STUDY PROTOCOL

Effectiveness and implementation of a lifestyle modification intervention for women with isolated impaired fasting glucose: Study protocol for a hybrid type 2 study in Kerala, India [version 1; peer review: 2 approved]

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Abstract

Background: Isolated impaired fasting glucose (i-IFG) constitutes a major group in the prediabetic spectrum among Indians, and thus it is imperative to identify effective diabetes prevention strategies. This study aims to evaluate the effects of an intensive community-based lifestyle modification program on regression to normoglycemia among women with i-IFG, compared to a control group at 24 months. The study also aims to evaluate the implementation of the intervention, via both process and implementation outcomes.

Methods: We will use a hybrid design (Effectiveness-implementation hybrid type 2 trial) to test the effectiveness and implementation of the lifestyle modification intervention. Effectiveness is evaluated using a randomized controlled trial among 950 overweight or obese women, aged 30 to 60 years, with i-IFG on an oral glucose tolerance test in the Indian state of Kerala. The intervention involves an intensive lifestyle modification program through group and individually mentored sessions using behavioural determinants and behavioural change techniques. The intervention group will receive the intervention for a period of 12 months and the control group will receive general health advice through a health education booklet. Data on behavioural, clinical, and biochemical measures will be collected using standard methods at 12 and 24 months. The primary outcome will be regression to normoglycemia at 24 months, as defined by the

Open Peer Review

Approval Status

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2. Priti Gupta , Centre for Chronic Disease Control, New Delhi, India		
Any reports and responses or comments on the article can be found at the end of the article.		

American Diabetes Association criteria.

Discussion: This study will provide the first evidence on the effects of lifestyle interventions on regression to normoglycemia in people with i-IFG among Indians.

CTRI registration: CTRI/2021/07/035289 (30/07/2021)

Keywords

Prediabetes, Isolated impaired fasting glucose, Lifestyle modification, Kerala, Women, RCT

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Introduction

Type 2 diabetes mellitus (T2DM), currently affects almost 537 million adults worldwide with a projected increase of nearly 50% by 2045¹. Low- and middle-income countries (LMICs) such as India are disproportionately affected, with the large majority (81%) of people with T2DM living in these countries¹. India has the second-largest number of people (74 million) living with T2DM and this is projected to increase to 125 million people by 2045¹. In addition, T2DM poses a significant economic burden in LMICs, affecting not just the health care system but also individuals and families with increased out-of-pocket spending for diabetes care². Therefore, much importance has been given to diabetes prevention, with a greater research focus on individuals who are at high risk for diabetes.

Prediabetes, a high-risk metabolic state for diabetes, comprises impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), wherein the glucose levels are higher than those considered to be normal, but lower than the threshold for T2DM³. A recent review of 19 studies globally showed that among those with prediabetes, the average proportions of isolated IFG (i-IFG), isolated IGT (i-IGT), and combined IFG and IGT were 43.9%, 41.0%, and 13.5%, respectively, in Caucasians, and 29.2%, 49.4%, and 18.2%, respectively, in Asians⁴. A large-scale study in 15 states of India showed that i-IFG is the most common form of prediabetes among adults, with a prevalence of 21%⁵. On average, nearly 5–10% of people with prediabetes develop T2DM every year, although the progression rate varies by population characteristics (including ethnicity) and the definition of prediabetes⁶. With no effective intervention, nearly 70% of people with prediabetes would eventually progress to develop T2DM⁶.

Lifestyle modification is recognized as an effective non-pharmacologic intervention to prevent or delay the onset of diabetes among individuals with prediabetes⁷. Most landmark lifestyle modification randomized controlled trials (RCTs) for diabetes prevention have been conducted in individuals with IGT⁸, with very limited evidence in the i-IFG group. Lifestyle modification in the trials for those with IGT have focused mainly on weight loss and promoting physical activity, although the intervention intensity, goals, and delivery methods have varied widely between the trials. These trials have shown that diabetes incidence could be reduced between 28.5% and 58% in the intervention group compared with the control group⁸. More importantly, a clinically meaningful reduction in diabetes incidence with lifestyle modification has been shown to persist in those with IGT even after 30 years of follow-up⁹.

Only a few RCTs have evaluated the effects of lifestyle modification on diabetes prevention in people with i-IFG¹⁰. RCTs conducted among 641 overweight Japanese¹¹ and 578 overweight Indian adults¹² showed hazard ratios of 1.17 (95% CI 0.50–2.74, n=379) and 0.88 (95% CI 0.43–1.20, n=166) respectively, in those with i-IFG at 3 years. Similarly, a trial among 880 adults with prediabetes in the UK showed a hazard ratio of 0.52 (95% CI 0.15–1.83, n=108) at 3 years in those with

i-IFG¹³. The Kerala Diabetes Prevention Program (K-DPP) from India showed a relative risk of 0.95 (95% CI 0.68, 1.33) in people with i-IFG (n=579) at 2 years among 1007 high-risk individuals¹⁴. However, the above-mentioned findings were from the sub-group analyses, which are constrained by small sample sizes, a limited number of events, and confounding¹⁵.

While preventing the progression of prediabetes to diabetes is important, regression to normoglycemia is also essential to achieve, even if transient, as this has been shown to be significantly associated with reduction in the development of diabetes¹⁰. To our knowledge, there are no data on regression to normoglycemia with lifestyle modification in the i-IFG group among Indians, an ethnic group with i-IFG being the most common prediabetes phenotype^{5,14}. In addition to being at high risk for diabetes, individuals with i-IFG are at an increased risk of developing micro- and macro-vascular complications, and of all-cause mortality⁶.

This study aims to evaluate the effects of an intensive community-based lifestyle modification program on regression to normoglycemia among women with i-IFG compared to a control group at 24 months. We will also evaluate the effects of the intervention on improving cardiometabolic risk factors. The study will use the RE-AIM framework to evaluate Reach, Adoption, Implementation and Maintenance¹⁶ and the intervention fidelity using process measures.

This two-arm parallel group randomized controlled trial targets women as the behavioural risk factors of overweight or obesity and physical inactivity are generally higher among women, compared to men, in the Indian context¹⁷ and the intervention outcomes reported so far are poorer among women¹² in India.

Methods

Study design and setting

The study uses a hybrid design (Hybrid type 2)¹⁸ that tests the effectiveness and implementation of a lifestyle modification program. A randomized controlled trial will evaluate the effectiveness of the intervention, and the intervention implementation and fidelity will be evaluated using implementation outcomes and process measures, respectively.

The study was registered with Clinical Trials Registry, India (CTRI/2021/07/035289, on 30th July 2021). The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines¹⁹.

The study will be conducted in Kasaragod district of Kerala (Figure 1). Kerala, the southernmost Indian state, has a higher prevalence of T2DM (nearly 20%) and a greater burden of several cardiometabolic risk factors than most other Indian states¹⁷. Further, the state is in the most advanced stage of epidemiological transition in the country²⁰ and said to be a harbinger of the future burden of diabetes and other chronic diseases in India²⁰. Thus, Kerala provides an ideal place to implement and evaluate lifestyle modification programs.

Figure 1. Map of the study area. A. India political. **B.** Kasaragod district (shaded) in the State of Kerala. **C.** Taluks of Kasaragod district.

Figure 2 shows the CONSORT diagram of the trial. Kasaragod is the northernmost district of Kerala, with a population of 1,307,375, a sex ratio of 1079 women for every 1000 men, and a literacy rate of 90%²¹. Kasaragod has four *taluks* (sub-district) with 777 wards (lowest administrative division with approximately 1300 individuals in each ward)²¹. From these four *taluks*, two were randomly selected, namely Hosdurg *taluk* and Kasaragod *taluk*. There are 465 wards in these two *taluks*, amongst which those wards within 20km distance from the institute were included (269 wards) considering the logistics and feasibility. Out of 269 wards, 25 wards with at least 1000 individuals in each ward were randomly selected. From these selected wards, individuals with i-IFG will be identified and recruited to the trial with a minimum of 23 participants per ward.

Study participants

Inclusion criteria: 1) Women aged 30–60 years; 2) overweight or obese (waist circumference ≥ 80 cm)²²; 3) no prior history of diabetes; 4) not taking any glucose-lowering medications; 5) no prior history of gestational diabetes mellitus (GDM); 6) able to read, write and speak Malayalam, the local language; 7) consents to participate in the trial; and 8) diagnosed with i-IFG (fasting plasma glucose [FPG] 5.6–6.9 mmol/l and 2-hr plasma glucose [2-hr PG] < 7.8 mmol/l) on a 2-hr oral glucose tolerance test (OGTT)³.

Exclusion criteria: 1) Women with known T2DM; 2) having GDM; 3) prior history of GDM; 4) breastfeeding women; 5) having major chronic illnesses including mental disorders, that are likely to impede consenting and participation in the intervention program; 6) taking medications that could alter glucose metabolism (e.g., corticosteroids); and 7) diagnosed with normoglycemia, IGT, and T2DM, as per the American Diabetes Association criteria³ on the OGTT.

Sample size and randomization

We assumed that the cumulative incidence of regression to normoglycemia at two years would be 18% in the control group (based on unpublished data from the K-DPP trial) and that there would be a 50% relative risk in conversion to normoglycemia with the intervention. The sample size required in each study group was 475 with a type 1 error of 5%, at least 80% power, a contamination rate of 15%, and a 10% loss to follow-up. The sample size required with same estimates and 90% power in each group is 625, and will be recruited, if logistically feasible.

The estimated sample size of 950 participants will be randomly allocated in a 1:1 ratio to the control group and the intervention group using a computer-generated randomization sequence using Microsoft excel by an independent statistician not involved in the trial. The independent statistician will generate the randomized sequence and allocate the individuals to the randomized groups. The participants and the Principal Investigator (EM) will be blinded to the allocation sequence until informed written consent for study participation is obtained. The outcome assessors, data entry personnel and statisticians who analyse the data will be blinded throughout the study as they are not part of the team that delivers intervention or manage the project.

This study uses individual randomization in order to avoid the methodological challenges of cluster randomization, including the clustering effect on statistical power and selection bias, possibility of imbalanced study groups, and the dilution effect²³. Trial conduct solutions will be put in place to address potential contamination, if any, between the study groups with individual randomization. This include using different staff for each group, education of the participants against contamination²³, and getting signed nondisclosure agreement from the intervention participants regarding the type of

^a Office of the Registrar General & Census Commissioner. Census 2011, India. <https://censusindia.gov.in> (accessed 10 June 2021)

^b Women and Men in India 2020. Social Statistics division. Ministry of Statistics and Program Implementation. Government of India. Accessed from www.mospi.gov.in

Figure 2. CONSORT diagram of the trial.

intervention being received. Furthermore, analytical methods that adjust for contamination will also be used. We will also quantify the contamination using a treatment fidelity framework based on the criteria advocated by the Behaviour Change Consortium²⁴ and NICE guidance on behaviour change²⁵.

Recruitment of participants and data collection

Screening and recruitment of participants and data collection will be conducted in 2 stages as described below:

Stage 1: Home visits. All women in the age group of 30–60 years will be selected from the voters' list of the selected wards. Eligibility for participation in the study will be ascertained during home visits using a screening questionnaire (includes demographics and eligibility criteria) by trained staff. Only one participant per household (randomly selected) will be screened. Those who meet the eligibility criteria and provide consent for study participation will be screened with a point-of-care glucometer (OneTouch Select Plus, LifeScan Inc.) and their waist circumference will be measured using SECA 201 ergonomic retractable tape with using a standard protocol²⁶. Those who are overweight or obese (waist circumference ≥ 80 cm)²² and with a random capillary blood glucose of >110 mg/dl²⁷ will be invited to undergo a 2-hr OGTT in clinics organized in their neighbourhoods. These individuals will be considered to be at high risk for having prediabetes or diabetes.

Stage 2: Clinics. The high-risk individuals will attend clinics organized in their neighbourhoods, where they will undergo a 2-hr OGTT, body composition, anthropometric, and blood pressure measurements, and interviews to complete the questionnaires. Those diagnosed with T2DM on the OGTT will be referred to the nearby health facility for treatment and care. Body fat composition will be assessed using TANITA DC 360 (pole). Blood pressure will be measured using an OMRON HEM-7120 blood pressure monitor using the standard protocol²⁶.

The weight and height will be measured using SECA 813 flat scale and SECA 213 stadiometer, respectively, with a standard protocol²⁶. Blood samples will be collected in a fasting state (8–10 hours of fasting) and will be centrifuged within 30 mins after collection and transported to a lab accredited by the National Accreditation Board for Testing and Calibration Laboratories (NABL)²⁸. Questionnaires will be administered by trained staff to collect information on demographics, diet²⁹, physical activity²⁶, tobacco use²⁶, alcohol use²⁶, diabetes knowledge³⁰, prediabetes knowledge³¹, health-related quality of life (HRQoL)³², self-efficacy for managing chronic diseases³³, risk perception for diabetes³⁴, social support³⁵, and sleep hygiene³⁶ using standardized questionnaires (Table 1). Those who are diagnosed with diabetes at 12th and 24th month assessment will be referred to the nearby health facility for treatment and care, and will continue to participate in the trial. All assessments done at the baseline will be repeated at 12 months and 24 months.

Staff conducting physical measurements and administering questionnaires at baseline and follow-up visits will be blinded

to participants' group allocation. Intervention staff will not be engaged in the data collection process and the statistician engaged in data analysis will be blinded to the group allocation.

All study materials can be found in the *Extended data*³⁷.

Outcomes

The primary outcome for the effectiveness study will be normoglycemia, defined as FPG <5.6 mmol/l and 2-hr PG <7.6 mmol/l, at 24 months³. Secondary outcomes will include incidence of T2DM (fasting plasma glucose ≥ 7.0 mmol/l or 2hr PG ≥ 11.1 mmol/l or HbA1c $\geq 6.5\%$), insulin sensitivity, beta cell function, weight, body mass index, waist circumference, FPG, 2-hr PG, blood pressure, body composition measures (fat percent and muscle mass) and psychosocial variables (health-related quality of life, self-efficacy/self-empowerment, risk-perception for diabetes, social support and sleep hygiene). Implementation outcomes include reach, effectiveness, adoption, implementation and maintenance of the intervention¹⁶.

Study groups

Control group. Participants in the control group will receive a health information leaflet at baseline in local language (*Malayalam*) on strategies for diabetes prevention. No further engagement will be there in the control group apart from follow-up assessments at 12 and 24 months.

Intervention group. The study participants in the intervention group will receive an intensive lifestyle modification program for a period of 12 months through group and individually mentored sessions. The intervention will include behavioural determinants such as self-efficacy, risk perception, social support, and behavioural change techniques, including knowledge enhancement, self-monitoring, goal setting and review, and peer support³⁸ (Table 2). The intervention will be intense as the engagement is not just limited to group sessions, but also involves individualized support through peer mentors and individualized instructions through a mobile application, specifically made for this trial.

Theory of intervention. The intervention program objectives, theory-based methods, and strategies for intervention engagement and implementation are given in Table 3. Briefly, the intervention was adapted from a successfully conducted lifestyle-based diabetes prevention trial in Kerala, the K-DPP³⁸. Program objectives will be achieved through “personal learning” and “environmental change” using evidence-based behaviour change techniques with strategies targeting participants at individual, interpersonal and community levels.

Intervention content

Figure 3 shows a thematic representation of the program goals with the targets and the strategies adopted at individual and group level using the behaviour techniques. The intervention will focus primarily on key behavioural risk factors, including unhealthy diet, physical inactivity, tobacco use, alcohol use, and sleep. Based on the dietary recommendations for the prevention of T2DM³⁹ and pertinent research findings among

Table 1. Outcomes, measurement tools, and data collection time points.

Outcome measures	Variable	Tools/tests used	Baseline	Regular assessment	12 months	24 months
Primary outcome for effectiveness						
Regression of i-IFG to normoglycemia at 12 and 24 months	Fasting plasma glucose and 2-hr post-load plasma glucose	OGTT in a NABL accredited laboratory ²⁸	✓		✓	✓
Secondary outcomes for effectiveness						
Incidence of diabetes	Fasting plasma glucose, 30 minutes and 2-hr post-load plasma glucose, HbA1c	NABL accredited laboratory ²⁸	✓		✓	✓
Insulin sensitivity	Fasting insulin, 2-h insulin, Homa IR	NABL accredited laboratory ²⁸	✓		✓	✓
Beta cell function	Fasting insulin, 2hr insulin, Homa B		✓		✓	✓
Lipid profile	Total cholesterol, triglycerides, HDL-cholesterol, and LDL-cholesterol	NABL accredited laboratory ²⁸	✓		✓	✓
Liver function tests	Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT)	NABL accredited laboratory ²⁸	✓		✓	✓
Blood Pressure	Systolic and diastolic blood pressure	OMRON electronic blood pressure monitor	✓		✓	✓
Anthropometrics	a. Weight b. Height c. Waist circumference	a. SECA weighing scale b. SECA stadiometer c. SECA non-elastic tape	✓		✓	✓
Body composition measures	a. Fat percent b. Muscle mass	TANITA body fat analyser	✓		✓	✓
Psychosocial variables	a. Diabetes knowledge b. Knowledge on prediabetes c. Health-related quality of life d. Self-efficacy/self-empowerment e. Risk-perception for diabetes f. Social support g. Sleep Hygiene	a. 24 Item Diabetes Knowledge Questionnaire ³⁰ b. Prediabetes Knowledge Questionnaire ³¹ c. WHO QoL BREF scale ³² d. Health Lifestyle and Personal Control Questionnaire ³³ e. Scale by Hivert <i>et al.</i> ³⁴ f. Scale by Sarason <i>et al.</i> ³⁵ g. Sleep Hygiene Index scale by Mastin <i>et al.</i> ³⁶	✓		✓	✓
Behavioural outcomes for effectiveness and implementation						
	a. Diet b. Physical activity and sedentary behaviour c. Tobacco use d. Alcohol use	a. Food frequency questionnaire ²⁵ b. Global Physical Activity Questionnaire ²⁶ c. WHO STEPS questionnaire ²⁶ d. WHO STEPS questionnaire ²⁶	✓		✓	✓

Outcome measures	Variable	Tools/tests used	Baseline	Regular assessment	12 months	24 months
Implementation outcomes (at community, provider and beneficiary levels)						
	a. Reach	a1. Database on recruitment a2. Database on meetings	✓	✓		
	a1. Participants approached a2. Frequency of contact with the <i>panchayat</i>		✓	✓		
	b. Effectiveness	b1. 24 Item Diabetes Knowledge Questionnaire ³⁰ b2. Risk perception Scale ³⁴ b3. Health Lifestyle and Personal Control Questionnaire ³³ b4. Social Support scale ³⁵	✓	✓	✓	✓
	b1. Improved knowledge on T2DM prevention b2. Risk perception b3. Self-efficacy b4. Social Support		✓	✓	✓	✓
	c. Adoption	c1. Participant attendance data c2. Participants feedback report c3. Behavioural change report ^{24,25} c4. Pre and post knowledge change evaluation report (Participant)	✓	✓		✓
	c1 Individuals attending the sessions (Number) c2. Individuals who set goals c3 Individuals achieving the behavioural targets c4. Change in knowledge on diabetes and its risk factors and behavioural targets		✓	✓		
	d. Implementation	d1. Peer mentors feedback report, Pre and post knowledge change evaluation report (Peer Mentors) d2. Participants feedback report, Session attendance data d4. 1. Peer mentors characteristics d5. Participant feedback report	✓	✓		
	d1. Peer mentor trainings (quality) d2. Participants group sessions (quality) d3. Sessions conducted d4. Peer mentor selection d5. Support received by peer mentors		✓	✓		
	e. Maintenance	e1. Behavioural assessment data ^{24,25}	✓	✓		
	e 1. Individuals achieving behavioural targets		✓	✓		

OGTT- Oral Glucose Tolerance Test, NABL-National Accreditation Board for Testing and Calibration Laboratories, WHO QoL BREF- World Health Organization Quality of Life , HDL- High density lipoprotein, LDL- Low density lipoprotein

Table 2. Program goals, theory-based methods, and strategies (Adapted from the Kerala Diabetes Prevention Program) [Source: Elezebeth *et al.* Cultural adaptation of a peer-led lifestyle intervention program for diabetes prevention in India: the Kerala Diabetes Prevention Program (K-DPP)³⁷].

Program Goals	Personal learning and Social environmental change objectives	Determinants based on theory and evidence	Behaviour change techniques	Feasible and culturally acceptable strategies to enhance engagement and implementation
a. Weight loss by 5–7% ⁶ b. Reduction in waist circumference by ≥ 4 cm ²² c. Reduction in body mass index ⁶ by ≥ 0.5 kg/m ² d. Increased consumption of fruit and vegetables (>5 servings/day) ³⁹ e. Increased physical activity through walking, exercise, and culturally appropriate activities (>150 minutes/week) ⁴⁰ f. Improved sleep hygiene ⁴¹	Personal learning objectives • Increase in awareness of risk factors of T2DM • Improve risk perception on T2DM • Improve self-efficacy in making lifestyle changes Social Environment change objectives • Enhance peer support for behaviour change • Enhance household/family support for behaviour change • Facilitate opportunities for healthy lifestyle in collaboration with group members • Empowerment for diabetes prevention	• Risk perception • Self-efficacy • Social support • Availability and accessibility of facilities for physical activity and healthy food options	• Provide information on the risk factors of T2DM • Provide information on the dietary and physical activity targets for individuals. • Self-monitoring • Goal setting and goal review with emphasis on participants and family member outcomes • Peer support • Social and practical support from family, neighbourhood members and community organizations (Panchayats) • Engage and empower family and group members to increase availability and accessibility of healthy food options and physical activity options	Individual-level • Educational sessions that focus on 'modifiable' determinants of risk on diabetes. • Sessions scheduled in local neighbourhoods (e.g. a reading room or <i>Kudumbashree's meeting rooms</i>) according to work, family and other cultural needs of participants Interpersonal-level (family) • Group-based delivery • Inclusion of family members in the sessions • Enabling ongoing peer and social support, with family members and friends of participants • Kitchen garden training to facilitate vegetable consumption and increase enjoyable physical activity • Forming walking groups or other activity groups such as yoga or aerobic dance groups as appropriate.

Table 3. Intervention sessions schedule.

Session	Individual/ Group	Theme	Activity (AV aid)	Duration	Facilitator
1	G	1.1 Introduce the project 1.2 Rapport building 1.3 Knowledge enhancement	1.1.1 Introduction about the project, requirements and commitments 1.2.1 Building rapport with the participants 1.2.2 Identification of peer mentor 1.3.1 Discuss about diabetes and prediabetes (IFG & IGT) (Flipchart & Mobile based application) 1.3.2 Discuss about risk factors of diabetes (Flipchart & Mobile based application)	20 Min 15 Min 30 Min 20 Min 20 Min	Research Team
2	G	2.1 Risk factor Modification- Unhealthy diet 2.2 Self-monitoring of dietary intake 2.3 Knowledge enhancement on dietary allowances and recommendation for fat/sugar/vegetables/fruits/salt/rice) 2.4 Goal setting 2.5 Diet monitoring	2.2.1 Self-monitoring work sheet (Flipchart & participant workbook) 2.3.1 Education on healthy diet practices [session+ activity] (Flip chart & Mobile based application) 2.4.1 Individualised goal setting (Flipchart & participant workbook) 2.5.1 Personalized diet planning tool using an interactive mobile application platform.	20 Min 20 Min 20 Min 15 Min	Research Team
3	I	3.1. Diet goal monitoring and revisiting the goals	3.1.1. Goal monitoring (participant workbook) 3.1.2. Identification of barriers 3.1.3. Goal resetting (if needed)	10 Min 10 Min 10 Min	Peer mentor
4	G	4.1 Demonstration of healthy diet option (Salad preparation) 4.2 Physical activity promotion 4.3 Self-monitoring 4.4 Knowledge enhancement on strategies to improve PA 4.5 Goal Setting	4.1.1 Demonstrate the preparation of healthy diet (salad) 4.2.1 Discuss on physical activity and its importance (Flip chart) 4.3.1 PA self-monitoring worksheet (participant workbook) 4.4.1 Discuss on the types of physical activities that are culturally appropriate and feasible (Flipchart & participant workbook) 4.5.1 Individualised goal setting (Participant workbook)	20 Min 15 Min 15 Min 25 Min 15 Min per participant	Research Team
5	I	5.1 PA goal monitoring and revisiting the goals 5.2 Diet goal monitoring and revisiting the goals	5.1.1 Goal monitoring (Participant workbook) 5.1.2 Identification of barriers 5.1.3 Goal resetting (if needed) 5.2.1 Goal monitoring (Participant workbook) 5.2.2 Identification of barriers 5.2.3 Goal resetting (if needed)	30 Min per participant	Peer mentor

Session	Individual/ Group	Theme	Activity (AV aid)	Duration	Facilitator
6	1	6.1 PA goal monitoring and revisiting the goals 6.2 Diet goal monitoring and revisiting the goals	6.1.1 Goal monitoring (Participant workbook) 6.1.2 Identification of barriers 6.1.3 Goal resetting (if needed) 6.2.1 Goal monitoring (Participant workbook) 6.2.2 Identification of barriers 6.2.3 Goal resetting (if needed)	30 Min per participant	Peer mentor
7	G	7.1 Knowledge enhancement - Effect of stress on diabetes and other chronic diseases 7.2 Strategies for Stress Management 7.3 Strategies to enhance Sleep hygiene	7.1.1 Awareness on impact of stress and importance of managing it (Flipchart & m health app) 7.2.1 Identification of Stress factors (Flipchart) 7.2.2 Demonstration of various stress management techniques (Breathing exercise and yoga) 7.3.1 Educate about the importance of maintaining sleep hygiene (Flipchart)	20 Min 20 Min 10 Min 15 Min	Research Team
8	I	8.1 PA goal monitoring and revisiting the goals 8.2 Diet goal monitoring and revisiting the goals	8.1.1 Goal monitoring (Participant workbook) 8.1.2 Identification of barriers 8.1.3 Goal resetting (if needed) 8.2.1 Goal monitoring (Participant workbook) 8.2.2 Identification of barriers 8.2.3 Goal resetting (if needed)	30 Min per participant	Peer mentor
9	I	9.1 PA goal monitoring and revisiting the goals 9.2 Diet goal monitoring and revisiting the goals	9.1.1 Goal monitoring (Participant workbook) 9.1.2 Identification of barriers 9.1.3 Goal resetting (if needed) 9.2.1 Goal monitoring (Participant workbook) 9.2.2 Identification of barriers 9.2.3 Goal resetting (if needed)	30 Min per participant	Peer mentor
10	G	10.1 Tobacco and alcohol cessation	10.1.1 Create awareness on impact of alcohol and tobacco in the development of T2DM 10.1.2 Refer the participants who use tobacco and alcohol to cessation clinics (if needed)	20 Min	Research Team
11	I	11.1 PA goal monitoring and revisiting the goals 11.2 Diet goal monitoring and revisiting the goals	11.1.1 Goal monitoring (Participant workbook) 11.1.2 Identification of barriers 11.1.3 Goal resetting (if needed) 11.2.1 Goal monitoring (Participant workbook) 11.2.2 Identification of barriers 11.2.3 Goal resetting (if needed)	30 Min per participant	Peer mentor

Session	Individual/Group	Theme	Activity (AV aid)	Duration	Facilitator
12	I	12.1 PA goal monitoring and revisiting the goals 12.2 Diet goal monitoring and revisiting the goals	12.1.1 Goal monitoring (Participant workbook) 12.1.2 Identification of barriers 12.1.3 Goal resetting (if needed) 12.2.1 Goal monitoring (Participant workbook) 12.2.2 Identification of barriers 12.2.3 Goal resetting (if needed)	30 Min per participant	Peer mentor

Figure 3. Thematic representation of the program goals, targets and individual-group tailored strategies using behaviour change techniques

individuals with IFG, the dietary intervention will include consumption of a low-calorie diet (~1500 calories per day i.e., 500 calories lower than the daily requirement for women)^{39,42–44} and consuming food with low glycaemic index. Other dietary recommendations include changing the quality of dietary fat from using saturated to unsaturated, increasing the intake of whole grains and foods rich in fibre and decreasing the intake of sugar-sweetened beverages, sweets, and highly processed products^{45–47}. The dietary goals are: <30% of total energy intake from fat, 400–600 grams of fruit and vegetable intake a day, 5 cups (400 gms of cooked rice intake per day), <25 gms of free sugar intake a day, and <5 gms of salt intake per day⁴⁵.

The adherence to diet will be assessed every month using a 24-hour dietary recall⁴⁸. Other measures of intervention goal include increasing physical activity to the recommended levels of at least 150 minutes of moderate-vigorous physical activity per week⁴⁰, 7–9 hours of sleep at night^{41,49}, and no use of alcohol and tobacco.

Intervention delivery

The intervention will be delivered through 12 sessions (individual and group based), one session per month, over a period of 1 year (Table 3). Intervention delivery will be supported using pretested and piloted educational materials such as flip charts

for group-based sessions and a mobile based application for individual sessions. The mobile application will also serve as an interactive platform for a personalized diet planning and reporting.

The group sessions (45–60 minutes duration) will be organised in the participants' neighbourhood, mostly in homes or local health centres, delivered by the research team (postgraduates in public health/ social work degree) in the initial phase, followed by trained volunteers as "peer mentors". Peer mentor, a group nominated volunteer, will undergo a five-day capacity building training program to guide and assist the participants in making realistic goals for lifestyle modification with the support of the extended community stakeholders.

Evaluation framework

In addition to the baseline, 12th month and 24th month assessment for the primary and secondary outcomes, process evaluation of core interventions at community, peer mentor and participant levels will be undertaken (Figure 4). Evaluation process will be facilitated through regular monitoring via participant feedback report, peer mentor feedback report, feedback on quality of training, pre- and post-training knowledge evaluation and other interactions (mobile app/telephonic contact).

Data analysis

Data will be collected and entered using a data entry template in an ODK platform by the data collectors and managed in a

cloud-based server which will only be accessed by the Principal Investigator (EM). Subsequent to the data collection, the data will be used only using a participant identity number and all the personal identifiers will be masked. Only deidentified data will be shared with other investigators, if required. Data quality will be ensured during data collection and data analysis. During the data collection, the research team will verify the data for missing values and if present, will be rectified then and there. Furthermore, randomly identified 5% of the participants data will be verified with the participants through telephone for quality check. The data from the ODK platform will be exported to SPSS and data cleaning will be done manually. Any outliers or implausible values will be identified and will be checked with participants over phone, if necessary.

The analysis will follow the intention-to-treat (ITT) principle. Characteristics of the participants at baseline will be compared between study groups using descriptive statistics. The primary outcome will be analysed using the generalized estimating equations (GEE) with an appropriate working correlation structure and a binomial family with 'log' link function to estimate the relative risk (and 95% confidence interval [CI], p value). Standard errors will be based on Huber-White sandwich estimator, which will provide valid CIs even in case of misspecification of the correlation structure⁵⁰. For secondary outcomes, continuous variables will be analysed using mixed-effects linear regression models, which will include all available data at baseline, 12 and 24 months. Study group (intervention vs. control),

Figure 4. Theory of change Framework.

timepoint (follow-up vs. baseline) and a study group-by-time point interaction will be specified as fixed effects. Random effects will be specified for wards, to account for the clustered study design, and for participants, to account for correlation between the repeated measurements on the same individual. Categorical variables will be analyzed using log-binomial models. All p values reported will be 2 tailed, and a p of 0.05 will be considered statistically significant. Analyses will be performed with *Stata* version 14.2 (StataCorp LP, College Station, Texas, USA).

Ethics approval

The study was approved by the Institutional Human Ethics Committee of the Central University of Kerala (CUK/IHEC/2019/034_A, 21st November 2019). Written informed consent will be obtained from all study participants. The risk from the intervention to the participants is anticipated to be negligible as the intervention involves only lifestyle modification and no pharmacological drugs. Data safety monitoring will be done by the research team.

Discussion

This paper describes the protocol for an intense lifestyle intervention program among women with i-IFG to facilitate regression to normoglycemia at 24 months. This study will provide the first evidence on the effects of lifestyle intervention in regressing i-IFG to normoglycemia among Indians. The findings of the study will be disseminated through public engagement, reports and publications.

Strengths and limitations

This is one of the first studies globally to evaluate the effects of a novel lifestyle intervention among women with i-IFG. Further, the community-based nature of the intervention would facilitate future sustainability and scalability in India and other similar settings. However, since the study population comprises only women, the findings cannot be generalized to men.

Trial status

The trial is currently in the screening phase.

Data availability

Underlying data

No underlying data are associated with this article.

Extended data

OSF: Randomized Controlled Trial on lifestyle modification intervention for women with isolated impaired fasting glucose. <https://doi.org/10.17605/OSF.IO/8K9XJ37>.

This project contains the following extended data:

- Participant information sheet (screening).pdf
- Informed consent form screening.pdf
- Screening tool.pdf
- Participant information sheet for the trial (English version).pdf
- Informed consent form for trial.pdf
- Baseline assessment.pdf
- 12th month assessment.pdf
- 24th month assessment.pdf
- Process evaluation tools- participants.pdf
- Process evaluation tools - peer mentor.pdf
- Health Information leaflet Control.pdf (for control participants)

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

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Priti Gupta

Centre for Chronic Disease Control, New Delhi, Delhi, India

This is a very well written protocol and addresses the importance of primary prevention, where the pre-diabetic who are at risk of developing diabetes in the next five years will be part of a 24-month intervention. There are very few RCTs in this area from India. So the study addresses an important research gap. This study will be carried out in Kerala, which has the highest diabetes prevalence in India. Protocol has elaborated on each and every step of the interventions and how they are going to deliver them. Statistical methods are also well explained.

However, few concerns are:

1. Why only women have been selected for trial because this effect the generalizability of this trial results, authors have mentioned it in the limitation but there is no intervention component which is specific for women only
2. Though the authors have stated why they have selected the individual level randomization and not cluster level, as it's a community based intervention chances of contamination will be very high which might dilute the effect of interventions
3. In the control group, they are providing leaflets for lifestyle interventions, people who are diagnosed with diabetes during their assessment should also be provided with these interventions along with referrals to health facilities.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Multimorbidity, implementation research and e-health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 13 January 2023

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David Flood

Departments of Medicine, University of Michigan, Ann Arbor, MI, USA

Summary:

This manuscript presents the study protocol for a type 2 hybrid trial of a lifestyle intervention to achieve normoglycemia among individuals with isolated impaired fasting glucose in Kerala, India. The study is well conceived, and the protocol is very well written. The intervention builds on the well-known Kerala Diabetes Prevention Project (K-DPP). This current protocol is an interesting trial in its focus on individuals with impaired fasting glucose, which is a prediabetes subtype of which there is limited evidence regarding preventative interventions. I look forward to seeing the results in a few years, as this trial will add important evidence on diabetes prevention in low- and middle-income countries where most people with diabetes reside. I have a few comments the authors may wish to consider in manuscript revisions.

Comments:

1. I wonder if the authors might provide more background and justification on the focus of regression to normoglycemia as the primary outcome rather than new diabetes. I understand that the K-DPP and other trials have been underpowered for incident diabetes among the isolated FBG population. The authors support this decision in the introduction with a citation to the Campbell paper (Campbell MD, et al. Nat Rev Endocrinol 2020;16:395-400), but my reading of that review is that the benefits of regression are primarily observed among the IGT prediabetes phenotype. I see that diabetes incidence is a secondary outcome. Unlike the authors, I am not a prediabetes content expert and I was a bit confused by this choice.
2. The protocol might be strengthened with a justification for a hybrid 2 effectiveness-implementation design. Would the authors consider this trial to be more in line with a hybrid 1? As the authors will be aware, type 1 trials are recommended when interventions

have strong face validity and low risk, but there is less evidence for effectiveness in a given context. I may be misreading, but the trial seems to be primarily motivated by the need for evidence on the effectiveness of lifestyle interventions among people with isolated FPG. The protocol has much less detail about the implementation outcomes than the effectiveness outcomes. I did not see a co-primary implementation outcome specified. The individually randomized nature of the trial (rather than cluster RCT) also limits the RE-AIM assessment at the provider/clinic/health system levels. If the authors deem this more in line with a type 2 design, they may wish to add more support for their thinking.

3. Regarding the effect size in the power calculation, for clarity, are the authors using 50% relative risk using "risk" as a desirable outcome? I.e., the RR of the development of normoglycemia would be hypothesized to be 1.5: 18% in control and 27 in intervention (not accounting for contamination)? These values work out when I try to duplicate the sample size calculation, but 1-2 sentences might be helpful for clarity here. Additionally, can the authors cite any effect size estimate beyond their unpublished K-DPP data? 50% RR seems relatively large but, again, I am not an expert in prediabetes like the authors.
4. Would the authors consider including the SPIRIT checklist (below)? I note that most of the checklist elements are included already, but there are a few elements that could be added very briefly.

<https://www.equator-network.org/reporting-guidelines/guidelines-for-reporting-outcomes-in-trial-protocols-the-spirit-outcomes-2022-extension/>

Butcher NJ, Monsour A, Mew EJ, et al. Guidelines for Reporting Outcomes in Trial Protocols: The SPIRIT-Outcomes 2022 Extension. *JAMA* 2022; 328(23): 2345-56.

5. I wanted to praise the authors for their research transparency in sharing about 300 pages of comprehensive study materials on the OSF website. It is nice that we get to see these materials, which also illustrate the immense work the authors have put in to conduct this large community RCT.

References

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Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Diabetes, global health, implementation research, health systems research

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.