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Complete List of Authors:	Stennett, Rosain; McMaster University Faculty of Health Sciences, Department of Health Research Methods, Evidence, and Impact Adamo, Kristi; University of Ottawa Anand, Sonia; McMaster University, Department of Medicine; Population Health Research Institute, Bajaj, Harpreet; LMC Healthcare Bangdiwala, Shrikant ; Population Health Research Institute Desai, Dipika; McMaster University Faculty of Health Sciences, Health Research Methods, Evidence & Impact ; Population Health Research Institute Gerstein, HC; McMaster University Faculty of Health Sciences, Department of Medicine; Population Health Research Institute Kandasamy, Sujane; McMaster University Faculty of Health Sciences, Health Research Methods, Evidence & Impact Khan, Farah; Population Health Research Institute Lear, Scott; Population Health Research Institute McDonald, Sarah; McMaster University Faculty of Health Sciences, Department of Health Research Methods, Evidence, and Impact; McMaster University Faculty of Health Sciences, Department of Obstetrics & Gynecology Poscai, Tayler; Population Health Research Institute Ritvo, Paul; York University, Kinesiology and Health Science Rogge, Andrea; Population Health Research Institute Schulze, Karleen; Population Health Research Institute Sherifali, Diana; McMaster University Faculty of Health Sciences, Department of Health Research Methods, Evidence, and Impact; McMaster University Faculty of Health Sciences, Division of Maternal-Fetal Medicine, Department of Obstetrics & Gynecology Stearns, Jennifer; McMaster University Faculty of Health Sciences, Department of Obstetrics & Gynecology; McMaster University, Farncombe Family Digestive Health Research Institute Wahi, Gita; McMaster University Faculty of Health Sciences, Department of Health Research Methods, Evidence, and Impact; McMaster University Faculty of Health Sciences, Department of Paedeatrics Williams , Natalie ; McMaster University, Department of Medicine Zulyniak, Michael; University of Leeds, Food Science and Nutrition de Souza, Russell; Hamilton, Department of Health Research Methods, Evidence, and Impact; Hamilton

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Stennett, RN[1], Adamo, K[2], Anand, SS[1,3], Bajaj, H[4], Bangdiwala, SI[1,3], Desai, D[1,3], Gerstein, HC[3,5], Kandasamy, S[1], Khan, F[3], Lear, SA[3], McDonald, SD[1,3,6], Poscai, T[3†], Ritvo, P[7], Rogge, A[3], Schulze, KM[3], Sherifali, D[1,3,8], Stearns, JC[6,9], Wahi, G[1,10], Williams, NC[5], Zulyniak, MA[11], de Souza, RJ[1,3]

Affiliations

[1]Department of Health Research Methods, Evidence, and Impact, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada

[2] School of Human Kinetics, Faculty of Health Sciences, University of Ottawa, Ottawa, ON, Canada

[3]Population Health Research Institute, Hamilton Health Sciences Corporation, Hamilton, ON, Canada

[4]LMC Healthcare, Brampton, Ontario, Canada

[5]Department of Medicine, McMaster University, Hamilton, Ontario, Canada

[6]Obstetrics & Gynecology, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada

[7]Department of Psychology, York University, North York, Ontario, Canada

[8]School of Nursing, McMaster University, Hamilton, Ontario, Canada

[9]Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Ontario, Canada

[10] Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada

[11]School of Food Science and Nutrition, University of Leeds, Leeds, United Kingdom

† Affiliation at time of preparation of manuscript

*Corresponding author: Russell J. de Souza, desouzrj@mcmaster.ca

Abstract

Introduction: South Asians are more likely to develop gestational diabetes mellitus (GDM) than White Europeans. Diet and lifestyle modifications may prevent GDM and reduce undesirable outcomes in both the mother and offspring. Our study seeks to evaluate the effectiveness and participant acceptability of a culturally-tailored, personalized nutrition intervention on the glucose area under the curve (AUC) after a 2-hour 75g oral glucose tolerance test (OGTT) in pregnant women of South Asian ancestry with GDM risk factors.

Methods and Analysis: One hundred ninety pregnant South Asians with at least 2 of the following GDM risk factors—pre-pregnancy body mass index (BMI) >23, age ≥29, poor-quality diet, family history of type 2 diabetes (T2DM) in a first-degree relative, or GDM in a previous pregnancy will be enrolled during gestational week 12-18, and randomly assigned in a 1:1 ratio to: 1) usual care, plus weekly text messages to encourage walking and paper handouts or 2) a personalized nutrition plan developed and delivered by a culturally-congruent dietitian and health coach; and FitBit® to track steps. The intervention lasts 6 – 16-weeks, depending on week-of-recruitment. The primary outcome is the glucose AUC from a 3-sample 75 g OGTT 24-28 weeks gestation. The secondary outcome is GDM diagnosis, based on Born-in-Bradford criteria (fasting glucose ≥ 5.2 mmol/L, or 2-hour post-load ≥7.2 mmol/L).

Ethics and Dissemination: The study has been approved by the Hamilton Integrated Research Ethics Board (HiREB #10942). Findings will be disseminated among academics and policy makers through scientific publications along with community orientated strategies.

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Key words: Gestational diabetes mellitus, South Asian, personalized nutrition intervention

Article Summary

Strengths and limitations of this study:

- Our randomized controlled trial focuses on the impact of a culturally-tailored personalized dietary intervention to reduce gestational dysglycemia among South Asian pregnant women.
- The DESI GDM study builds upon the findings of previous a study which assessed barriers and facilitators of lifestyle changes to prevent GDM, as well a birth cohort study completed in a similar population such end user co-developed approaches to intervention studies improves participant engagement and buy-in.
- This study assesses exposure to the intervention only after becoming pregnant and thus the pre-pregnancy dietary intake will not be explored.

Introduction

Gestational diabetes mellitus (GDM) is a condition in which a woman without existing diabetes develops high blood sugar levels during pregnancy.[1] Complications for the baby include neonatal hypoglycemia and intensive-care admission.[2] GDM is a strong risk factor for future type 2 diabetes (T2DM): up to 50% of women with GDM develop T2DM within 5 years of giving birth[3 4], and face up to seven-fold higher lifetime risk of T2DM compared with women who have a non-GDM pregnancy.[3 5] Additionally, GDM is associated with future atherosclerosis and cardiovascular disease (CVD) in the mother and increases the risk of T2DM in offspring up to eight-fold.[5-8]

South Asians (SA), whose ancestors are from India, Pakistan, Bangladesh, or Sri Lanka, are the largest non-white ethnic group in Canada, and are at high risk of T2DM and early CVD. SA women have at least double the risk of GDM of white European women[9 10], and risk factors for future T2DM in the offspring including higher birthweight, more adipose tissue, and reduced insulin sensitivity, are more common in SA infants of mothers with GDM than infants born to mothers without GDM.[9] Furthermore a low quality diet (diet higher in meat, meat dishes, processed meats, organ meats, poultry, fish, seafood, rice, fried foods, refined grains (breads and cereals), fast foods and eggs) during pregnancy increases one's odds of developing GDM (odds ratio [OR]: 1.62; 95% CI: 1.20 to 2.19).[9] It is assumed that approximately 13% of GDM cases in SA could be prevented by a healthy diet (population attributable risk [PAR]: 12.8%). [9]

Food-based interventions show the most potential for preventing GDM.[11-13] A network meta-analysis (21 randomized trials during pregnancy; n=1,865 women) [14] reported that diets with reduced glycemic load and/or increased fibre intake, compared to gestational weight gain advice, improved fasting glucose levels. In another meta-analysis of randomized control trials,

diet modification alone led to the largest reduction in risk of excessive maternal weight gain and (3 trials; n=409 women) reduced the incidence of GDM (relative risk [RR]: 0.68; 95% CI: 0.48 to 0.96), however the overall evidence rating was low to very low for the latter outcome [15]. There is a need for more robust food-based intervention studies that consider additional factors in the development of GDM in order to provide optimal prevention strategies for women at higher risk of developing the condition.

Few randomized trials of the effect of diet and/or physical activity on incident GDM have been conducted. One recent randomized trial conducted in Ireland (n=565) found that an exercise and nutrition program delivered via smartphone did not reduce GDM in overweight and obese women randomized at a mean gestational age of 15.3 weeks (RR: 1.1; 95% CI: 0.71 to 1.66) [16]. However, this study aimed to modify only one aspect of diet, which was reducing the glycemic index. A second trial conducted in Spain (n=1000) found that a Mediterranean dietary pattern supplemented with extra virgin olive oil and pistachios, reduced the incidence of GDM (RR: 0.73; 95% CI: 0.56 to 0.95) compared with standard low-fat dietary advice [17]. A third trial, Project SARAS in Mumbai, India[18], was an unblinded, individually randomized controlled trial of diet to prevent GDM in women living in slums. The intervention included a daily snack made from leafy green vegetables, fruit, and milk for the treatment group, compared with low-micronutrient vegetables (e.g., potato and onion) for the control group, on top of the usual diet. Of 6,513 women, 35% became pregnant; of these, 89% reached a gestation of 28 wks., and 50% (n=1,008) attended an OGTT. In total, 9.9% (n=100) developed GDM using the World Health Organization's 1999 defintion.[19] Although there were many challenges of conducting this trial (i.e., 50% lost to follow-up), in an intention-to-treat (ITT) analysis, GDM was reduced in the treatment group (7.3% compared with 12.4% in controls; OR: 0.56; 95% CI: 0.36, 0.86; P =

0.008). The reduction remained significant after adjusting for pre-pregnancy adiposity and fat or weight gain during pregnancy.

In a qualitative interpretive descriptive study of barriers and facilitators to healthy eating encountered by pregnant and recently pregnant South Asian women and health care providers living and working in the Peel Region of Ontario, Canada [20], women voiced several facilitators to healthy eating such as: ***i)*** knowledge of culturally appropriate healthy foods; and ***ii)*** access to a health care provider able to provide resources and support in a timely fashion. Participants also identified barriers to healthy eating, including difficulty: ***i)*** changing long-held cultural diet practices; ***ii)*** adapting standard dietary advice to personal health beliefs; ***iii)*** navigating food choices at family gatherings; and ***iv)*** accommodating meal needs of others in the household. Women expressed a desire to learn more about healthy eating to prevent diabetes during pregnancy and were keen to use mobile health technology. Health care providers identified two major challenges to providing appropriate advice to members of this community: ***i)*** insufficient time for counselling; and ***ii)*** lack of familiarity with South Asian foods. These findings are consistent with other studies of sociocultural influences on behaviour in pregnancy in South Asian women. [21 22]

These observations have led us to design and evaluate the effectiveness and participant acceptability of a randomized controlled trial of a culturally-tailored, personalized nutrition intervention, delivered by a health coach, on the glucose area under the curve (AUC) after a 2-hour 75-g oral glucose tolerance test (OGTT) to pregnant South Asian women at risk of GDM living in Southern Ontario, Canada. The trial protocol follows the guidelines for protocol development and reporting described by the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement (*see* Additional file 1).

Methods

Design: The study is a two-arm parallel RCT. The allocation ratio will be 1:1 to the intervention or usual care (control) group. The study schema diagram illustrates the referral and screening procedure (**Figure 1**).

Setting: The study will be conducted in Southern Ontario with the primary recruitment site being the Regional Municipality of Peel, which consists of three municipalities to the west and northwest of the city of Toronto: the cities of Mississauga and Brampton, and the town of Caledon. More than half of the residents of the Region of Peel identify as South Asian.[23] The region has >800 family physicians and >60 obstetricians who see approximately 5,000 South Asian women/year in the second trimester of pregnancy. Expectant women routinely attend their first visit between 12 - 18 weeks of pregnancy and then every four weeks until 30 weeks' gestation; every two weeks from 32 to 36 weeks' gestation; and once a week from 37 weeks' gestation until birth.[24]

Sample size: With 86 participants per group (total n = 172), the study will have 90% power to detect at least a 15% between-group difference in AUC glucose, the primary outcome, assuming 70% adherence to the intervention (i.e. goal setting, health coach contacts, food tracking) and SD of AUC glucose = 173 mmol/min [9]. A change in glucose of at least this magnitude has been observed in trials of similar design to test fibre supplements [25], high-protein [26], or high-fat diets[27]. A 10% loss-to-follow up is assumed, which is low for dietary interventions, however given the frequent expected contact with health care providers during pregnancy, the virtual nature of our intervention, and our pilot data,[28] it is believed to be feasible. The sample size has been inflated to 95 per group (total n = 190) to account for the expected high

lost-to-follow up. The study will have low power to detect a moderate treatment effect on the secondary outcome of GDM (i.e., 20-30% between-treatment difference), and higher power to detect very large treatment effects in GDM (i.e., 80% power to detect a 61% relative risk reduction). The study will look to see if GDM incidence, measured as a dichotomous outcome, is nominally improved.

Inclusion criteria: Singleton pregnant South Asian women will be enrolled between 12 – 18 weeks gestation. This timeframe avoids the early pregnancy window, when women are most likely to experience nausea, and is past the highest period of risk for spontaneous abortion. In addition to being South Asian, a high-risk ethnic group for GDM [29], participants will also need to meet at least 2 GDM risk factors: age>29[9], low diet quality (assessed with a short diet screener) [9 30], family history of DM/GDM during a previous pregnancy[29 31], or a pre-pregnancy BMI ≥23.[9]

Exclusion criteria: Expectant mothers with any of the following will be excluded from the study: a) pre-existing type 1 or type 2 diabetes[29]; b) hypertension (≥140 mmHg systolic or ≥90 mmHg diastolic) or on medication for the condition[32-34]; c) serious difficulty understanding health information in English, based on the screening conversation, that would preclude informed consent and participation (93% of Canadian South Asian women in the National Household Survey could conduct a conversation in one or both official languages (English and French) [35 36]; d) those unwilling or unable to modify their eating habits, based on a screening question; e) those at high risk of adverse pregnancy outcomes other than GDM (e.g., twins or higher-order multiples[32 37], use of fertility treatments[38], history of hypertension/pre-eclampsia, history[34] of placenta previa[39] or pre-term delivery[40]); or f) enrolment in another intervention study that would compromise full participation in the DESI-GDM) trial.

Recruitment: Because of the COVID-19 pandemic, and the university research policies the study recruitment was delayed but began in November 2021 and is expected to be completed by March 2024. The study team will provide study information to primary care physicians and obstetricians who will identify and refer participants into the study.

Randomization and blinding: Women will be randomized 1:1 to intervention or control using a centralized integrated web response system (IWRS) at the Population Health Research Institute (PHRI) in Hamilton, Ontario. A statistician will generate a randomization list using a permuted blocks algorithm with randomly chosen block sizes to ensure balance in numbers and avoid predictability.[41] The nature of the intervention precludes blinding of the participants to the treatment assignment, however, those providing the analysis of blood glucose levels for assessing the primary and secondary outcomes will be blinded to treatment assignment.

At the baseline visit, the research assistant (RA) will confirm eligibility and obtain consent, either in person, verbally via telephone or web conferencing, or electronically via REDCap. These three options are believed to be flexible and responsive to participant preference, and possible regulations regarding COVID-19 public health measures. After confirming eligibility and the informed consent discussion, the RA will collect baseline measures.

After collecting baseline physical measures, the study personnel completing the visit will activate the IWRS to randomly allocate participants to control or intervention in a concealed fashion using a computer-generated random sequence. Those assigned to the intervention will be assigned to a health coach, who will contact the participant for a baseline nutrition assessment, and goal-setting session. Planned assessment visits take place at 3 time points regardless of the

study arm: 1) baseline 12 – 18 weeks gestation; 2) follow-up 24–28 weeks of gestation; and 3) post-delivery – pregnancy and birth outcomes.

Intervention

In our intervention study which seeks to address behavioral changes, we used goal setting, behavioral contracting through bi-weekly checkups, and tailored health communication (text messaging). These strategies were drawn from the Social Cognitive Theory of behavioral changes[42] and applied stages of change construct of the Transtheoretical Model[43]. The activities used in the intervention are guided by the findings of 1) the START birth cohort study[9], which identified diet as a key modifiable risk factor for GDM, and 2) a qualitative study of barriers and facilitators to healthy eating encountered by pregnant and recently pregnant South Asian women and health care providers living and working in Ontario[20].

Duration: Treatment/ intervention duration will be between 6 and 16 weeks, depending on the gestational age at enrollment. Effects of dietary intervention on glycemic endpoints are detectable in ≤6 week[44 45], and reach maximal effectiveness after 8-10 weeks (~2 months) of intervention[46]. In-person or Zoom study visit contact will occur 2 times: once for the baseline visit and once for the OGTT. Between these visits, all participants receive weekly text messages, and intervention participants will also have bi-weekly telephone or video conferencing (Zoom/WhatsApp).

***Treatment group*:** A personalized nutrition plan will be developed for each woman by a culturally-congruent dietitian. Our dietary intervention will focus on:

i) providing personalized food recommendations that consider a woman's current dietary habits by identifying food choices and substitutions that will optimize the diet;

ii) providing dietary advice that is sensitive to religious belief/practice if desired by the participant (e.g., vegetarian foods maybe preferred by *Hindu*, *Buddhists*, *Jainists*; etc.; while inclusion of meat may be more appropriate for *Sikhs* and *Christians*) and regional (e.g., Northern vs. Southern India, Sri Lanka, Bangladesh, Pakistan) culinary practices; and

iii) involving the household meal preparer, if this is not the participant herself, in the coaching contacts; and use mobile health technology to reduce the amount of in-office time a health care practitioner spends on dietary counselling. Additionally, participants assigned to the intervention group will be given a Fitbit to track their steps along with encouragement to increase walking.

The health coach will co-design a plan with each participant that considers baseline dietary intake, energy balance for recommended gestational weight gain, personal values, and preferences, and set 2-4 "SMART" goals. Nutrition and behaviour change experts have developed text messages that support 11 categories of nutrition goals (Table 1), targeted to address eating behaviours identified by participants in our qualitative study, designed to optimize energy balance for weight gain and improve dietary quality.

Table 1. Categories of nutrition goals

1. Eating out healthy	2. Reduce indulgence in sweets/desserts
3. Controlling over-eating	4. Reduce intake of sugary beverages
5. Reducing high-fat, fried foods	6. Cooking meals at home more
7. Reducing highly refined carbohydrates	8. Improving meal planning

9. Encouraging mindful eating	10. Eating more fruits and vegetables
11. Increasing quality protein intake	

Both groups: Participants in both groups receive weekly text messages, aimed at increasing walking, as this was identified as a way to increase physical activity during pregnancy that was acceptable to South Asian women to undertake during pregnancy,[20] and is critical for glucose homeostasis during pregnancy.[47 48] Both groups will be given resources that provide advice on healthy eating, physical activity, and other lifestyle factors during pregnancy(paper handouts) plus additional materials adapted specifically for the South Asian community. Health care providers in Peel Region use these tools routinely (Diabetes Canada: https://bit.ly/2m8r2tT; or Heart & Stroke: https://bit.ly/2lDubl7).

Study Measurements and Schedule

Baseline assessment (for both intervention and control participants): At the baseline visit, participants' physical measurement (height, weight, blood pressure, skinfold thickness and mid-upper arm circumference), fasting urine and blood sample will be collected. Additionally, an ayurvedic assessment and 3 questionnaires (baseline instrument, INTERHEART Food Frequency Questionnaire (FFQ) and COVID-19 and vaccine questionnaire) will be administered. The baseline instrument is researcher developed and has 4 sections: 1. Socio-demographics; 2. medical history; 3. obstetric history; and 4. lifestyle history.

The Ayurvedic "prakriti" assessment is a way of characterizing a population into set subgroups, based on traditional Indian medicine called Ayurveda. This is a method of taking a person-centered approach to health care[49], based on phenotypic characteristics such as

appearance, mannerisms, etc. and is used for personalizing medicine and ways of healthy living for individual. We will use the validated TNMC questionnaire from 2004.[50] The decision to use this tool was taken during the development of the protocol, through conversations with members of the team and potential participants who practice Ayurveda. We may explore differences in the primary outcome according to prakriti, however these are post-hoc, exploratory analyses only.

The INTERHEART FFQ (modified for use in pregnancy) is a semiquantitative food frequency questionnaire (FFQ) that assesses intake of fruits and vegetables, and fast foods consumption. The FFQ was adapted from the 19-item INTERHEART FFQ [51], which has been used in studies that included South Asians.[52 53]

The COVID-19 and vaccine questionnaire a short two-part, self-administered questionnaire. We have decided to administer this because the COVID-19 pandemic has impacted all aspects of day-to-day life, and its impact on our participants will help contextualize our findings. The first part is the Vaccination Attitudes Examination (VAX) scale[54], a validated, and reliable tool that assesses general vaccination attitudes across 4 domains: 1. Mistrust of vaccine benefit; 2. Worries about unforeseen future events; 3. Concerns about commercial profiteering; and 4. Preference for natural immunity. The second section comprises additional questions about preferred types of vaccines, preferred location of receiving the vaccine, and general attitudes/concerns about vaccines.

Participants will be given an option to provide their health card number, which will enable future linkage with administrative data sources from Ontario such as the Institute for Clinical Evaluative Sciences (ICES) for potential health economic evaluation and for long-term follow-up of the mother and her child.

Weekly and Health Coach Visit: Participants in both control and intervention groups receive 1 text message every week up to the date of the OGTT with 1 of the 6 walking tips, sent by an automated outbound messaging system developed by MemoTXT (Toronto, ON). The intervention group only will also be sent weekly text messages to reinforce individual nutrition goals at times of day requested by the participant. Participants assigned to the intervention group will be given a Fitbit to track their steps; and will be requested to track food consumption in Bitesnap, a photo food journal app, for 2 weekdays and 1 weekend day bi-weekly (up to 8 assessments). Health coaches will be able to view both Fitbit and Bitesnap data via the Health Coaching Platform.

Coaching contacts to the intervention group will be made bi-weekly up to the date of their OGTT. These coaching calls will be recorded using an audio recording device. At each scheduled contact, intervention participants review agreed-upon diet goals, and assess, on a Likert scale, how often they were able to achieve the goals (ranging from "never" to "all of the time"); the coach will work with the participant to overcome barriers using our Brief Action Planning Guide. After each coaching call, participants and Health Coaches will complete a Visit Reflection questionnaire.

The central coordinator will review data regularly for completion, and *ad* hoc calls may be made to clarify items for either arm, but no counseling is provided to control group participants (see Table 2 for details).

Table 2. Schedule of study activities

Activity	Baseline Visit	Weekly	Health Coach Visits (bi-weekly)	OGTT Visit	Post-Birth Follow-up
Screening	x				
Informed Consent	x				
Randomization	x				

Activity	**Baseline Visit**	**Weekly**	**Health Coach Visits (bi-weekly)**	**OGTT Visit**	**Post-Birth Follow-up**
Physical Measures (height, weight, blood pressure, skinfold thickness, mid upper arm circumference)	x				
INTERHEART Food Frequency Questionnaire	x			x	
Finger Stick for Glucose	x				
75-g OGTT				x	
Urine Sample Collection	x			x	
Blood Sample Collection (optional)	x			x	
Baseline Questionnaire	x				
Ayurvedic Assessment	x				
Device Identification*	x				
FitBit Distribution*	x				
Bitesnap Downloaded*	x				
Resource Handouts	x				
Walking tips via *MemoTXT*		x			
Diet reinforcement via *MemoTXT**		x			
Calls With Health Coach (set and review SMART goals, Brief Action Planning Guide) *			x		
Visit Reflection*			x		
Bitesnap Food Journal*		x			
FitBit Return*				x	
Exit Questionnaire				x	
Mother-reported Infant Physical Measures					x

* Intervention group only

Follow-up Assessment/ Second Visit: At the second clinic visit (24-28 weeks gestation), INTERHEART food frequency questionnaire, fasting urine sample collection and fasting blood sample collection are repeated (this may be done virtually, or in-person) and a 75-g OGTT is performed. Additional blood samples will be collected at 3-time points (0 hr, 1 hr and 2 hr) during the OGTT (based on referral and participant willingness) and stored for future analysis.

In Peel, pregnant women usually undergo a 50-g glucose challenge at 24-28 weeks, with a 1-h value ≥7.8 mmol/L being an indication for a 75-g OGTT.[55] Rather than this 2-step process, we have chosen to administer the 75- g OGTT to all women because: 1. it was used to establish South Asian-specific diagnostic criteria for GDM, and thus the study's outcomes will be directly comparable [10]; 2. it avoids the high false-negative rate of the 50-g Glucose Challenge Test (GCT) among South Asians[56 57]; 3. one-step screening has potential for long-term cost-saving[58-60]; and 4. Diabetes Canada recognizes that the one-step strategy can identify a subset of women who would not otherwise be identified as having GDM and who may benefit with regard to certain perinatal outcomes [29]. The study team will coordinate with the health care provider to ensure participants receive the 75-g OGTT between 24-28 weeks, avoiding the two-step screen.

At the completion of their OGTT, each woman will be asked to complete the DESI-GDM exit survey. This is a 9-item questionnaire based on previous tools created and used by the study team. Responses to each question are provided using a 5-item Likert scale (Strongly Disagree through Strongly Agree).

Postnatal Assessment: Study participants will be contacted after delivering their baby to self-report the birth weight and length of their baby. Participants will also be asked to provide details of any complications during delivery.

Study outcomes

The primary clinical outcome of this trial is the area under the glucose curve (AUC) of the 3-sample OGTT. A measure of glycemic response, glucose AUC is a continuous measure of the response to a 75-g OGTT that accounts for variations in fasting plasma glucose levels between individuals. It is calculated by the trapezoidal method using the fasting, 1-hour, and 2-hour

glucose[61] (**Figure 2**). The AUC is superior to a single measure, i.e., fasting or 2-hour glucose only, which may not provide complete information regarding plasma glucose processing after a load.[62]

The secondary outcome is GDM, classified using the cut-offs derived in the Born-in-Bradford (BiB) cohort, which were found to be associated with 75% higher risk of LGA or infant adiposity [infant birth weight >90th percentile for gestational age or adiposity (sum of skinfold measurements >90th percentile for gestational age) in a study of 5,408 SA women]. These values are fasting glucose ≥ 5.2 mmol/L, or 2-hour post-load ≥7.2 mmol/L [10]. Current clinical cut-offs for the 75-g OGTT used to diagnose GDM in the general population as defined by the Diabetes Canada's clinical practice guidelines are: fasting glucose ≥ 5.3 mmol/L, 1-hour ≥ 10.6 mmol/L, or 2-hour ≥9.0 mmol/L.[29] The study team will assess the sensitivity and specificity of the BiB definition against the International Association of the Diabetes and Pregnancy Study Groups (IASPSG) or World Health Organization (WHO) criteria (see Table 3 for diagnostic criteria).

Table 3. Diagnostic criteria for secondary outcome, gestational diabetes mellitus (GDM)

Threshold	Fasting	1-h	2-h
BiB	>=5.2	-	>=7.2
IADPSG	>=5.1	>=10.0	>=8.5
WHO	>=7.0	-	>=7.8
Diabetes Canada	>=5.3	>=10.6	>=9.0

Planned data analysis

The study will assess the main effect of the diet intervention (β1) based on two outcomes as well as conduct process and acceptability assessments:

a) Primary clinical outcome: The study will assess the main effect of the diet intervention (β1) on the primary outcome of glucose AUC with a linear regression model with ***intervention*** as the main effect (a dummy variable, where 1=treatment; 0=control).

b) Secondary clinical outcome: The study will assess the main effect of the diet intervention (β1) on the secondary outcome of GDM by fitting a logistic regression model with ***intervention*** as the main effect (a dummy variable, where 1=treatment; 0=control).

Table 4 provides a summary of the planned analysis objectives, outcome, hypothesis and methods of analysis, and **Figure 3** is our proposed CONSORT flow diagram.

Table 4. Analysis Plan: objectives, outcome, hypothesis, and methods of analysis

Objective	Outcomes	Measurement	Criteria for success	Method of analysis
Primary clinical	Glycemic response to the 75-g oral glucose tolerance test	Area under the curve of glucose	Mean statistically significant reduction of 15% in the intervention arm	Linear regression*
Secondary clinical	Gestational diabetes diagnosed by 75-g oral glucose tolerance test	Fasting glucose ≥5.2 mmol/L, or 2-hour post 75-g load ≥7.2 mmol/L	OR <0.9 = signal of benefit OR > 1.1 = signal of harm	Logistic regression*
Acceptability	Acceptability	Answer to the question "Would you recommend this program to a friend?"	≥80% of participants reply "agree or strongly agree"	Descriptive statistic (proportion)

*Mixed models will be considered to adjust for centre effects using random intercepts.

c) Process and acceptability assessments: These data will be presented descriptively and include monthly process feedback (e.g., recruitment, retention, adherence), which the team will discuss on an ongoing basis (e.g., adherence, unmet goals/targets). The study team will review qualitative and quantitative data to refine implementation processes. Acceptability will be

explored using semi-structured exit interviews after the OGTT visit, which allow each participant to reflect on their experiences with the program and convey what they liked and disliked about the study, and if they would recommend the program to a friend, as we have in previous studies of similar design.[63 64]

e) Handling of missing outcome data: Missing outcome data (OGTT) will be handled via multiple imputation as a sensitivity analysis if we have >30% missing outcome data.

f) Sensitivity analyses (for primary and secondary outcomes only): The study team anticipate possible variation in treatment effect according to time in study and by clinic site (if multiple clinics refer participants). Women will be enrolled in the study between weeks 12-18 of pregnancy. The outcome will be assessed at week 24-28 of pregnancy. Therefore, the length of time that each woman will receive the intervention may vary. The first sensitivity analysis will adjust the primary outcome for time in study (OGTT date minus enrolment date). The second sensitivity analysis, if there is multiple sites of enrolment, the study team will consider a random effect of study site.

d) Interim data analysis: No interim data analysis is planned.

Ethical considerations

The study has been approved by the Hamilton Integrated Research Ethics Board (HiREB #10942), and the trial is registered with clinical trials.gov (NCT03607799). Participants will provide written, verbal, or electronic informed consent. If providing verbal consent, participants will be sent the full consent via email or paper mail, to read and refer to while being consented. If providing electronic consent via Research Electronic Data Capture (REDCap), participants will be sent a link that contains the full consent and will review the consent over telephone or web-conferencing with study staff. The participant will select whether they agree to participate at

the bottom of the consent page. Participant data will be deidentified to protect confidentiality and will only be reported and published in aggregate. Any modifications made to the study protocol will be shared with HiREB as stipulated and we will follow their advice regarding implementation and dissemination.

Data monitoring and management

Study Coordination and Management: The principal investigator will take responsibility for the oversight of the study. The coordinating centre for the trial will be Population Health Research Institute (PHRI) in Hamilton, ON. The coordinating centre, under the direction of the study statistician, will receive all data, and take process steps to reduce missing data. A junior project manager, along with a graduate student will oversee the of recruitment of participants and handle central trial coordination. At weekly meetings, the study will review recruitment, minor adverse events, study inventories, and review any expressed concerns by participants or the team. The steering committee will direct operational/process, nutrition, coaching, and statistical aspects of the trial.

Data and Safety Monitoring: For a previous pilot study, the study team had convened a Data and Safety monitoring committee (DSMC), consisting of two internal medicine specialists (one being an experienced endocrinologist), and a biostatistician. This committee advised that a DSMC was not required for the pilot, voting for a safety officer, and disbanded. The committee advised the same for this trial. Therefore, at pre-specified meeting times, the safety officer, trained in internal medicine, will review data, noting any of the 8 minor (mother – induced labour, anemia, urinary tract infection, fall/injury/accident related to study, low mood or high blood pressure; child - premature labour (<36 weeks) or shoulder dystocia), or 6 major maternal

events (hyperemesis gravidarum, caesarean section, pre-eclampsia, primary post-partum hemorrhage >500mL, miscarriage or maternal mortality,); or 2 major infant events (mortality – (fetal and neonatal) or stillbirth). The safety officer will determine whether they are related to study participation. To evaluate safety outcomes, maternal blood pressure at baseline and the OGTT follow-up visit will be measured, and notes of any pregnancy complications at coaching contacts.

The safety officer will review an interim data analysis, comparing a) mean AUC glucose; and b) GDM incidence between treatment and control (blinded) after the first 25 participants have completed their OGTT visit. Thereafter, the safety officer will review the data following each additional 50 participants. There is no early stopping rule for this study. The study will only collect data at baseline and the OGTT visit.

Patient and Public Involvement

The study included recently pregnant SA women living in Peel (ON), public health practitioners, and primary care providers that work with pregnant SA women in the development of our intervention through focus groups and semi-structured interviews. The co-investigators who work with the SA community and serve on guidelines committees have been closely involved with developing this research proposal. The study's physician collaborators will be involved in the recruitment progress, to help troubleshoot challenges, and refine intervention implementation strategies during the grant cycle.

Dissemination plans

The findings of the study will be important in guiding future evidence-based recommendations and public health policies to manage gestational glycemia in pregnant women at risk of GDM.

Throughout the study, a strategy for integrated Knowledge Translation will be used to develop a series of digital projects (short digital story-based videos) that capture: 1. participant experiences that include key messages about successful approaches to healthy eating that women would like to share with their communities; and 2. key study findings regarding effective dietary changes to reduce risk of GDM, and public health messages tailored for researchers, practitioners, and policy makers. A community event will be organized to share participant results with the group.

The study team involved community organizations that they have worked with over the past 10 years to engage the SA community and health care professionals. The study will disseminate its findings among academics and policy makers using traditional methods including scientific publications, and if indicated, guideline development. The study will collaborate with family physicians, Region of Peel Public Health, and Diabetes Canada through talks and briefing reports to disseminate to community partners and Health Canada, Diabetes Canada, Heart and Stroke, Canadian Medical Association, as well as targeted communication. Peel Public Health supports "scale-up" of individual interventions using population health methods that complement clinician efforts, including mass media, social media, and text messaging campaigns. If the study demonstrate that providing tailored, culturally specific dietary advice during pregnancy to SA women is feasible and effective, the study foresee adapting the approach to other at-risk populations, including White European, African Canadian, or First Nations communities.

Discussion and implications

This study protocol describes the first RCT that examines the effect of a culturally tailored, personalized nutrition intervention on gestational glycemia in South Asian women living in Canada. In addition to proximal complications for the newborn, including life-threatening low

blood sugar (hypoglycemia) and intensive-care admission, GDM is a risk factor for future atherosclerosis and cardiovascular disease (CVD) in the mother and childhood adiposity, type 2 diabetes, and cardiovascular disease in her offspring.[28] Over the past two decades, studies have shown that starting interventions as early as infancy and perhaps before - may be an especially effective approach to maintaining lifelong heart health.[65] This intervention in pregnancy, aimed at reducing glycemia and its effect on the newborn infant, has great potential to "break the cycle" of maternal hyperglycemia and excess infant adiposity and insulin resistance, and eventually cardiovascular disease in both mother and baby.

Previous intervention studies that have sought to reduce the risk of GDM have reported mixed results, perhaps due to population heterogeneity of the maternal metabolic profile, inconsistent application of GDM diagnostic criteria, along with varied implementation.[11-13 66]

The DESI GDM study is unique because it is culturally tailored for South Asian pregnant women living in Canada, and it builds upon a qualitative study of the barriers and facilitators of lifestyle changes to prevent GDM [20], as well a birth cohort study completed in a similar population.[67] Such culturally tailored and participant/end user co-developed approaches to intervention studies improve engagement, by adding relevance to the intervention for participants.[68 69] By involving the members of the community likely to benefit from the intervention in the design of the study through previous and ongoing work, the DESI-GDM intervention is tailored to the needs and challenges of participants and is feasible. The study team's connections with family physicians help encourage high rates of recruitment and engagement as well as transferability and scale-up, as appropriate, of study results.

A limitation of the study is that participants in our study will be exposed to the intervention only after becoming pregnant. Some researchers have posited that GDM prevention

measures are most effective prior to pregnancy so that modifiable risk factors can be "optimized" prior to pregnancy.[70] However, an umbrella review by Giannakou, et al. [71] found that among 61 risk factors for GDM, pre-pregnancy BMI was associated with increased risk of GDM, and the authors assessed the level of evidence to be "highly suggestive". Furthermore, a prevalence meta-analysis of 70 studies involving 671 945 women found that every 1-unit increase in pre-pregnancy BMI increased the prevalence of GDM by 0.92% (95% CI: 0.73 to 1.10).[72]

The study is unique in that it is designed to deliver and test the uptake of a dietary intervention to reduce gestational dysglycemia in a high-risk population in Canada. This intervention in pregnancy, aimed at reducing dysglycemia, has great potential to "break the cycle" of maternal gestational dysglycemia and excess infant adiposity and insulin resistance, and eventual CVD and T2DM, both of which are complications of GDM in both mother and baby.

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None.

Contributorship statement

RNS drafted the manuscript. RJdS, KA, SSA, HB, SIB, HCG, SK, SAL, SDM, PR, DS, and GW conceived and designed the study. RJdS, HB, SIB, DD, FK, TP, AR, KMS, DS, JCS, NCW participated in the development of the protocol and data acquisition methods. RJdS, KMS, and SIB developed the statistical analysis plan. RJdS, DD, FK, TP, AR, KMS, DS participated in the design of the visits. All authors read and approved the final manuscript.

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Competing interests

RJ de Souza has served as an external resource person to the World Health Organization's Nutrition Guidelines Advisory Group on *trans* fats, saturated fats, and polyunsaturated fats. The WHO paid for his travel and accommodation to attend meetings from 2012-2017 to present and discuss this work. He has presented updates of this work to the WHO in 2022. He has also done contract research for the Canadian Institutes of Health Research's Institute of Nutrition, Metabolism, and Diabetes, Health Canada, and the World Health Organization for which he received remuneration. He has received speaker's fees from the University of Toronto, and McMaster Children's Hospital. He has held grants from the Canadian Institutes of Health Research, Canadian Foundation for Dietetic Research, Population Health Research Institute, and Hamilton Health Sciences Corporation as a principal investigator, and is a co-investigator on several funded team grants from the Canadian Institutes of Health Research. He has served as an independent director of the Helderleigh Foundation (Canada). He serves as a member of the Nutrition Science Advisory Committee to Health Canada (Government of Canada), and a co-opted member of the Scientific Advisory Committee on Nutrition (SACN) Subgroup on the Framework for the Evaluation of Evidence (Public Health England). S Kandasamy received a CIHR video talks Prize for the Knowledge Translation (KT) video created for the South Asian Grandmothers Qualitative Substudy. She was also funded by a CIHR Vanier Doctoral scholarship to develop and evaluate the SMART START KT tools. Gita Wahi has held grants from the Canadian Institutes of Health Research, and she is currently the recipient of a Research Early Career Award from Hamilton Health Sciences Foundation. P Ritvo is currently funded by the Canadian Institutes of Health (CIHR) (2021–2025). He coordinates research with NexJ Health, Inc., which provides a software platform to convey the psychosocial and psychiatric programming he develops and assesses. Ritvo receives no personal compensations for studies coordinated with NexJ but does receive free-of-charge platform support. All other authors declare no conflicts of interest.

Availability of data and materials

The principal investigator Russell de Souza will have access to the final trial data set. Any data required to support the protocol can be supplied on request.

Ethics declarations

The study has been approved by the Hamilton Integrated Research Ethics Board (HiREB #10942).

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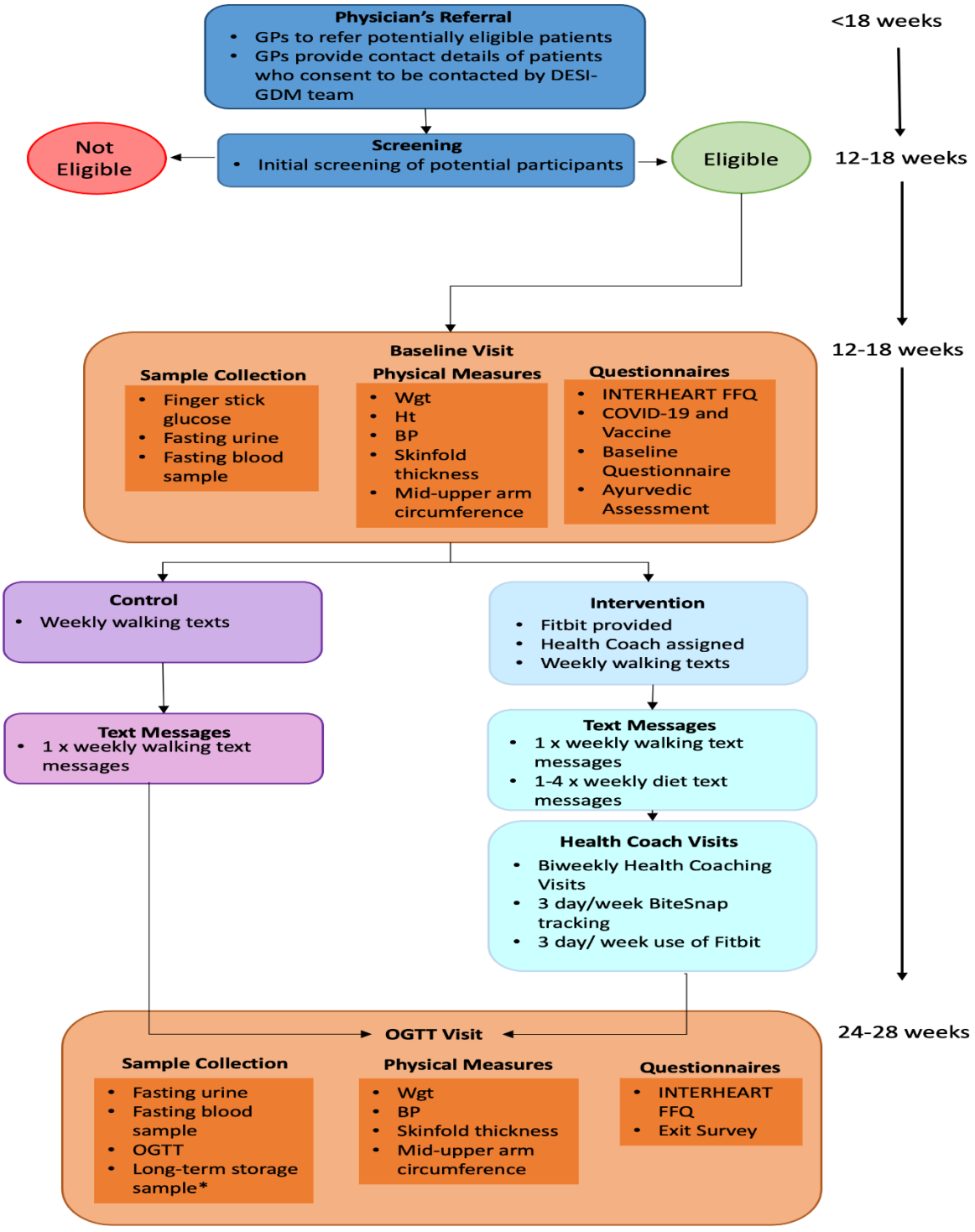
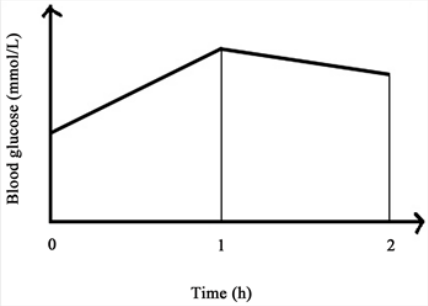


Note: GP – general practitioner; Wgt – weight; Ht – height; BP – blood pressure; FFQ – food frequency questionnaire; OGTT – Oral glucose tolerance test



The area-under-the curve of the 75-g OGTT. This is calculated by the trapezoidal method using the fasting, 1-h, and 2-h glucose. The AUC of the time-blood glucose curve of the OGTT approximately equals the areas of two trapezoids as follows: (0 h blood glucose + 1 h blood glucose) × 1/2 + (1 h blood glucose + 2 h blood glucose) × 1/2, which equals the following: 1 h blood glucose + (0 h blood glucose + 2 h blood glucose)/2.

Fig 2. AUC calculation.

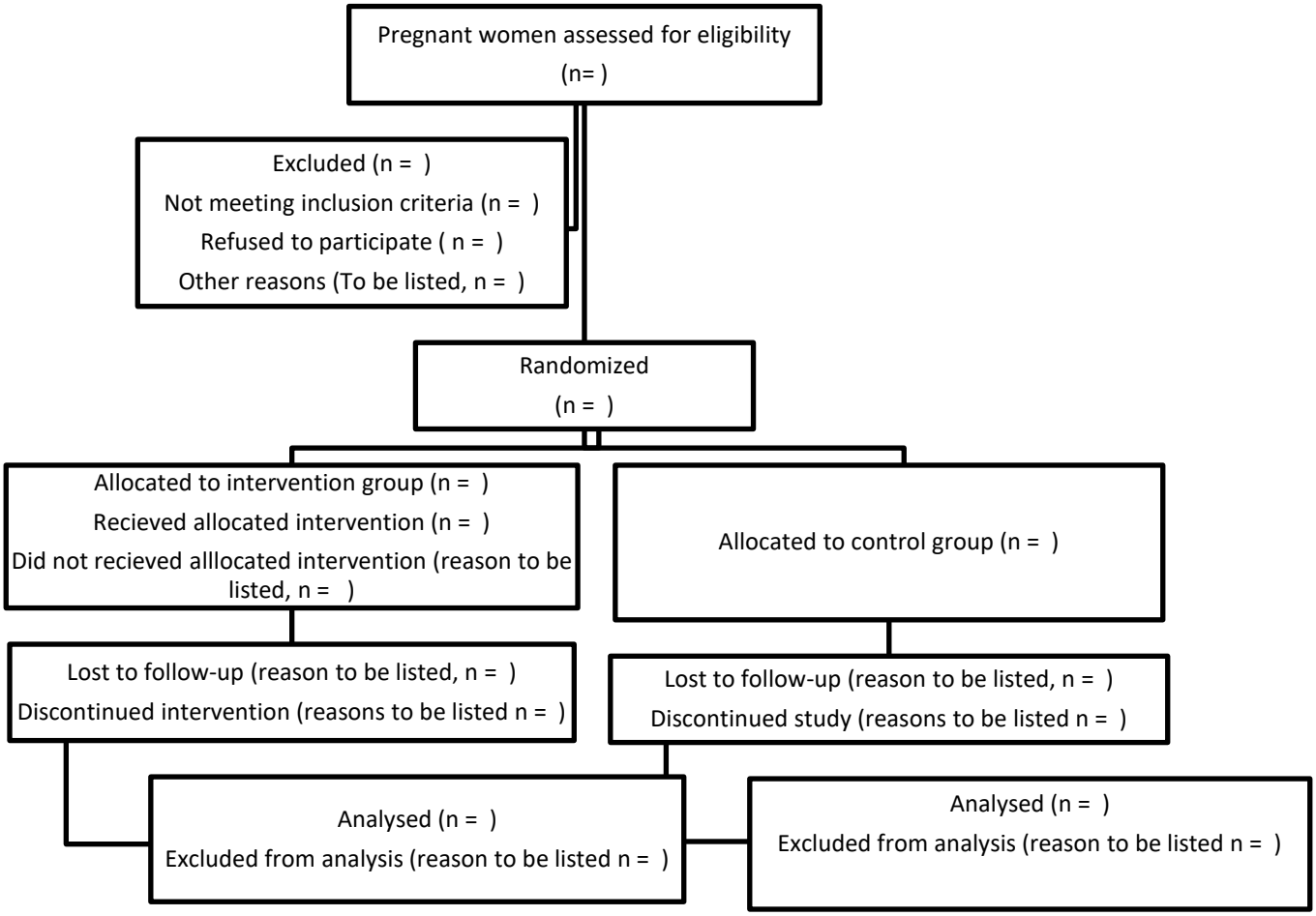


Fig 3. PRISMA Flow Diagram exemplar

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on 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	3
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1&3
	5b	Name and contact information for the trial sponsor	N/A
	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	N/A
	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)	20-21

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	4-6
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	6
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, noninferiority, exploratory)	7
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 obtained	7
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)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	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)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12-16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	16-17
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)	7&fig 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	7-8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
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	9
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	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9-10
Methods: Data collection, management, and analysis			
Data collection methods	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 protocol	9
	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	13-16

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	___19-20____
Statistical methods	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	___17-18____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___18-19____
	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)	___18-19____
Methods: Monitoring			
Data monitoring	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	_____20_____
	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	___19-20____
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	____19-20___
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____N/A_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____2&19____
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)	_____19_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24-25
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	25
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	N/A
Dissemination policy	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	21-22
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
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	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Study protocol: A culturally-tailored personalizeD nutrition intErvention in South ASIan women at risk of Gestational Diabetes Mellitus--a randomized trial (DESI-GDM)

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Complete List of Authors:	Stennett, Rosain; McMaster University Faculty of Health Sciences, Department of Health Research Methods, Evidence, and Impact Adamo, Kristi; University of Ottawa Anand, Sonia; McMaster University, Department of Medicine; Population Health Research Institute, Bajaj, Harpreet; LMC Healthcare Bangdiwala, Shrikant ; Population Health Research Institute Desai, Dipika; McMaster University Faculty of Health Sciences, Health Research Methods, Evidence & Impact ; Population Health Research Institute Gerstein, HC; McMaster University, Department of Medicine; Population Health Research Institute Kandasamy, Sujane; McMaster University Faculty of Health Sciences, Health Research Methods, Evidence & Impact Khan, Farah; Population Health Research Institute Lear, Scott; Population Health Research Institute McDonald, Sarah; McMaster University Faculty of Health Sciences, Department of Health Research Methods, Evidence, and Impact; McMaster University Faculty of Health Sciences, Department of Obstetrics & Gynecology Poscai, Tayler; Population Health Research Institute Ritvo, Paul; York University, Kinesiology and Health Science Rogge, Andrea; Population Health Research Institute Schulze, Karleen; Population Health Research Institute Sherifali, Diana; McMaster University Faculty of Health Sciences, Department of Health Research Methods, Evidence, and Impact; McMaster University Faculty of Health Sciences, Division of Maternal-Fetal Medicine, Department of Obstetrics & Gynecology Stearns, Jennifer; McMaster University Faculty of Health Sciences, Department of Obstetrics & Gynecology; McMaster University, Farncombe Family Digestive Health Research Institute Wahi, Gita; McMaster University Faculty of Health Sciences, Department of Health Research Methods, Evidence, and Impact; McMaster University Faculty of Health Sciences, Department of Paedeatrics Williams , Natalie ; McMaster University, Department of Medicine Zulyniak, Michael; University of Leeds, Food Science and Nutrition de Souza, Russell; Hamilton, Department of Health Research Methods, Evidence, and Impact; Hamilton

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Study protocol: A culturally-tailored personalizeD nutrition intErvention in South ASIan women at risk of Gestational Diabetes Mellitus--a randomized trial (DESI-GDM)

Stennett, RN[1], Adamo, K[2], Anand, SS[1,3], Bajaj, H[4], Bangdiwala, SI[1,3], Desai, D[1,3], Gerstein, HC[3,5], Kandasamy, S[1], Khan, F[3], Lear, SA[3], McDonald, SD[1,3,6], Poscai, T[3†], Ritvo, P[7], Rogge, A[3], Schulze, KM[3], Sherifali, D[1,3,8], Stearns, JC[6,9], Wahi, G[1,10], Williams, NC[5], Zulyniak, MA[11], de Souza, RJ[1,3]

Affiliations

[1]Department of Health Research Methods, Evidence, and Impact, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada

[2] School of Human Kinetics, Faculty of Health Sciences, University of Ottawa, Ottawa, ON, Canada

[3]Population Health Research Institute, Hamilton Health Sciences Corporation, Hamilton, ON, Canada

[4]LMC Healthcare, Brampton, Ontario, Canada

[5]Department of Medicine, McMaster University, Hamilton, Ontario, Canada

[6]Obstetrics & Gynecology, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada

[7]Department of Psychology, York University, North York, Ontario, Canada

[8]School of Nursing, McMaster University, Hamilton, Ontario, Canada

[9]Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Ontario, Canada

[10] Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada

[11]School of Food Science and Nutrition, University of Leeds, Leeds, United Kingdom

† Affiliation at time of preparation of manuscript

*Corresponding author: Russell J. de Souza, desouzrj@mcmaster.ca

Abstract

Introduction: South Asians are more likely to develop gestational diabetes mellitus (GDM) than White Europeans. Diet and lifestyle modifications may prevent GDM and reduce undesirable outcomes in both the mother and offspring. Our study seeks to evaluate the effectiveness and participant acceptability of a culturally-tailored, personalized nutrition intervention on the glucose area under the curve (AUC) after a 2-hour 75g oral glucose tolerance test (OGTT) in pregnant women of South Asian ancestry with GDM risk factors.

Methods and Analysis: One hundred ninety pregnant South Asians with at least 2 of the following GDM risk factors—pre-pregnancy body mass index (BMI) >23, age ≥29, poor-quality diet, family history of type 2 diabetes (T2DM) in a first-degree relative, or GDM in a previous pregnancy will be enrolled during gestational week 12-18, and randomly assigned in a 1:1 ratio to: 1) usual care, plus weekly text messages to encourage walking and paper handouts or 2) a personalized nutrition plan developed and delivered by a culturally-congruent dietitian and health coach; and FitBit® to track steps. The intervention lasts 6 – 16-weeks, depending on week-of-recruitment. The primary outcome is the glucose AUC from a 3-sample 75 g OGTT 24-28 weeks gestation. The secondary outcome is GDM diagnosis, based on Born-in-Bradford criteria (fasting glucose ≥ 5.2 mmol/L, or 2-hour post-load ≥7.2 mmol/L).

Ethics and Dissemination: The study has been approved by the Hamilton Integrated Research Ethics Board (HiREB #10942). Findings will be disseminated among academics and policy makers through scientific publications along with community orientated strategies.

Word count: 249

Trial Registration: ClinicalTrials.gov NCT03607799. Registered July 31, 2018

Key words: Gestational diabetes mellitus, South Asian, personalized nutrition intervention

Article Summary

Strengths and limitations of this study:

- The DESI GDM study intervention is informed by the findings of a previous qualitative study which assessed barriers and facilitators of lifestyle changes to prevent GDM, as well a birth cohort study completed in a similar population.
- This study utilizes an end user co-developed approach to intervention study which seeks to improve participant engagement and buy-in.
- The study is powered to detect a moderate treatment effect on the glycemic response to the oral glucose tolerance test however, not GDM.

Introduction

Gestational diabetes mellitus (GDM) is a condition in which a woman without existing diabetes develops high blood sugar levels during pregnancy.[1] Complications for the baby include neonatal hypoglycemia and intensive-care admission.[2] GDM is a strong risk factor for future type 2 diabetes (T2DM): up to 50% of women with GDM develop T2DM within 5 years of giving birth[3 4], and face up to seven-fold higher lifetime risk of T2DM compared with women who have a non-GDM pregnancy.[3 5] Additionally, GDM is associated with future atherosclerosis and cardiovascular disease (CVD) in the mother and increases the risk of T2DM in offspring up to eight-fold.[5-8]

South Asians (SA), whose ancestors are from India, Pakistan, Bangladesh, or Sri Lanka, are the largest non-white ethnic group in Canada, and are at high risk of T2DM and early CVD. GDM increases the risk of future T2DM and CVD. The development of GDM is influenced by several factors, notably ethnicity and diet. SA are two times more likely to develop GDM relative to white European women[9 10], and risk factors for future T2DM in the offspring including higher birthweight, more adipose tissue, and reduced insulin sensitivity, are more common in SA infants of mothers with GDM than infants born to mothers without GDM.[9] Furthermore a low quality diet (diet higher in meat, meat dishes, processed meats, organ meats, poultry, fish, seafood, rice, fried foods, refined grains (breads and cereals), fast foods and eggs) during pregnancy increases one's odds of developing GDM (odds ratio [OR]: 1.62; 95% CI: 1.20 to 2.19).[9] It is assumed that approximately 13% of GDM cases in SA could be prevented by a healthy diet (population attributable risk [PAR]: 12.8%). [9]

Food-based interventions show the most potential for preventing GDM.[11-13] A network meta-analysis (21 randomized trials during pregnancy; n=1,865 women) [14] reported that diets

with reduced glycemic load and/or increased fibre intake, compared to gestational weight gain advice, improved fasting glucose levels. In another meta-analysis of randomized control trials, diet modification alone led to the largest reduction in risk of excessive maternal weight gain and (3 trials; n=409 women) reduced the incidence of GDM (relative risk [RR]: 0.68; 95% CI: 0.48 to 0.96), however the overall evidence rating was low to very low for the latter outcome [15]. There is a need for more robust food-based intervention studies that consider additional factors in the development of GDM in order to provide optimal prevention strategies for women at higher risk of developing the condition.

Few randomized trials of the effect of diet and/or physical activity on incident GDM have been conducted. One recent randomized trial conducted in Ireland (n=565) found that an exercise and nutrition program delivered via smartphone did not reduce GDM in overweight and obese women randomized at a mean gestational age of 15.3 weeks (RR: 1.1; 95% CI: 0.71 to 1.66) [16]. However, this study aimed to modify only one aspect of diet, which was reducing the glycemic index. A second trial conducted in Spain (n=1000) found that a Mediterranean dietary pattern supplemented with extra virgin olive oil and pistachios, reduced the incidence of GDM (RR: 0.73; 95% CI: 0.56 to 0.95) compared with standard low-fat dietary advice [17]. A third trial, Project SARAS in Mumbai, India[18], was an unblinded, individually randomized controlled trial of diet to prevent GDM in women living in slums. The intervention included a daily snack made from leafy green vegetables, fruit, and milk for the treatment group, compared with low-micronutrient vegetables (e.g., potato and onion) for the control group, on top of the usual diet. Of 6,513 women, 35% became pregnant; of these, 89% reached a gestation of 28 wks., and 50% (n=1,008) attended an OGTT. In total, 9.9% (n=100) developed GDM using the World Health Organization's 1999 defintion.[19] Although there were many challenges of conducting this trial

(i.e., 50% lost to follow-up), in an intention-to-treat (ITT) analysis, GDM was reduced in the treatment group (7.3% compared with 12.4% in controls; OR: 0.56; 95% CI: 0.36, 0.86; P = 0.008). The reduction remained significant after adjusting for pre-pregnancy adiposity and fat or weight gain during pregnancy.

In a qualitative interpretive descriptive study of barriers and facilitators to healthy eating encountered by pregnant and recently pregnant South Asian women and health care providers living and working in the Peel Region of Ontario, Canada [20], women voiced several facilitators to healthy eating such as: ***i)*** knowledge of culturally appropriate healthy foods; and ***ii)*** access to a health care provider able to provide resources and support in a timely fashion. Participants also identified barriers to healthy eating, including difficulty: ***i)*** changing long-held cultural diet practices; ***ii)*** adapting standard dietary advice to personal health beliefs; ***iii)*** navigating food choices at family gatherings; and ***iv)*** accommodating meal needs of others in the household. Women expressed a desire to learn more about healthy eating to prevent diabetes during pregnancy and were keen to use mobile health technology. Health care providers identified two major challenges to providing appropriate advice to members of this community: ***i)*** insufficient time for counselling; and ***ii)*** lack of familiarity with South Asian foods. These findings are consistent with other studies of sociocultural influences on behaviour in pregnancy in South Asian women. [21 22]

These observations have led us to design and evaluate the effectiveness and participant acceptability of a randomized controlled trial of a culturally-tailored, personalized nutrition intervention, delivered by a health coach, on the glucose area under the curve (AUC) after a 2-hour 75-g oral glucose tolerance test (OGTT) to pregnant South Asian women at risk of GDM living in Southern Ontario, Canada. The trial protocol follows the guidelines for protocol

development and reporting described by the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement (*see* Additional file 1).

Methods

Design: The study is a two-arm parallel RCT. The allocation ratio will be 1:1 to the intervention or usual care (control) group. The study schema diagram illustrates the referral and screening procedure (**Figure 1**).

Setting: The study will be conducted in Southern Ontario with the primary recruitment site being the Regional Municipality of Peel, which consists of three municipalities to the west and northwest of the city of Toronto: the cities of Mississauga and Brampton, and the town of Caledon. More than half of the residents of the Region of Peel identify as South Asian.[23] The region has >800 family physicians and >60 obstetricians who see approximately 5,000 South Asian women/year in the second trimester of pregnancy. Expectant women routinely attend their first visit between 12 - 18 weeks of pregnancy and then every four weeks until 30 weeks' gestation; every two weeks from 32 to 36 weeks' gestation; and once a week from 37 weeks' gestation until birth.[24]

Sample size: With 86 participants per group (total n = 172), the study will have 90% power to detect at least a 15% between-group difference in AUC glucose, the primary outcome, assuming 70% adherence to the intervention (i.e. goal setting, health coach contacts, food tracking) and SD of AUC glucose = 173 mmol/min [9]. A change in glucose of at least this magnitude has been observed in trials of similar design to test fibre supplements [25], high-protein [26], or high-fat diets[27]. A 10% loss-to-follow up is assumed, which is low for dietary interventions, however given the frequent expected contact with health care providers during

pregnancy, the virtual nature of our intervention, and our pilot data,[28] it is believed to be feasible. The sample size has been inflated to 95 per group (total n = 190) to account for the expected high lost-to-follow up. The study will have low power to detect a moderate treatment effect on the secondary outcome of GDM (i.e., 20-30% between-treatment difference), and higher power to detect very large treatment effects in GDM (i.e., 80% power to detect a 61% relative risk reduction). The study will look to see if GDM incidence, measured as a dichotomous outcome, is nominally improved.

Inclusion criteria: Singleton pregnant South Asian women will be enrolled between 12 – 18 weeks gestation. This timeframe avoids the early pregnancy window, when women are most likely to experience nausea, and is past the highest period of risk for spontaneous abortion. In addition to being South Asian, a high-risk ethnic group for GDM [29], participants will also need to meet at least 2 GDM risk factors: age>29[9], low diet quality (assessed with a short diet screener) [9] [30], family history of DM/GDM during a previous pregnancy[29] [31], or a pre-pregnancy BMI ≥23.[9]

Exclusion criteria: Expectant mothers with any of the following will be excluded from the study: a) pre-existing type 1 or type 2 diabetes[29]; b) hypertension (≥140 mmHg systolic or ≥90 mmHg diastolic) or on medication for the condition[32-34]; c) serious difficulty understanding health information in English, based on the screening conversation, that would preclude informed consent and participation (93% of Canadian South Asian women in the National Household Survey could conduct a conversation in one or both official languages (English and French) [35] [36]; d) those unwilling or unable to modify their eating habits, based on a screening question; e) those at high risk of adverse pregnancy outcomes other than GDM (e.g., twins or higher-order multiples[32] [37], use of fertility treatments[38], history of hypertension/pre-eclampsia,

history[34] of placenta previa[39] or pre-term delivery[40]); or f) enrolment in another intervention study that would compromise full participation in the DESI-GDM) trial.

Recruitment: Because of the COVID-19 pandemic, and the university research policies the study recruitment was delayed but began in November 2021 and is expected to be completed by March 2024. The study team will provide study information to primary care physicians and obstetricians who will identify and refer participants into the study.

Randomization and blinding: Women will be randomized 1:1 to intervention or control using a centralized integrated web response system (IWRS) at the Population Health Research Institute (PHRI) in Hamilton, Ontario. A statistician will generate a randomization list using a permuted blocks algorithm with randomly chosen block sizes to ensure balance in numbers and avoid predictability.[41] The nature of the intervention precludes blinding of the participants to the treatment assignment, however, those providing the analysis of blood glucose levels for assessing the primary and secondary outcomes will be blinded to treatment assignment.

At the baseline visit, the research assistant (RA) will confirm eligibility and obtain consent, either in person, verbally via telephone or web conferencing, or electronically via REDCap. These three options are believed to be flexible and responsive to participant preference, and possible regulations regarding COVID-19 public health measures. After confirming eligibility and the informed consent discussion, the RA will collect baseline measures.

After collecting baseline physical measures, the study personnel completing the visit will activate the IWRS to randomly allocate participants to control or intervention in a concealed

fashion using a computer-generated random sequence. Those assigned to the intervention will be assigned to a health coach, who will contact the participant for a baseline nutrition assessment, and goal-setting session. Planned assessment visits take place at 3 time points regardless of the study arm: 1) baseline 12 – 18 weeks gestation; 2) follow-up 24–28 weeks of gestation; and 3) post-delivery – pregnancy and birth outcomes.

Intervention

In our intervention study which seeks to address behavioral changes, we used goal setting, behavioral contracting through bi-weekly checkups, and tailored health communication (text messaging). These strategies were drawn from the Social Cognitive Theory of behavioral changes[42] and applied stages of change construct of the Transtheoretical Model[43]. The activities used in the intervention are guided by the findings of 1) the START birth cohort study[9], which identified diet as a key modifiable risk factor for GDM, and 2) a qualitative study of barriers and facilitators to healthy eating encountered by pregnant and recently pregnant South Asian women and health care providers living and working in Ontario[20].

Duration: Treatment/ intervention duration will be between 6 and 16 weeks, depending on the gestational age at enrollment. Effects of dietary intervention on glycemic endpoints are detectable in ≤6 week[44 45], and reach maximal effectiveness after 8-10 weeks (~2 months) of intervention[46]. In-person or Zoom study visit contact will occur 2 times: once for the baseline visit and once for the OGTT. Between these visits, all participants receive weekly text messages, and intervention participants will also have bi-weekly telephone or video conferencing (Zoom/WhatsApp).

***Treatment group*:** A personalized nutrition plan will be developed for each woman by a culturally-congruent dietitian. Our dietary intervention will focus on:

i) providing personalized food recommendations that consider a woman's current dietary habits by identifying food choices and substitutions that will optimize the diet;

ii) providing dietary advice that is sensitive to religious belief/practice if desired by the participant (e.g., vegetarian foods maybe preferred by *Hindu*, *Buddhists*, *Jainists*; etc.; while inclusion of meat may be more appropriate for *Sikhs* and *Christians*) and regional (e.g., Northern vs. Southern India, Sri Lanka, Bangladesh, Pakistan) culinary practices; and

iii) involving the household meal preparer, if this is not the participant herself, in the coaching contacts; and use mobile health technology to reduce the amount of in-office time a health care practitioner spends on dietary counselling. Additionally, participants assigned to the intervention group will be given a Fitbit to track their steps along with encouragement to increase walking.

The health coach will co-design a plan with each participant that considers baseline dietary intake, energy balance for recommended gestational weight gain, personal values, and preferences, and set 2-4 "SMART" goals. Nutrition and behaviour change experts have developed text messages that support 11 categories of nutrition goals (Table 1), targeted to address eating behaviours identified by participants in our qualitative study, designed to optimize energy balance for weight gain and improve dietary quality.

Table 1. Categories of nutrition goals

1. Eating out healthy	2. Reduce indulgence in sweets/desserts
3. Controlling over-eating	4. Reduce intake of sugary beverages
5. Reducing high-fat, fried foods	6. Cooking meals at home more
7. Reducing highly refined carbohydrates	8. Improving meal planning
9. Encouraging mindful eating	10. Eating more fruits and vegetables
11. Increasing quality protein intake	

Both groups: Participants in both groups receive weekly text messages, aimed at increasing walking, as this was identified as a way to increase physical activity during pregnancy that was acceptable to South Asian women to undertake during pregnancy,[20] and is critical for glucose homeostasis during pregnancy.[47 48] Both groups will be given resources that provide advice on healthy eating, physical activity, and other lifestyle factors during pregnancy(paper handouts) plus additional materials adapted specifically for the South Asian community. Health care providers in Peel Region use these tools routinely (Diabetes Canada: https://bit.ly/2m8r2tT; or Heart & Stroke: https://bit.ly/2lDubl7).

Study Measurements and Schedule

Baseline assessment (for both intervention and control participants): At the baseline visit, participants' physical measurement (height, weight, blood pressure, skinfold thickness and mid-upper arm circumference), fasting urine and blood sample will be collected. Additionally, an ayurvedic assessment and 3 questionnaires (baseline instrument, INTERHEART Food Frequency Questionnaire (FFQ) and COVID-19 and vaccine questionnaire) will be administered.

The baseline instrument is researcher developed and has 4 sections: 1. Socio-demographics; 2. medical history; 3. obstetric history; and 4. lifestyle history.

The Ayurvedic "prakriti" assessment is a way of characterizing a population into set subgroups, based on traditional Indian medicine called Ayurveda. This is a method of taking a person-centered approach to health care[49], based on phenotypic characteristics such as appearance, mannerisms, etc. and is used for personalizing medicine and ways of healthy living for individual. We will use the validated TNMC questionnaire from 2004.[50] The decision to use this tool was taken during the development of the protocol, through conversations with members of the team and potential participants who practice Ayurveda. We may explore differences in the primary outcome according to prakriti, however these are post-hoc, exploratory analyses only.

The INTERHEART FFQ (modified for use in pregnancy) is a semiquantitative food frequency questionnaire (FFQ) that assesses intake of fruits and vegetables, and fast foods consumption. The FFQ was adapted from the 19-item INTERHEART FFQ [51], which has been used in studies that included South Asians.[52 53]

The COVID-19 and vaccine questionnaire a short two-part, self-administered questionnaire. We have decided to administer this because the COVID-19 pandemic has impacted all aspects of day-to-day life, and its impact on our participants will help contextualize our findings. The first part is the Vaccination Attitudes Examination (VAX) scale[54], a validated, and reliable tool that assesses general vaccination attitudes across 4 domains: 1. Mistrust of vaccine benefit; 2. Worries about unforeseen future events; 3. Concerns about commercial profiteering; and 4. Preference for natural immunity. The second section comprises additional questions about preferred types of vaccines, preferred location of receiving the vaccine, and general attitudes/concerns about vaccines.

Participants will be given an option to provide their health card number, which will enable future linkage with administrative data sources from Ontario such as the Institute for Clinical Evaluative Sciences (ICES) for potential health economic evaluation and for long-term follow-up of the mother and her child.

Weekly and Health Coach Visit: Participants in both control and intervention groups receive 1 text message every week up to the date of the OGTT with 1 of the 6 walking tips, sent by an automated outbound messaging system developed by MemoTXT (Toronto, ON). The intervention group only will also be sent weekly text messages to reinforce individual nutrition goals at times of day requested by the participant. Participants assigned to the intervention group will be given a Fitbit to track their steps; and will be requested to track food consumption in Bitesnap, a photo food journal app, for 2 weekdays and 1 weekend day bi-weekly (up to 8 assessments). Health coaches will be able to view both Fitbit and Bitesnap data via the Health Coaching Platform.

Coaching contacts to the intervention group will be made bi-weekly up to the date of their OGTT. These coaching calls will be recorded using an audio recording device. At each scheduled contact, intervention participants review agreed-upon diet goals, and assess, on a Likert scale, how often they were able to achieve the goals (ranging from "never" to "all of the time"); the coach will work with the participant to overcome barriers using our Brief Action Planning Guide. After each coaching call, participants and Health Coaches will complete a Visit Reflection questionnaire.

The central coordinator will review data regularly for completion, and *ad* hoc calls may be made to clarify items for either arm, but no counseling is provided to control group participants (see Table 2 for details).

Table 2. Schedule of study activities

Activity	Baseline Visit	Weekly	Health Coach Visits (bi-weekly)	OGTT Visit	Post-Birth Follow-up
Screening	x				
Informed Consent	x				
Randomization	x				
Physical Measures (height, weight, blood pressure, skinfold thickness, mid upper arm circumference)	x				
INTERHEART Food Frequency Questionnaire	x			x	
Finger Stick for Glucose	x				
75-g OGTT				x	
Urine Sample Collection	x			x	
Blood Sample Collection (optional)	x			x	
Baseline Questionnaire	x				
Ayurvedic Assessment	x				
Device Identification*	x				
FitBit Distribution*	x				
Bitesnap Downloaded*	x				
Resource Handouts	x				
Walking tips via *MemoTXT*		x			
Diet reinforcement via *MemoTXT**		x			
Calls With Health Coach (set and review SMART goals, Brief Action Planning Guide) *			x		
Visit Reflection*			x		
Bitesnap Food Journal*		x			
FitBit Return*				x	
Exit Questionnaire				x	
Mother-reported Infant Physical Measures					x

* Intervention group only

Follow-up Assessment/ Second Visit: At the second clinic visit (24-28 weeks gestation), INTERHEART food frequency questionnaire, fasting urine sample collection and fasting blood sample collection are repeated (this may be done virtually, or in-person) and a 75-g OGTT is

performed. Additional blood samples will be collected at 3-time points (0 hr, 1 hr and 2 hr) during the OGTT (based on referral and participant willingness) and stored for future analysis.

In Peel, pregnant women usually undergo a 50-g glucose challenge at 24-28 weeks, with a 1-h value ≥7.8 mmol/L being an indication for a 75-g OGTT.[55] Rather than this 2-step process, we have chosen to administer the 75- g OGTT to all women because: 1. it was used to establish South Asian-specific diagnostic criteria for GDM, and thus the study's outcomes will be directly comparable [10]; 2. it avoids the high false-negative rate of the 50-g Glucose Challenge Test (GCT) among South Asians[56 57]; 3. one-step screening has potential for long-term cost-saving[58-60]; and 4. Diabetes Canada recognizes that the one-step strategy can identify a subset of women who would not otherwise be identified as having GDM and who may benefit with regard to certain perinatal outcomes [29]. The study team will coordinate with the health care provider to ensure participants receive the 75-g OGTT between 24-28 weeks, avoiding the two-step screen.

At the completion of their OGTT, each woman will be asked to complete the DESI-GDM exit survey. This is a 9-item questionnaire based on previous tools created and used by the study team. Responses to each question are provided using a 5-item Likert scale (Strongly Disagree through Strongly Agree).

Postnatal Assessment: Study participants will be contacted after delivering their baby to self-report the birth weight and length of their baby. Participants will also be asked to provide details of any complications during delivery.

Study outcomes

The primary clinical outcome of this trial is the area under the glucose curve (AUC) of the 3-sample OGTT. A measure of glycemic response, glucose AUC is a continuous measure of the

response to a 75-g OGTT that accounts for variations in fasting plasma glucose levels between individuals. It is calculated by the trapezoidal method using the fasting, 1-hour, and 2-hour glucose[61] (**Figure 2**). The AUC is superior to a single measure, i.e., fasting or 2-hour glucose only, which may not provide complete information regarding plasma glucose processing after a load.[62]

The secondary outcome is GDM, classified using the cut-offs derived in the Born-in-Bradford (BiB) cohort, which were found to be associated with 75% higher risk of LGA or infant adiposity [infant birth weight >90th percentile for gestational age or adiposity (sum of skinfold measurements >90th percentile for gestational age) in a study of 5,408 SA women]. These values are fasting glucose $\geq$ 5.2 mmol/L, or 2-hour post-load $\geq$7.2 mmol/L [10]. Current clinical cut-offs for the 75-g OGTT used to diagnose GDM in the general population as defined by the Diabetes Canada's clinical practice guidelines are: fasting glucose $\geq$ 5.3 mmol/L, 1-hour $\geq$ 10.6 mmol/L, or 2-hour $\geq$9.0 mmol/L.[29] The study team will assess the sensitivity and specificity of the BiB definition against the International Association of the Diabetes and Pregnancy Study Groups (IASPSG) or World Health Organization (WHO) criteria (see Table 3 for diagnostic criteria).

Table 3. Diagnostic criteria for secondary outcome, gestational diabetes mellitus (GDM)

Threshold	Fasting	1-h	2-h
BiB	>=5.2	-	>=7.2
IADPSG	>=5.1	>=10.0	>=8.5
WHO	>=7.0	-	>=7.8
Diabetes Canada	>=5.3	>=10.6	>=9.0

Planned data analysis

The study will assess the main effect of the diet intervention (β1) based on two outcomes as well as conduct process and acceptability assessments:

a) Primary clinical outcome: The study will assess the main effect of the diet intervention (β1) on the primary outcome of glucose AUC with a linear regression model with ***intervention*** as the main effect (a dummy variable, where 1=treatment; 0=control).

b) Secondary clinical outcome: The study will assess the main effect of the diet intervention (β1) on the secondary outcome of GDM by fitting a logistic regression model with ***intervention*** as the main effect (a dummy variable, where 1=treatment; 0=control).

Table 4 provides a summary of the planned analysis objectives, outcome, hypothesis and methods of analysis, and **Figure 3** is our proposed CONSORT flow diagram.

Table 4. Analysis Plan: objectives, outcome, hypothesis, and methods of analysis

Objective	Outcomes	Measurement	Criteria for success	Method of analysis
Primary clinical	Glycemic response to the 75-g oral glucose tolerance test	Area under the curve of glucose	Mean statistically significant reduction of 15% in the intervention arm	Linear regression*
Secondary clinical	Gestational diabetes diagnosed by 75-g oral glucose tolerance test	Fasting glucose ≥5.2 mmol/L, or 2-hour post 75-g load ≥7.2 mmol/L	OR <0.9 = signal of benefit OR > 1.1 = signal of harm	Logistic regression*
Acceptability	Acceptability	Answer to the question "Would you recommend this program to a friend?"	≥80% of participants reply "agree or strongly agree"	Descriptive statistic (proportion)

*Mixed models will be considered to adjust for centre effects using random intercepts.

c) Process and acceptability assessments: These data will be presented descriptively and include monthly process feedback (e.g., recruitment, retention, adherence), which the team will discuss

on an ongoing basis (e.g., adherence, unmet goals/targets). The study team will review qualitative and quantitative data to refine implementation processes. Acceptability will be explored using semi-structured exit interviews after the OGTT visit, which allow each participant to reflect on their experiences with the program and convey what they liked and disliked about the study, and if they would recommend the program to a friend, as we have in previous studies of similar design.[63 64]

e) Handling of missing outcome data: Missing outcome data (OGTT) will be handled via multiple imputation as a sensitivity analysis if we have >30% missing outcome data.

f) Sensitivity analyses (for primary and secondary outcomes only): The study team anticipate possible variation in treatment effect according to time in study and by clinic site (if multiple clinics refer participants). Women will be enrolled in the study between weeks 12-18 of pregnancy. The outcome will be assessed at week 24-28 of pregnancy. Therefore, the length of time that each woman will receive the intervention may vary. The first sensitivity analysis will adjust the primary outcome for time in study (OGTT date minus enrolment date). The second sensitivity analysis, if there is multiple sites of enrolment, the study team will consider a random effect of study site.

d) Interim data analysis: No interim data analysis is planned.

Ethical considerations

The study has been approved by the Hamilton Integrated Research Ethics Board (HiREB #10942), and the trial is registered with clinical trials.gov (NCT03607799). Participants will provide written, verbal, or electronic informed consent. If providing verbal consent, participants will be sent the full consent via email or paper mail, to read and refer to while being consented. If providing electronic consent via Research Electronic Data Capture (REDCap), participants

will be sent a link that contains the full consent and will review the consent over telephone or web-conferencing with study staff. The participant will select whether they agree to participate at the bottom of the consent page. Participant data will be deidentified to protect confidentiality and will only be reported and published in aggregate. Any modifications made to the study protocol will be shared with HiREB as stipulated and we will follow their advice regarding implementation and dissemination.

Data monitoring and management

Study Coordination and Management: The principal investigator will take responsibility for the oversight of the study. The coordinating centre for the trial will be Population Health Research Institute (PHRI) in Hamilton, ON. The coordinating centre, under the direction of the study statistician, will receive all data, and take process steps to reduce missing data. A junior project manager, along with a graduate student will oversee the of recruitment of participants and handle central trial coordination. At weekly meetings, the study will review recruitment, minor adverse events, study inventories, and review any expressed concerns by participants or the team. The steering committee will direct operational/process, nutrition, coaching, and statistical aspects of the trial.

Data and Safety Monitoring: For a previous pilot study, the study team had convened a Data and Safety monitoring committee (DSMC), consisting of two internal medicine specialists (one being an experienced endocrinologist), and a biostatistician. This committee advised that a DSMC was not required for the pilot, voting for a safety officer, and disbanded. The committee advised the same for this trial. Therefore, at pre-specified meeting times, the safety officer, trained in internal medicine, will review data, noting any of the 8 minor (mother – induced

labour, anemia, urinary tract infection, fall/injury/accident related to study, low mood or high blood pressure; child - premature labour (<36 weeks) or shoulder dystocia), or 6 major maternal events (hyperemesis gravidarum, caesarean section, pre-eclampsia, primary post-partum hemorrhage >500mL, miscarriage or maternal mortality,); or 2 major infant events (mortality – (fetal and neonatal) or stillbirth). The safety officer will determine whether they are related to study participation. To evaluate safety outcomes, maternal blood pressure at baseline and the OGTT follow-up visit will be measured, and notes of any pregnancy complications at coaching contacts.

The safety officer will review an interim data analysis, comparing a) mean AUC glucose; and b) GDM incidence between treatment and control (blinded) after the first 25 participants have completed their OGTT visit. Thereafter, the safety officer will review the data following each additional 50 participants. There is no early stopping rule for this study. The study will only collect data at baseline and the OGTT visit.

Patient and Public Involvement

The study included recently pregnant SA women living in Peel (ON), public health practitioners, and primary care providers that work with pregnant SA women in the development of our intervention through focus groups and semi-structured interviews. The co-investigators who work with the SA community and serve on guidelines committees have been closely involved with developing this research proposal. The study's physician collaborators will be involved in the recruitment progress, to help troubleshoot challenges, and refine intervention implementation strategies during the grant cycle.

Dissemination plans

The findings of the study will be important in guiding future evidence-based recommendations and public health policies to manage gestational glycemia in pregnant women at risk of GDM. Throughout the study, a strategy for integrated Knowledge Translation will be used to develop a series of digital projects (short digital story-based videos) that capture: 1. participant experiences that include key messages about successful approaches to healthy eating that women would like to share with their communities; and 2. key study findings regarding effective dietary changes to reduce risk of GDM, and public health messages tailored for researchers, practitioners, and policy makers. A community event will be organized to share participant results with the group.

The study team involved community organizations that they have worked with over the past 10 years to engage the SA community and health care professionals. The study will disseminate its findings among academics and policy makers using traditional methods including scientific publications, and if indicated, guideline development. The study will collaborate with family physicians, Region of Peel Public Health, and Diabetes Canada through talks and briefing reports to disseminate to community partners and Health Canada, Diabetes Canada, Heart and Stroke, Canadian Medical Association, as well as targeted communication. Peel Public Health supports "scale-up" of individual interventions using population health methods that complement clinician efforts, including mass media, social media, and text messaging campaigns. If the study demonstrate that providing tailored, culturally specific dietary advice during pregnancy to SA women is feasible and effective, the study foresee adapting the approach to other at-risk populations, including White European, African Canadian, or First Nations communities.

Discussion and implications

This study protocol describes the first RCT that examines the effect of a culturally tailored, personalized nutrition intervention on gestational glycemia in South Asian women living in Canada. In addition to proximal complications for the newborn, including life-threatening low blood sugar (hypoglycemia) and intensive-care admission, GDM is a risk factor for future atherosclerosis and cardiovascular disease (CVD) in the mother and childhood adiposity, type 2 diabetes, and cardiovascular disease in her offspring.[28] Over the past two decades, studies have shown that starting interventions as early as infancy and perhaps before - may be an especially effective approach to maintaining lifelong heart health.[65] This intervention in pregnancy, aimed at reducing glycemia and its effect on the newborn infant, has great potential to "break the cycle" of maternal hyperglycemia and excess infant adiposity and insulin resistance, and eventually cardiovascular disease in both mother and baby.

Previous intervention studies that have sought to reduce the risk of GDM have reported mixed results, perhaps due to population heterogeneity of the maternal metabolic profile, inconsistent application of GDM diagnostic criteria, along with varied implementation.[11-13 66]

The DESI GDM study is unique because it is culturally tailored for South Asian pregnant women living in Canada, and it builds upon a qualitative study of the barriers and facilitators of lifestyle changes to prevent GDM [20], as well a birth cohort study completed in a similar population.[67] Such culturally tailored and participant/end user co-developed approaches to intervention studies improve engagement, by adding relevance to the intervention for participants.[68 69] By involving the members of the community likely to benefit from the intervention in the design of the study through previous and ongoing work, the DESI-GDM intervention is tailored to the needs and challenges of participants and is feasible. The study

team's connections with family physicians help encourage high rates of recruitment and engagement as well as transferability and scale-up, as appropriate, of study results.

A limitation of the study is that participants in our study will be exposed to the intervention only after becoming pregnant. Some researchers have posited that GDM prevention measures are most effective prior to pregnancy so that modifiable risk factors can be "optimized" prior to pregnancy.[70] However, an umbrella review by Giannakou, et al. [71] found that among 61 risk factors for GDM, pre-pregnancy BMI was associated with increased risk of GDM, and the authors assessed the level of evidence to be "highly suggestive". Furthermore, a prevalence meta-analysis of 70 studies involving 671 945 women found that every 1-unit increase in pre-pregnancy BMI increased the prevalence of GDM by 0.92% (95% CI: 0.73 to 1.10).[72]

The study is unique in that it is designed to deliver and test the uptake of a dietary intervention to reduce gestational dysglycemia in a high-risk population in Canada. This intervention in pregnancy, aimed at reducing dysglycemia, has great potential to "break the cycle" of maternal gestational dysglycemia and excess infant adiposity and insulin resistance, and eventual CVD and T2DM, both of which are complications of GDM in both mother and baby.

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Contributorship statement

RNS drafted the manuscript. RJdS, KA, SSA, HB, SIB, HCG, SK, SAL, SDM, PR, DS, MAZ and GW conceived and designed the study. RJdS, HB, SIB, DD, FK, TP, AR, KMS, DS, JCS, NCW and MAZ participated in the development of the protocol and data acquisition methods.

RJdS, KMS, and SIB developed the statistical analysis plan. RJdS, DD, FK, TP, AR, KMS, DS participated in the design of the visits. All authors read and approved the final manuscript.

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Competing interests

RJ de Souza has served as an external resource person to the World Health Organization's Nutrition Guidelines Advisory Group on *trans* fats, saturated fats, and polyunsaturated fats. The WHO paid for his travel and accommodation to attend meetings from 2012-2017 to present and discuss this work. He has presented updates of this work to the WHO in 2022. He has also done contract research for the Canadian Institutes of Health Research's Institute of Nutrition, Metabolism, and Diabetes, Health Canada, and the World Health Organization for which he received remuneration. He has received speaker's fees from the University of Toronto, and McMaster Children's Hospital. He has held grants from the Canadian Institutes of Health Research, Canadian Foundation for Dietetic Research, Population Health Research Institute, and Hamilton Health Sciences Corporation as a principal investigator, and is a co-investigator on several funded team grants from the Canadian Institutes of Health Research. He has served as an independent director of the Helderleigh Foundation (Canada). He serves as a member of the Nutrition Science Advisory Committee to Health Canada (Government of Canada), and a co-opted member of the Scientific Advisory Committee on Nutrition (SACN) Subgroup on the Framework for the Evaluation of Evidence (Public Health England). S Kandasamy received a CIHR video talks Prize for the Knowledge Translation (KT) video created for the South Asian Grandmothers Qualitative Substudy. She was also funded by a CIHR Vanier Doctoral scholarship to develop and evaluate the SMART START KT tools. Gita Wahi has held grants from the Canadian Institutes of Health Research, and she is currently the recipient of a Research Early Career Award from Hamilton Health Sciences Foundation. P Ritvo is currently funded by the Canadian Institutes of Health (CIHR) (2021–2025). He coordinates research with NexJ Health, Inc., which provides a software platform to convey the psychosocial and psychiatric programming he develops and assesses. Ritvo receives no personal compensations for studies coordinated with NexJ but does receive free-of-charge platform support. All other authors declare no conflicts of interest.

Availability of data and materials

The principal investigator Russell de Souza will have access to the final trial data set. Any data required to support the protocol can be supplied on request.

Ethics declarations

The study has been approved by the Hamilton Integrated Research Ethics Board (HiREB #10942).

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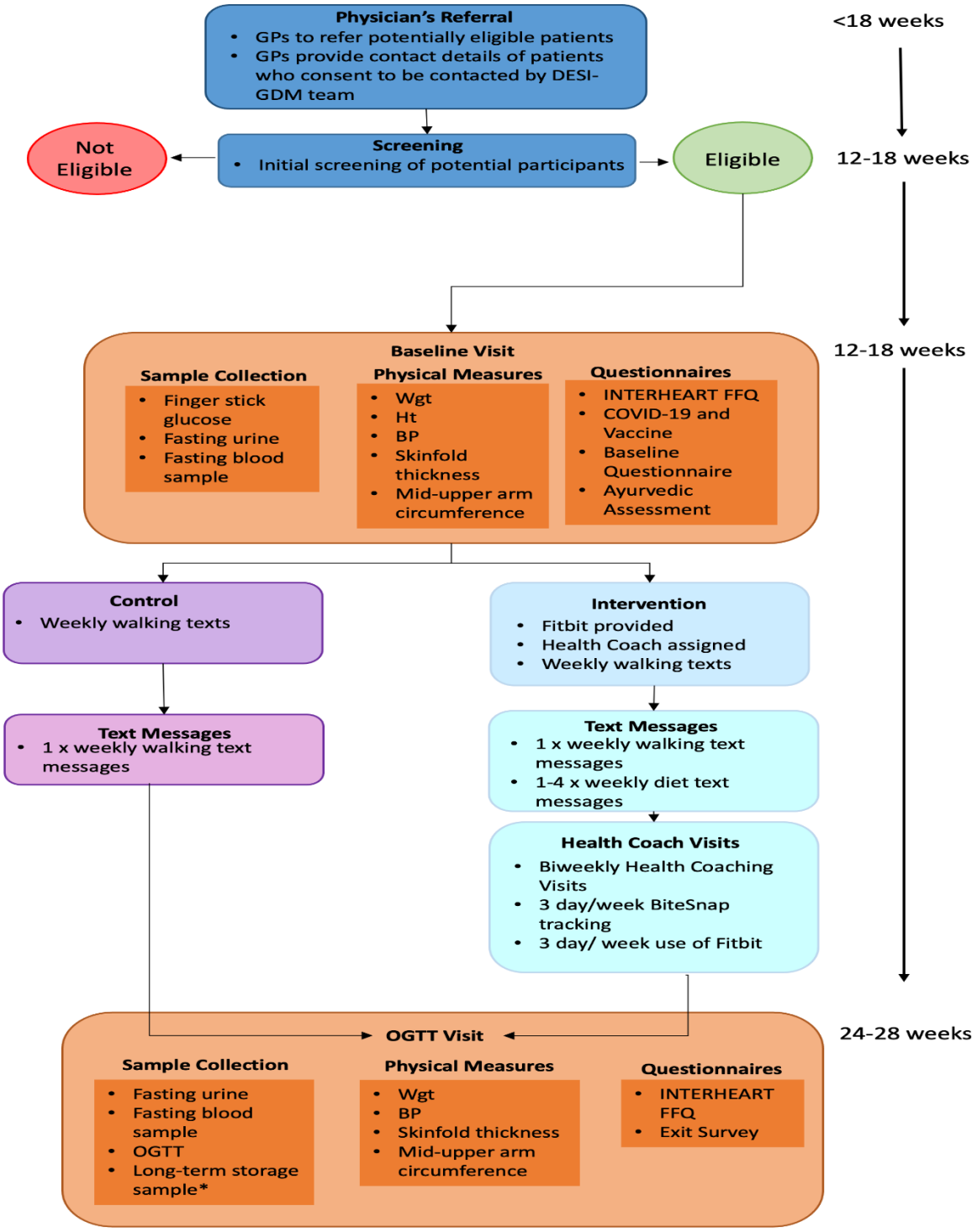
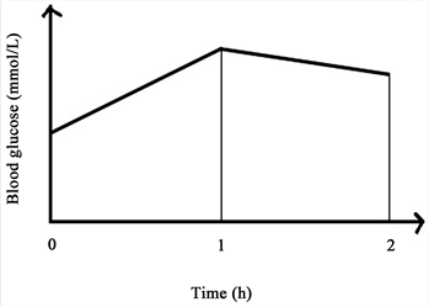


Note: GP – general practitioner; Wgt – weight; Ht – height; BP – blood pressure; FFQ – food frequency questionnaire; OGTT – Oral glucose tolerance test



The area-under-the curve of the 75-g OGTT. This is calculated by the trapezoidal method using the fasting, 1-h, and 2-h glucose. The AUC of the time-blood glucose curve of the OGTT approximately equals the areas of two trapezoids as follows: (0 h blood glucose + 1 h blood glucose) × 1/2 + (1 h blood glucose + 2 h blood glucose) × 1/2, which equals the following: 1 h blood glucose + (0 h blood glucose + 2 h blood glucose)/2.

Fig 2. AUC calculation.

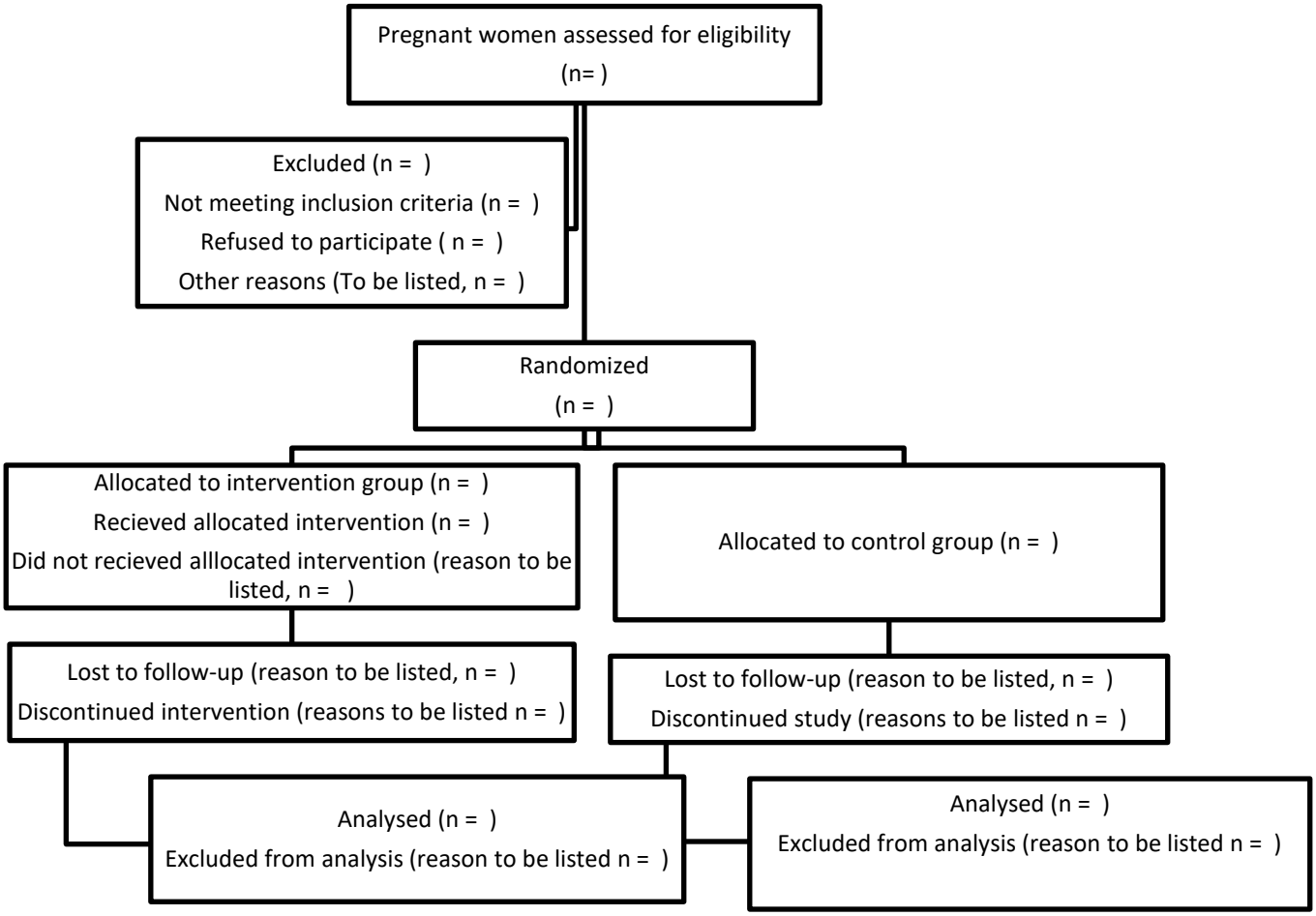


Fig 3. PRISMA Flow Diagram exemplar

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on 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	3
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1&3
	5b	Name and contact information for the trial sponsor	N/A
	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	N/A
	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)	20-21

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	4-6
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	6
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, noninferiority, exploratory)	7
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 obtained	7
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)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	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)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12-16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	16-17
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)	7&fig 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	7-8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
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	9
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	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9-10
Methods: Data collection, management, and analysis			
Data collection methods	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 protocol	9
	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	13-16

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	___19-20____
Statistical methods	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	___17-18____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___18-19____
	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)	___18-19____
Methods: Monitoring			
Data monitoring	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	_____20_____
	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	___19-20____
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	____19-20___
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____N/A_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____2&19____
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)	_____19_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24-25
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	25
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	N/A
Dissemination policy	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	21-22
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
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	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.