviours	Nutrition	Breastfeeding behaviours and the Baby Eating Behaviour Questionnaire (BEBQ) and Child Eating Behaviour Questionnaire (CEBQ)[122,123]
	Physical Activity and screen time	Questions adapted from the Canadian Health Measures Survey[92] and the Canadian 24-hour Movement Guidelines for the Early Years (0-4 years)[93]
	Child Sleep	Parent-report questionnaire and the Brief Screening Questionnaire for Infant Sleep Problems (BSQI)[124]
Child Development and Mental Health	Language Development	Infant Toddler Checklist (ITC)[125] and the MacArthur Communicative Development Inventories (CDIs)[126]
	Behavioural Development	Strengths and Difficulties Questionnaire[94]
	Socio-emotional Development	Ages and Stages Questionnaire Social Emotional scale (ASQ-SE)[128]
	Temperament	Early Childhood Behavior Questionnaire (ECBQ)[127] and Children's Behavioural Questionnaire (CBQ)[95]
	Developmental Delay	Ages and Stages Questionnaire (ASQ-3)[96] and the Global Scale for Early Development (GSED)[129].
	Executive function	Behaviour Rating Inventory of Executive Function (BRIEF)[130,131]
	School Readiness	Early Development Instrument (EDI)[97]
Parental Outcomes		**Outcome Measure**
Parental Anthropometry, Adiposity and Cardiometabolic Risk	Overweight and Obesity rates	BMI ≥25 and ≥30 kg/m^2[98]; BMI (continuous)
	Waist circumference	WHO reference ranges
	Blood pressure	Systolic and Diastolic Blood Pressure
	Blood measures	Glucose, HbA1c, CBC, CRP
Parental Health Behaviours	Nutrition	PrimeScreen[99]
	Physical Activity and sedentary behaviours	Global Physical Activity Questionnaire (GPAQ)[100,101] and questions adapted from the International Physical Activity Questionnaires(IPAQ)[102]
	Sleep	Pittsburgh Sleep Quality Index (PSQI)[103]

Parental Mental Health	Depressive Symptoms (pregnancy and up to 1 year postpartum)	Edinburgh Postnatal Depression Scale (EPDS)[104]
	Depressive Symptoms	Patient Health Questionnaire (PHQ-9)[105]
	Anxiety Symptoms	Generalized Anxiety Disorder (GAD7)[106]
	Life Stress	Perceived Stress Scale (PSS)[107]
	Loneliness	Three-Item Loneliness Scale[108]
Parental Relationships	Relationship Satisfaction	Dyadic Adjustment Scale (DAS)[109]
	Intimate partner violence	Woman Abuse Screening Tool (WAST)[110]
	Social Support	Social Provisions Scale (SPS)[111]
Parenting Behaviours	Co-parenting	Coparenting Relationship Scale[115]
	Parenting Style	Parenting Scale[116]
	Parenting Competence	Parenting Sense of Competence Scale (PSOC)[117]
	Parenting Stress	Parenting Stress Index Short-Form (PSI-SF)[118]
Home environment	Exposure to tobacco smoke, alcohol and substance abuse, and home/work toxins	CAGE-AID questionnaire[112], the Alcohol Use Disorders Identification Test (AUDIT),[113] and environmental toxin questions adapted from the INTERBIO-21ST Study[114]
Sociodemographic indicators	Income, education, immigration status, food and housing insecurity, changes in residence, and development of chronic diseases	HeLTI Canada Socio- Demographic Questionnaire[119]
Pregnancy Outcomes		**Outcome Measure**
Data will be obtained from either provincial databases (e.g., BORN Ontario) or from the Canadian Institutes for Health Information Discharge Abstract Database (CIHI-DAD), all linked using health card numbers.	Weight gain	Net weight gained (kg)[120] (continuous)
	Gestational diabetes	OGTT; Gestational diabetes diagnosis
	Gestational Hypertension	Gestational Hypertension diagnosis; Blood Pressure
	Pre-eclampsia	Pre-eclampsia diagnosis
	Preterm delivery	Born <37 weeks gestational age
	Weight for gestational age, birthweight	Small for gestational age <10th percentile; large for gestational age = >90th percentile
	Maternal Exposure	Maternal Exposure to tobacco smoke, prescribed medication use, alcohol and substance use
Health Service Utilization		ICES Linkage (Ontario)
Nature Of And Satisfaction With Intervention		Intervention Activity Log and Intervention Satisfaction Questionnaire
Economic Evaluation		Cost-effectiveness of the preconception lifecourse intervention[137; 138;139-141]
Epigenetics And Genetics Outcomes		Genetic and epigenomic analyses will be planned when additional funding is received.

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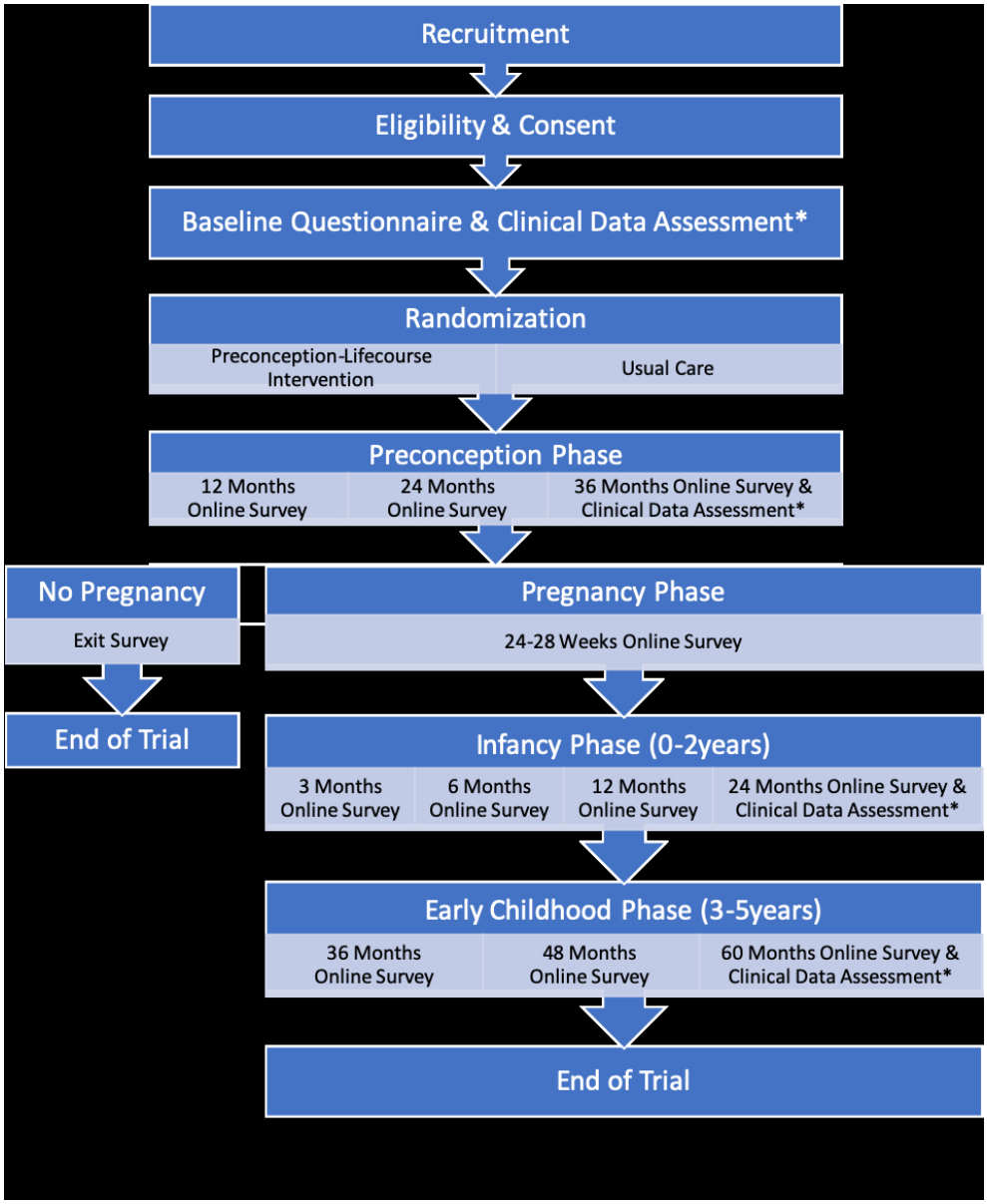

Figure 1 - HeLTI Canada flow diagram

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2;9
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2;9
Protocol version	#3	Date and version identifier	9
Funding	#4	Sources and types of financial, material, and other support	9
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1;9

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	9
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	8;9
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3;4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4;6
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4;5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be	5

		obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6;7;10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6;7; Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5;8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6;8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the	6;7

		protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7;8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7;8
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7;8
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	8
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	#23	Frequency and procedures for auditing trial conduct, if	8

		any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2;8;9
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	8
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6;8
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	9
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2;9
Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	8;9

authorship		professional writers	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	8;9
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	6;7

Notes:

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BMJ Open

Protocol for a randomised trial evaluating a preconception-early childhood telephone-based intervention with tailored e-health resources for women and their partners to optimise growth and development among children in Canada: A Healthy Life Trajectory Initiative (HeLTI Canada)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-046311.R1
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Protocol for a randomised trial evaluating a preconception-early childhood telephone-based intervention with tailored e-health resources for women and their partners to optimise growth and development among children in Canada: A Healthy Life Trajectory Initiative (HeLTI Canada)

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ABSTRACT

Introduction: The "Developmental Origins of Health and Disease (DOHaD)" hypothesis suggests that a healthy trajectory of growth and development in pregnancy and early childhood is necessary for optimal health, development, and lifetime wellbeing. The purpose of this paper is to present the protocol for a randomized controlled trial evaluating a preconception-early childhood telephone-based intervention with tailored e-health resources for women and their partners to optimise growth and development among children in Canada: A Healthy Life Trajectory Initiative (HeLTI Canada). The primary objective of HeLTI Canada is to determine whether a 4-phase "preconception to early childhood" lifecourse intervention can reduce the rate of child overweight and obesity. Secondary objectives include improved child: (1) growth trajectories; (2) cardiometabolic risk factors; (3) health behaviours including nutrition, physical activity, sedentary behaviour, and sleep; and (4) development and school readiness at age 5 years.

Method and analysis: A randomized controlled multicenter trial will be conducted in two of Canada's highly populous provinces – Alberta and Ontario – with 786 nulliparous (15%) and 4444 primiparous (85%) women, their partners, and, when possible, the first "sibling child." The intervention is telephone-based collaborative care delivered by experienced public health nurses trained in healthy conversation skills that includes detailed risk assessments, individualized structured management plans, scheduled follow-up calls, and access to a web-based app with individualized, evidence-based resources. An "index child" conceived after randomization will be followed until age 5 years and assessed for the primary and secondary outcomes. Pregnancy, infancy (age 2 years), and parental outcomes across time will also be assessed.

Ethics and dissemination: The study has received approval from Clinical Trials Ontario (CTO 1776). The findings will be published in peer-reviewed journals and disseminated to policymakers at local, national and international agencies. Findings will also be shared with study participants and their communities.

Trial registration: ISRCTN13308752

Keywords: Non-communicable disease; Developmental Origins of Health and Disease, preconception care, childhood obesity, child development, Healthy Life Trajectory Initiative

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The HeLTI Canada study will be the first trial to determine whether a public health nurse facilitated telephone-based

intervention with e-health resources, from preconception through early childhood, compared to a standard care control group, will reduce child obesity and adiposity while improving BMI trajectories, cardiometabolic risk factors, health behaviours and child development at age 5 years.

- The HeLTI Canada study will examine outcomes of the whole family, including the mother, father, the index child, and any sibling child who will be 3-12 months old at trial enrollment.
- Harmonization of core study measures and outcomes with the four HeLTI studies (Canada, China, India, and South Africa) will enable pooled analyses of outcomes and direct comparisons.
- Participation level of fathers is unknown and may require different approaches and incentives.
- Detailed measures of body composition, such as air displacement plethysmography, are not feasibly measured in HeLTI Canada and more practical measures of anthropometry including BMI will be used.

BACKGROUND

Non-communicable diseases (NCDs), including cardiovascular disease, type 2 diabetes mellitus and mental illness, are major global contributors to premature death and disability[1,2]. In Canada, NCDs account for an estimated 89% of all mortality of which cardiovascular disease accounts for 33% of all deaths[3]. Cardiometabolic disease -- hypertension, coronary artery disease, and diabetes -- has risen in prevalence globally in parallel with economic development, urbanization, an obesogenic lifestyle, and obesity[4-6]. In Canada, 60% of men and 50% of women are overweight or obese[7], forecasting serious economic, societal, and individual health consequences[8]. Today, 27% of children in Canada are overweight or obese with rates steadily increasing[9]. Accelerated growth in infancy and early childhood is a strong risk factor for obesity in older children. A higher body mass index (BMI) in the preschool-aged child is associated with subclinical atherosclerosis in adulthood[10]. Childhood overweight and obesity can also impact child development[11-13], with negative effects found related to cognitive function[14], social achievement, and emotional wellbeing [15-18]. This is important given that as 1 in 5 Canadian children has a mental health problem[19].

Intrauterine and early infancy exposures appear to influence a person's risk of adult-onset chronic diseases[20] – the core idea of the "Developmental Origins of Health and Disease" (DOHaD hypothesis[21]. Sub-optimal maternal nutrition in pregnancy can lead to fetal growth restriction, and a sequence of over-compensatory responses that predispose to cardiometabolic disease in adulthood[22]. Low birth weight and *in utero* exposure to maternal diabetes, hypertension, and obesity are each associated with elevated blood pressure, plasma glucose, insulin, and lipid concentrations in children at age 5 years[23-25]. These childhood risk markers at age 5 years and beyond further predict cardiometabolic disease in adulthood[26-31]. A similar sequence has been described with a well-studied list of exposures in pregnancy or early infancy: (1) maternal obesity[27,28,32]; (2) gestational diabetes (associated with fetal hyper-insulinemia and excess fetal

adiposity)[23-25,33]; (3) maternal smoking[34,35]; (4) formula feeding in infancy[36]; and (5) fetal/infant exposure to stress or parental depression[37-39].

The preconception period represents an important life stage when exposures can damage germline DNA and epigenetically alter gene expression, subsequently impacting offspring outcomes[40-43]. A narrative review of preconception interventions to prevent obesity and NCD in children found that no study reported directly on obesity and NCD in children but rather research to date has focussed mainly on pregnancy outcomes and birthweight[44]. Existing approaches tend to focus solely on the mother. Increasingly, scientific evidence shows that the preconception health of the future father is also important[45], representing an unrealized, under-developed, and under-studied opportunity.

A meta-analysis of 38 studies found a consistent relationship between maternal pre-pregnancy weight and child obesity[46]. Maternal pre-pregnancy obesity is also linked to the hypertensive disorders of pregnancy, gestational diabetes, high infant birthweight, and shorter breastfeeding duration[45,47-54]. A meta-analysis of 23 trials[55] found that preconception interventions can positively modify maternal health behaviours, including calorie restriction with increased physical activity, that when reinforced by a support system and monitoring can be sustained over longer time periods[56]. Importantly, growing evidence suggests that health behaviour interventions, even those producing a modest change, can successfully and efficiently reduce metabolic disease risk in pregnancy[57-59]. A meta-analysis of 23 studies found maternal exposure to smoking in pregnancy was associated with increased risk of child obesity[46]. Fetal exposure to maternal smoking impacts prematurity, low birthweight, congenital malformations, and sudden infant death syndrome[60-65] suggesting psychosocial smoking cessation programs[66] are warranted *before* conception. Paternal smoking is also associated with childhood cancer, cardiovascular disease, and obesity, not only in the child but grandchildren as well possibly through epigenetic mechanisms[67,68]. Mental illness is common in women and men of reproductive age of which a substantial proportion go untreated, especially during pregnancy and postpartum. Parental mental illness negatively affects the entire family and increases a child's risk for poor cognitive, behavioural, and emotional developmental trajectories. The recognized association between mental illness and obesity supports evaluation of whether treating the former preconceptionally can reduce the latter[69]. Accordingly, we will deliver evidence-based preconception interventions targeting both a woman and her partner, that align with current evidence suggesting that parental BMI, diet, lifestyle, and mental health might alter pregnancy and child health outcomes.

The Healthy Life Trajectories Initiative (HeLTI) was developed in partnership with research teams from Canada, China, India, and South Africa and in collaboration with the World Health Organization to address the increasing burden of NCDs around the world. Four separate randomized controlled trials implemented in Soweto (South Africa), Mysore (India), Shanghai (China), and the provinces of Ontario and

Alberta (Canada) have been harmonized. All trials are focused on developing evidence-based interventions that span from preconception across pregnancy and into the postnatal period with the primary goal of reducing child obesity and improving maternal, paternal, and child health and wellbeing. The protocol described here is for HeLTI Canada, one of the four trials in the HeLTI Initiative.

Consistent with the international HeLTI studies, our main objectives are to determine whether the complete 4-phase (preconception, pregnancy, infancy, and early childhood) intervention, compared to standard care, can among index children at age 5 years: (1) reduce overweight and obese status; (2) reduce zBMI and improve zBMI trajectories; (3) reduce adiposity; (4) improve cardiometabolic risk factors; (5) enhance development and school readiness; and (6) improve health behaviours including nutrition, physical activity, screen time, and sleep. We will also examine the impact of the intervention on parental outcomes across time. We will determine the 'cumulative-impact' of the 4-phase intervention, including the effect of the ***preconception phase*** on parental outcomes at the time of conception; the effect of the ***preconception + pregnancy phases*** on pregnancy outcomes; and the effect of the ***preconception + pregnancy + infancy phases*** on child outcomes at age 2 years. Our unique study design also provides an opportunity to understand the effect of the ***infancy + early childhood phases*** of the intervention on "sibling child" outcomes at age 5 years. The Glass and McAtee[70] childhood obesity model provides a general overarching conceptual framework modified based on meta-analytic data on child obesity risk factors[46]. Our study will target modifiable risk factors for childhood obesity during the 4 phases of the intervention.

METHODS/DESIGN

STUDY DESIGN

A randomized controlled multicenter trial will be conducted in Canada with **5230** women who are planning to be pregnant within the next 3 years. We will recruit up to **786** nulliparous (15%) and at least **4444** primiparous (85%) women, their partners, and, when possible, the first "sibling child." These women will be randomly allocated in a 1:1 ratio to the 4-phase preconception-early childhood intervention or to usual care, using individual, web-based, central randomization. An "index child" conceived after randomization (n = 3660; 70%) will be followed until age 5 years and assessed for the primary and secondary outcomes. Pregnancy, infancy (at age 2 years), and parental outcomes will also be assessed. In addition, among the 4444 primiparous women planning their second pregnancy, their preceding first child (called the "sibling child"), eligible range 3 to 12 months when the mother is randomized, will also be followed until age 5 years. This concurrent randomized trial will compare those intervention phases specific to infancy and early childhood vs. usual care in these "sibling" children. This added component will allow us to estimate the additional effectiveness of the ***preconception + pregnancy phases*** of the intervention (which are only received by the index child), beyond that of the ***infancy + early childhood phases*** of the intervention (which are also received by the sibling child), while fully preserving

randomization. Couples who do not conceive will complete an exit assessment 3 years post-randomization.

SETTING

The trial will be conducted in two of Canada's high populous provinces, Alberta (4.4 million) and Ontario (14.6 million), from three main recruitment settings: (1) public health regions; (2) obstetric and postpartum clinics; and (3) primary care practices and community healthcare centres that provide postpartum and well-child care in Alberta and Ontario. The selected public health regions are strategically located in Edmonton and across Ontario, including rural regions to promote participant diversity. In total, five public health regions have agreed to participate of which four are in Southern Ontario (Toronto, York, Peel, and Niagara) and one is in Alberta (Edmonton). In Edmonton, the Healthy Living, Population, Public and Indigenous Health team in Alberta Health Services will participate. The obstetric clinics that will participate include those at Mount Sinai Hospital, Sunnybrook Hospital, and North York General Hospital. The selected primary care practices are all affiliated with *TARGetKids* in the Greater Toronto Area, where healthy children and their parents are enrolled in a prospective cohort with embedded studies at their primary care practices and followed at their well-child visits. We will also recruit participants via postpartum health centres (Monarch centres) in Ottawa and social media.

INCLUSION / EXCLUSION CRITERIA

The target population consists of non-pregnant women who meet the following entry criteria: (1) nulliparous (no children), or primiparous (one child) between 3-12 months postpartum; (2) planning a pregnancy in the next 3 years; and (3) understands spoken and written English. Excluded are women with (1) type 1 diabetes; (2) parity ≥ 2; and (3) residence outside of the five participating health regions or Ottawa area. If a woman has a twin birth, the first child born will be the index child. Single women and those with same-sex partners will be included.

STUDY DESIGN OVERVIEW

Our intervention will take a 'cumulative-impact' approach designed to improve health behaviours (e.g., nutrition, physical activity, screen time, and sleep) and reduce modifiable risk factors that influence child obesity. The intervention will start prior to conception and continue through to early childhood. It will be evidence-based, professionally-facilitated, proactive, individualized, multifaceted, and sex- and gender-specific. It will build on existing research and clinical resources while recognizing the growing trend of e-Health[71]. Local stakeholders, such as public health nurses/family physicians, will participate in providing services and referrals to ensure the intervention is tailored to local circumstances. Our intervention will target not only women but also their partners and other key individuals in the child's environment who can influence child health such as grandparents, if appropriate. Among primiparous women, we will also provide information and support to promote healthy growth and development with the sibling child with the goal of taking a family-approach to care. Our intervention, with its foundation on

public health and primary care platforms and e-Health technologies, is structured to facilitate scalability across Canada, if effective.

PRECONCEPTION-EARLY CHILDHOOD INTERVENTION

The intervention will be provided in 4 phases: (1) preconception, (2) pregnancy, (3) infancy [0-2 years], and (4) early childhood [3-5 years]. Each phase has time-sensitive goals based on child obesity risk factor meta-analyses[46]. To achieve these goals, two core strategies will be used throughout the 4 phases: (1) public health nurse collaborative care and (2) an individualized webpage as part of the responsive HeLTI Canada app that will include expert-selected ehealth resources. Systematic reviews for each of these intervention strategies have demonstrated their growing effectiveness in improving health behaviours and clinical outcomes[72-76]. We will combine these two different strategies which will allow us to: (1) reach participants, including those in rural/remote locations or those with transportation limitations; (2) provide support that is convenient and accessible 24-hours per day; (3) offer multiple options for peer/professional support; and (4) deliver care at a low cost[77].

A. Public Health Nurse Collaborative Care. Women allocated to the intervention group will be assigned an experienced public health nurse (HeLTI nurse) hired and trained by the team to provide telephone-based collaborative care starting within a week of randomization. The HeLTI nurses are trained in Healthy Conversation Skills, an evidence-based client-centered program developed by UK researchers at Southampton University, designed to support health behaviour change[78]. The activities provided will include the standard criteria for collaborative care: (1) individual assessment; (2) structured management plan; and (3) scheduled follow-up. ***Part I: Telephone Assessment***. At the beginning of each of the 4 intervention phases, the assigned HeLTI nurse will telephone the woman, complete an assessment based on phase goals, and identify potential risks. ***Part II: Structured Management Plan***. The HeLTI nurses' role will be to: (1) educate the woman and her partner (if applicable) about identified risks and management options; (2) assess management barriers and preferences; and (3) coordinate a management plan with appropriate public health, primary care, and community services. ***Part III: Scheduled Follow-Up***. The HeLTI nurse will telephone participants every 2 weeks to follow-up on management plans and track targeted behaviours. Based on behaviour modification and reduced risk, the participant will move from the 'active phase' of the intervention to the 'continuation phase'. During this phase, participants will receive telephone follow-up every 2 months until completion of the phase. All participants have the option to proactively call their HeLTI nurse as needed. All intervention activities will be documented.

B. Responsive HeLTI App. A responsive HeLTI Canada app will be developed with easy access functionality. Each woman and her partner will be provided with their own secure login to a site that includes personalized web-based educational materials and apps based on the needs identified by their HeLTI nurse. Our expert-recommended e-health resources and apps will be easily accessible on a mobile device, tablet, or computer and will enable us to provide innovative and engaging support to participants with diverse health issues.

C. Usual Care – Control Group. Women allocated to the control group will have access to standard care provided to all women from preconception to early childhood (child age 5) but they will not receive the preconception-early childhood intervention. However, as a retention strategy they will also have access to their own individualized webpage with secure log-in to receive injury prevention and child safety eHealth resources based on recommendations from experts from York University and the University of British Columbia[79]. Focus groups with parents suggested this would be useful information and the content will not be related to the trial primary and secondary outcomes.

OUTCOMES AND FREQUENCY OF FOLLOW-UP

All participants will be asked to complete online questionnaires via REDCap[80], a secure encrypted web based electronic data capturing system, at baseline and at scheduled intervals during preconception (12, 24 and 36 months post-randomization or until conception), pregnancy (24-28 weeks' gestation), infancy (3, 6, 12 and 24 months following delivery) and early childhood (36, 48 and 60 months following delivery) phases of the trial (Figure 1). Specific outcomes measures are presented in Table 1. Participants who do not complete any follow-up questionnaires within 2 weeks will be telephoned by a trained research assistant blinded to group allocation to provide a reminder and the REDCap questionnaire link will be resent via email. All women and their partners who complete a questionnaire will be provided with a $15 (CAD) gift card. Participants will also be asked to provide clinical data (height, weight, arm and waist circumference, and blood pressure[46-48,81,82]) via a scheduled visit to designated community-based clinics or by home visits, if requested by the participant. Biospecimen data (e.g., blood) will also be collected from a voluntary sub-sample of participants (N=1000) who live in the Greater Toronto Area. We will link health card numbers of consenting mothers, partners, and children to provincial health administrative data that will allow for long-term follow-up for inpatient and outpatient physician diagnoses and procedures, including emergency department and hospitalization data, and Early Development Instrument (EDI) data for children. In Ontario, this includes linkage to BORN Ontario[83], a clinical registry with detailed obstetrical and neonatal data for all Ontario in-hospital and out-of-hospital births. Relevant to the current study, this clinical registry will be used to collect data on birth outcomes including infant birthweight and gestational age. In Alberta, we will use the Alberta Perinatal Health Program, which captures information about all births (and pregnancies).

Biospecimen Collection and Management. It is anticipated that future sub-studies may require additional biospecimens and supplementary external funding. At baseline, biospecimens will be collected, processed, and aliquoted by trained technicians at a province-wide professional lab (LifeLabs) using established standard operating procedures (SOPs) aligned with those outlined at the Global Alliance to Prevent Prematurity and Stillbirth (GAPPS) Repository. Biospecimens will be stored at Lunenfeld-Tanenbaum Research Institute's established biorepository. The laboratory fully complies with the Canadian laboratory accreditation program.

SAMPLE SIZE

Current estimates in Canada suggest that ~25% of children at age 5 years are overweight or obese, defined as greater than the 85th percentile for age and sex standardized BMI[84]. A reduction of overweight and obesity rates of 20% is aligned with the goals of the *National Framework for Action to Promote Healthy Weights*[85] and provincial recommendations including the Ontario Ministry of Health. At age 5 years, 1464 children per group (2928 in total) are required to detect a clinically meaningful 20% relative reduction, corresponding to an absolute reduction of 5% with 90% power at a two-sided alpha of 0.05 for the primary randomized comparison of the preconception-lifecourse intervention versus control. Allowing for 20% attrition from conception to age 5 years, 3660 viable conceptions are required. We expect that an average of 70% of women will conceive within 3 years of recruitment and subsequently give birth. This estimate is conservative: The 2013 guidelines on assessing and treating fertility problems of the UK National Institute of Health and Care Excellence (NICE) estimate the cumulative probability to conceive a viable pregnancy after 2 years (24 cycles) among women without contraception to be 98% for age 19 to 26 to 90% for age 35 to 39 years[86] based on data from a contemporaneous cohort of 782 women from Western European centers[81]. Estimates in a frequently cited article by Heffner[87] are somewhat lower, but these are 1-year estimates based on historical cohorts of women[88] and are still compatible with our assumptions, with an estimated probability of conception of 86% in women aged 20 to 24 to 70% in women aged 35 to 39 years after 3 years (36 cycles). Therefore, 5230 women will need to be recruited[81,89]. The sample size for this trial will also yield more than 95% power to detect a minimal clinically important difference in age- and sex-standardized BMI z-score of 0.25 between groups[90,91]. Our sample size will yield more than 95% power to detect the minimally clinically important difference of 0.25 standard deviation units between groups. The study design will also allow for evaluation of the infancy to early childhood phase of the intervention for the sibling child: Assuming that 85% of women will be primiparous and be randomised when their first, sibling child is aged 6 months (eligible range 3 to 12 months), 4444 children will be included in a concurrent, powered second randomized comparison of the lifecourse intervention received during infancy to early childhood phase versus control. This sample size provides more than 95% power for the same outcome and treatment effect as above after accounting for 20% attrition.

PATIENT AND PUBLIC INVOLVEMENT

Formative work with over 1300 Canadian families was completed to understand preconception needs, prevalence of preconception risk factors, trial recruitment strategies, intervention preferences and key strategies for disseminating trial results.

PLANNED ANALYSES

Primary and concurrent secondary randomized comparisons will be analyzed independently and hypothesis testing will use a two-sided 0.05 significance level for both comparisons. Since outcomes are identical in the two concurrent comparisons, the same methods will be used. Primary outcome and binary secondary outcomes will be compared

by means of a Chi-square test and treatment effects will be expressed as absolute risk differences with 95% CI. Continuous secondary outcomes will be compared by an independent t-test and treatment effect will be expressed as the mean difference with 95% CI. Additional analyses of pregnancy and parental outcomes will be done using the same approaches. If baseline values are available for continuous parental outcomes, however, we will use analysis of covariance adjusted for baseline values for these outcomes. As secondary outcomes are considered exploratory in nature, we will not adjust for multiple comparisons.

All outcome data will be analysed according to the intention-to-treat principle, analysing all individuals in the group they were originally allocated to. The primary approach for these analyses will be a complete case analysis, including all individuals with available data. Two types of sensitivity analyses will be performed to account for missing outcome data, using multiple imputation[92] and inverse-probability weighting[93]. Results from these sensitivity analyses will be reported along with the primary analyses. For multiple imputation, we will use baseline characteristics of mothers and outcomes of children in the imputation model to create 20 imputed datasets. Standard errors will be calculated using Rubin's rules[94], taking the variability in results between the imputed datasets into account. For inverse-probability weighting, we will calculate the probability of having complete outcome data for each individual using logistic regression; observations will then be weighted by the inverse of these probabilities and outcome models will be built to approximate results of a trial with no missing information[93]. To determine the relative effectiveness of the preconception intervention as compared with the infancy intervention, we will do indirect comparisons that fully preserve randomization[95]. As up to two children per mother can be included in these analyses, we will use mixed maximum-likelihood logistic and linear regression models, which allow for the correlation of children within families. Pre-specified subgroup analyses will be performed by sex and by number of children in the family (one versus two) and accompanied by tests for interaction between treatment effect and subgroup.

DATA MANAGEMENT AND OVERSIGHT

We will work with the international HeLTI research teams to establish a detailed collaborative plan and governance/management structure to ensure that the HeLTI initiative objectives are met. A Data Monitoring Committee (DMC) has been established. The DMC is independent of sponsors and competing interests. The Principal Investigators (PIs; Dennis and Birken) of the Canadian team will sit on the international HeLTI Research Committee, while Canadian workgroup leads will contribute to the international HeLTI working groups. At the HeLTI Canada Office, an experienced research manager will oversee the whole HeLTI Canada study while a trial coordinator will be responsible for the day-to-day trial management. Research assistants will be hired to perform recruitment activities (detailed explanation about the study, consent form, and eligibility screening) while others, blinded to group allocation, will complete follow-up data collection activities for non-responders and gift card management; they will also receive

extensive training and will be able to collect all REDCap outcome data via telephone if necessary. HeLTI nurses will be hired and extensively trained to deliver and document the intervention. Women and their partners in both groups will have access to usual standard care across all intervention phases. During depression screens, any participant who has a positive response on the EPDS self-harm ideation item will be further assessed by trained research staff[96]. In addition, for ethical reasons, local public health nurses will be notified of all participants scoring very high (>20) on any EPDS or PHQ-9 assessment. We will follow a protocol for infant/child harm if we suspect any potential child abuse/neglect. All these safety strategies have been effectively used previously by Dennis [lead PI][97–101]. Negative intervention effects will be assessed through participant evaluations. All data will be managed through REDCap, which is fully configurable and incorporates validation rules to ensure high quality data. It allows for remote web-based data entry directly from the participating sites. REDCap will be managed by the Applied Health Research Centre (AHRC) at the Li Ka Shing Knowledge Institute, St. Michael's Hospital (Toronto).

Nearly 1 in 3 Canadian children are overweight or obese, and interventions to prevent obesity have been largely unsuccessful. This randomized controlled trial, conducted with pregnancy planning women and their partners, will evaluate whether an intervention starting in the preconception period and continued to early childhood can reduce child overweight and obesity and improve developmental trajectories and mental health, compared to usual standard care. The harmonization of the intervention and outcomes across the four HeLTI studies (Canada, India, China, and South Africa) will enable pooled analysis and direct comparisons. If effective, this telephone-based intervention with e-health resources may be scalable to other sites and settings.

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PROTOCOL REGISTRATION
This study is registered with ISRCTN, ID ISRCTN13308752, and has received the approval from Clinical Trials Ontario (CTO1776) on January 14, 2020.

FUNDING STATEMENT
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ETHICS AND DISSEMINATION
The study has received the approval from Clinical Trials Ontario (CTO 1776). All other participating sites ceded review to the CTO. The study has received approval from Clinical Trials Ontario (CTO 1776).

The findings will be published in peer-reviewed journals and disseminated to policymakers at local, national and international agencies. Findings will also be shared with study participants and their communities.

DATA SHARING STATEMENT

The final trial dataset will be available to study investigators, Steering Committee members and the Research Ethic Boards at all participating sites.

AUTHOR'S CONTRIBUTION: Drs. C-L. Dennis and C.S. Birken are co-Principal Investigators for HeLTI Canada. Drs. C-L Dennis, C.S. Birken and F.C. Marini wrote the initial protocol draft. Drs. J. Abbass-Dick, S.A. Atkinson, J. Barrett, R. Bell, A. Bérard, H. Berger, H. Brown, E. Constantin, D. Da Costa, A. Feller, A. Guttmann, M. Janus, K.S. Joseph, P. Juni, S. Kimmins, N. Letourneau, P. Li, S. Lye, J. Maguire, S.G. Matthews, D. Millar, D. Misita, K. Murphy, A.N. Nuyt, D. O'Connor, R. Parekh, A. Paterson, M. Puts, J. Ray, P. Roumeliotis, S. Scherer, D. Sellen, S. Semenic, P.S. Shah, G. Smith, R. Stremler, P. Szatmari, D. Telnner, K. Thorpe, M. Tremblay, S. Vigod and M. Walker read and contributed to the final version. All authors provided edits and critiqued the manuscript for intellectual content.

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WORD COUNT: 3989 words.

Table 1 – HeLTI Canada Outcome Measures

Primary Outcome		
Outcome (At Age 5 Years)		**Outcome Measure**
Child Overweight and Obesity Prevalence		BMI >85th percentile[102]
Secondary Outcomes		
Child Outcomes(At Ages 2 And 5 Years)		**Outcome Measure**
Child Anthropometry and Adiposity	BMI (Age- and sex-standardize)	zBMI[103]
	BMI Growth Trajectories	zBMI growth rates[87,103]
	Waist circumference	WHO reference ranges[102,103]
	Mid-upper arm circumference	WHO reference ranges[102,103]
	Head Circumference	WHO reference ranges[102,103]
	Adiposity	Bioelectrical Impendence Analysis (BIA)[82,104]
Child Cardiometabolic Risk	Blood Pressure	Systolic and Diastolic Blood Pressure[105]
	Biomarkers	Total cholesterol; HDL-cholesterol; Triglycerides; Non-HDL cholesterol; LDL-cholesterol (friedewald equation); Insulin, glucose, hsCRP[105]
	Insulin Sensitivity and Beta-cell function	HOMA-IS; HOMA B-cell function[105]
	Cardiometabolic Risk Score	CMR score = z-WC + z-TRG + z- HDL(*-1) + z-glucose + z-SBP[106]
Child Health Behaviours	Nutrition	Breastfeeding behaviours and the Baby Eating Behaviour Questionnaire (BEBQ) and Child Eating Behaviour Questionnaire (CEBQ)[107,108]
	Physical Activity and screen time	Questions adapted from the Canadian Health Measures Survey[109] and the Canadian 24-hour Movement Guidelines for the Early Years (0-4 years)[110]
	Child Sleep	Parent-report questionnaire and the Brief Screening Questionnaire for Infant Sleep Problems (BSQI)[111]
Child Development and Mental Health	Language Development	Infant Toddler Checklist (ITC)[112] and the MacArthur Communicative Development Inventories (CDIs)[113]
	Behavioural Development	Strengths and Difficulties Questionnaire[114]
	Socio-emotional Development	Ages and Stages Questionnaire Social Emotional scale (ASQ-SE)[115]
	Temperament	Early Childhood Behavior Questionnaire (ECBQ)[116] and Children's Behavioural Questionnaire (CBQ)[117]
	Developmental Delay	Ages and Stages Questionnaire (ASQ-3)[118] and the Global Scale for Early Development (GSED)[119].
	Executive function	Behaviour Rating Inventory of Executive Function (BRIEF)[120,121]
	School Readiness	Early Development Instrument (EDI)[122]
Parental Outcomes		**Outcome Measure**
Parental Anthropometry, Adiposity and Cardiometabolic Risk	Overweight and Obesity rates	BMI ≥25 and ≥30 kg/m^2[123]; BMI (continuous)
	Waist circumference	WHO reference ranges
	Blood pressure	Systolic and Diastolic Blood Pressure
	Blood measures	Glucose, HbA1c, CBC, CRP
Parental Health Behaviours	Nutrition	PrimeScreen[124]
	Physical Activity and sedentary behaviours	Global Physical Activity Questionnaire (GPAQ)[125,126] and questions adapted from the International Physical Activity Questionnaires(IPAQ)[127]
	Sleep	Pittsburgh Sleep Quality Index (PSQI)[128]

Parental Mental Health	Depressive Symptoms (pregnancy and up to 1 year postpartum)	Edinburgh Postnatal Depression Scale (EPDS)[96]
	Depressive Symptoms	Patient Health Questionnaire (PHQ-9)[129]
	Anxiety Symptoms	Generalized Anxiety Disorder (GAD7)[130]
	Life Stress	Perceived Stress Scale (PSS)[131]
	Loneliness	Three-Item Loneliness Scale[132]
Parental Relationships	Relationship Satisfaction	Dyadic Adjustment Scale (DAS)[133]
	Intimate partner violence	Woman Abuse Screening Tool (WAST)[134]
	Social Support	Social Provisions Scale (SPS)[135]
Parenting Behaviours	Co-parenting	Coparenting Relationship Scale[136]
	Parenting Style	Parenting Scale[97]
	Parenting Competence	Parenting Sense of Competence Scale (PSOC)[137]
	Parenting Stress	Parenting Stress Index Short-Form (PSI-SF)[99]
Home environment	Exposure to tobacco smoke, alcohol and substance abuse, and home/work toxins	CAGE-AID questionnaire[100], the Alcohol Use Disorders Identification Test (AUDIT),[101] and environmental toxin questions adapted from the INTERBIO-21ST Study[138]
Sociodemographic indicators	Income, education, immigration status, food and housing insecurity, changes in residence, and development of chronic diseases	HeLTI Canada Socio- Demographic Questionnaire
Pregnancy Outcomes		**Outcome Measure**
Data will be obtained from either provincial databases (e.g., BORN Ontario) or from the Canadian Institutes for Health Information Discharge Abstract Database (CIHI-DAD), all linked using health card numbers.	Weight gain	Net weight gained (kg) (continuous)
	Gestational diabetes	OGTT; Gestational diabetes diagnosis
	Gestational Hypertension	Gestational Hypertension diagnosis; Blood Pressure
	Pre-eclampsia	Pre-eclampsia diagnosis
	Preterm delivery	Born <37 weeks gestational age
	Weight for gestational age, birthweight	Small for gestational age <10th percentile; large for gestational age = >90th percentile
	Maternal Exposure	Maternal Exposure to tobacco smoke, prescribed medication use, alcohol and substance use
Health Service Utilization		ICES Linkage (Ontario)
Nature Of And Satisfaction With Intervention		Intervention Activity Log and Intervention Satisfaction Questionnaire
Economic Evaluation		Cost-effectiveness of the preconception lifecourse intervention[139,140]
Epigenetics And Genetics Outcomes		Genetic and epigenomic analyses will be planned when additional funding is received.

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- Figure legends included at the end of the main manuscript, as requested by the Editorial Office,

Figure 1 – HeLTI Canada Study Flow Diagram

** Biospecimen data (e.g., blood, urine) will also be collected at these time-points from a voluntary sub-sample of participants who live in the Greater Toronto Area.*

Figure 1 – HeLTI Canada Study Flow Diagram

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2;9
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2;9
Protocol version	#3	Date and version identifier	9
Funding	#4	Sources and types of financial, material, and other support	9
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1;9

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	9
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	8;9
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3;4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4;6
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4;5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be	5

		obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6;7;10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6;7; Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5;8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6;8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the	6;7

		protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7;8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7;8
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7;8
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	8
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	#23	Frequency and procedures for auditing trial conduct, if	8

		any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2;8;9
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	8
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6;8
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	9
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2;9
Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	8;9

authorship		professional writers	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	8;9
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	6;7

Notes:

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