High-Intensity Interval Training for Individuals with Isolated Impaired Fasting Glucose: A Proof-of-Concept Study Protocol

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Submitted to: JMIR Research Protocols
on: April 23, 2024

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Abstract

Background: Standard lifestyle interventions have shown limited efficacy in preventing type 2 diabetes among individuals with isolated impaired fasting glucose (i-IFG). Hence, tailored intervention approaches are necessary for this high-risk group.

Objective: 1) To assess the feasibility of conducting a high-intensity interval training (HIIT) study and the intervention acceptability among individuals with i-IFG, and 2) To examine the efficacy of HIIT in reducing fasting hyperglycemia and addressing the underlying pathophysiology of i-IFG.

Methods: This study is a 1:1 proof-of-concept randomized controlled trial (RCT) involving 34 physically inactive individuals aged 35-65 years who are overweight or obese and have i-IFG. Participants identified through various sources will undergo eligibility screening via phone calls. Potentially eligible participants will be invited to the Georgia Clinical and Translational Science Alliance at Emory University Hospital in Atlanta. During their visit, they will complete questionnaires, undergo an oral glucose tolerance test, and provide blood samples for analysis of insulin and alanine aminotransferase levels. Intervention participants will engage in supervised HIIT sessions using stationary 'Spin' cycle ergometers in groups of five or fewer. They will wear continuous glucose monitoring (CGM) devices for 10 days before the intervention, throughout the 8-week intervention period, and for 10 days post-intervention. The intervention will take place three times a week for eight weeks at the Aerobic Exercise Laboratory in the Rehabilitation Hospital at Emory University. Control participants will be advised to maintain their usual physical activity levels and will also wear CGM devices for the same duration as the intervention participants. All participants will be instructed to adhere to their routine dietary habits throughout the study duration. Baseline and eight-week assessments will include measurements of weight, blood pressure, body composition, waist and hip circumferences, as well as levels of glucose, insulin, and alanine aminotransferase. Intervention participants will additionally complete an intervention acceptability questionnaire upon completion of the intervention. Outcomes will comprise feasibility parameters, intervention acceptability, and between-group changes in CGM metrics and clinical measures. Data analysis will involve descriptive statistics as well as correlation and regression analyses.

Results: The study is scheduled to commence recruitment in June 2024, with the completion of follow-up assessments by the end of November 2024. We anticipate publishing the results by mid-2025.

Conclusions: The study findings are expected to guide the design and execution of an adequately powered RCT for evaluating HIIT efficacy in preventing type 2 diabetes among individuals with i-IFG. Clinical Trial: ClinicalTrials.gov ID (NCT06143345).

(JMIR Preprints 23/04/2024:59842)

DOI: https://doi.org/10.2196/preprints.59842

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Trial Registration: ClinicalTrials.gov ID (NCT06143345).

Keywords: isolated impaired fasting glucose; prediabetes; high-intensity interval training; fasting hyperglycemia; diabetes incidence

Introduction

The prevalence of type 2 diabetes is increasing globally [1-3], driven predominantly by a rising number of individuals with prediabetes [2]. Globally, an estimated 860 million (8.4%) adults are living with prediabetes, a condition that increases the risk of developing type 2 diabetes [2], micro- and macro-vascular complications, and mortality [4].

Prediabetes is not a singular entity but rather a heterogeneous group of metabolic defects that often precede type 2 diabetes [5-7]. Prediabetes phenotypes include isolated impaired fasting glucose (i-IFG), isolated impaired glucose tolerance (i-IGT), and IFG plus IGT. Each prediabetes phenotype exhibits distinct pathophysiological abnormalities [5-7]. i-IFG is marked by impaired early-phase insulin secretion and hepatic insulin resistance. Conversely, i-IGT involves impairments in both early- and late-phase insulin secretion and skeletal muscle insulin resistance [5, 7]. IFG plus IGT

presents a combination of defects observed in both i-IFG and i-IGT [5, 7]. i-IFG accounts for a substantial portion of the global prediabetes population, ranging from 43.9% to 58.0% among Caucasians and 29.2% to 48.1% among Asians, depending on the diagnostic criteria [2]. Individuals with i-IFG exhibit a 4 to 5.5 times higher rate of progression to type 2 diabetes, depending on the diagnostic criteria, compared to those with normoglycemia [8].

Individuals with prediabetes are typically advised to adopt standard lifestyle interventions that emphasize improving diet quality with a modest calorie restriction and increasing moderate-intensity physical activity to reduce the risk of developing type 2 diabetes [9, 10]. However, recent research highlights the varied effectiveness of these interventions among different prediabetes phenotypes. While these approaches prove highly effective for individuals with i-IGT and IFG plus IGT, their efficacy is notably limited for those with i-IFG [6, 11, 12]. Thus, there arises a necessity for alternative lifestyle intervention strategies tailored specifically to individuals with i-IFG.

One of the promising approaches is high-intensity interval training (HIIT), recognized as a time-efficient exercise option with significant benefits for metabolic health [13]. HIIT entails alternating short bursts of high-intensity exercise with periods of less active or passive recovery [14]. It is noteworthy that HIIT represents a more intensive exercise regimen compared to the current physical activity recommendations for individuals with prediabetes [9, 10].

Studies conducted among individuals diagnosed with type 2 diabetes have shown the efficacy of HIIT in improving hepatic insulin sensitivity [15, 16] and β-cell function [17, 18], and reducing hepatic fat content [19]. These modifications in the underlying pathophysiological abnormalities of type 2 diabetes have been associated with reductions in fasting hyperglycemia [16, 20-24]. However, the efficacy of HIIT has not been specifically assessed in individuals with i-IFG [6, 25], for whom

reducing fasting hyperglycemia is crucial in preventing the onset of type 2 diabetes [6, 25]. Figure 1 visually illustrates how HIIT intervention may potentially target the pathophysiological abnormalities and fasting hyperglycemia in i-IFG. We aim to test this hypothesis in a definitive RCT aimed at preventing type 2 diabetes in individuals with i-IFG. To facilitate the design and implementation of this RCT, we propose conducting a “proof of concept” trial among individuals with i-IFG, with the following objectives:

Primary objectives:

1) Assess the feasibility of recruiting and retaining participants, and performing the study procedures.
2) Evaluate the acceptability of the HIIT intervention among participants.

Secondary objectives:

1) Examine the efficacy of HIIT in addressing the pathophysiological abnormalities of i-IFG.
2) Investigate the efficacy of HIIT in reducing fasting hyperglycemia.

Methods

Study design, Study setting, and Participants

This is a "Proof-of-Concept" 1:1 parallel-group RCT involving 34 physically inactive individuals aged 35-65 years who are overweight or obese and have i-IFG. Figure 2 shows the study flowchart. The Georgia Clinical Research Center (GCRC) at Emory University Hospital will serve as the site for participant recruitment and conducting study procedures. A highly trained and experienced study coordinator will conduct screening and recruitment of participants. This process will involve identifying potential participants through Emory’s 'MyChart Research Recruitment' program and the 'ResearchMatch.org', a national database of research volunteers [26], and by seeking physician

referrals. Queries will be generated against the databases to identify individuals who meet most of the study's inclusion criteria, and invitation messages will be sent to them via the same platforms. The recruitment process follows a two-step procedure.

Step 1 screening (via phone calls): Those expressing interest to participate in the study will be contacted via phone calls. During these calls, participants will receive a comprehensive explanation of the study and have any questions addressed. Subsequently, they will be requested to sign a consent form online via Emory's REDCap platform [27]. Following this, participants will be asked to respond to a brief questionnaire, which will include basic demographic information (age and sex), along with the following eligibility criteria.

Inclusion criteria:

- Aged 35-65 years
- Overweight (body mass index (BMI) ≥25 to <29 kg/m² or ≥23 to <29 kg/m² if Asian descent) or Obese (BMI ≥30 kg/m²) [28]
- Physically inactive (<150 minutes per week of moderate-intensity physical activity or <75 minutes per week of vigorous-intensity physical activity) [29]
- Diagnosis of prediabetes or score ≥5 on the American Diabetes Association (ADA) risk test [30]

Exclusion criteria:

- Diagnosis of diabetes
- Diagnosis of other chronic illnesses (e.g., cardiovascular disease)
- Current smoker
- Currently enrolled in weight loss programs

- Currently enrolled in any regular exercise programs
- Currently following a specific diet (e.g., ketogenic diet, Mediterranean diet)
- Currently taking weight-loss medications or drugs known to influence glucose tolerance (steroids and antipsychotics)
- Ever underwent bariatric surgery
- Plans to relocate outside the study area during the study period
- Pregnant or planning to become pregnant during the study period
- Breastfeeding

Step 2 screening (via in-person clinic visits): Potentially eligible individuals will be invited to visit the GCRC at Emory University Hospital after fasting overnight for a minimum of 8 hours [30]. During the visit, they will complete questionnaires and undergo physical measurements using standardized tools [31], as per the GCRC protocol. Following these assessments, individuals will undergo an oral glucose tolerance test (OGTT) and provide blood samples for additional biochemical measures. Individuals diagnosed with i-IFG, defined as fasting plasma glucose 100-125 mg/dl and 2-hr plasma glucose <140 mg/dl [30], will be deemed eligible to participate in the study. Individuals without i-IFG will be excluded from further participation in the study. They will receive general healthy lifestyle advice and will be referred to their general practitioner if they have IGT or undiagnosed diabetes for further management.

Randomization and Blinding

Participants will be equally randomized into either the intervention or control group after completing baseline assessments and being found eligible, using a computer-generated randomization sequence by a statistician not involved in the trial. Given the nature of the study, only specific personnel such as nursing staff, laboratory personnel, and the data analyst will be blinded to participant allocation to

the study groups. However, participants, the study coordinator, the HIIT intervention instructor, and the principal investigator will not be blinded to participation allocation.

Intervention

Following the recommendation of the American College of Sports Medicine [32], participants in the intervention group will be required to obtain medical clearance from their general practitioner before starting the HIIT sessions. These sessions, led by a qualified exercise physiologist (the instructor) and adhering to a standardized protocol [33, 34], will take place in the Aerobic Exercise Laboratory at Emory University's Rehabilitation Hospital. Using 'Spin cycle ergometers' (Schwinn, Canada), sessions will be conducted in small groups of five or fewer participants at specified times on Mondays, Wednesdays, and Fridays, spanning eight weeks. Each session will consist of a 5-minute warm-up, followed by an interval-based workout phase with steady up-tempo cadences, sprints, climbs, and interspersed recovery periods. A 5-minute cooldown will conclude each session. The duration of the workout session will progress from 20 minutes during the initial familiarization week up to a maximum of 45 minutes. This progression will be tailored to participants' advancements and the instructor's recommendations. To monitor and maintain intensity within the target heart rate range throughout each session, participants will wear Polar H10 chest strap heart rate sensors [35]. The target heart rate will be calculated using the Karvonen method [36]. Intensity will start at 65-75% of maximal heart rate reserve [HRR]) and may increase by 5% weekly, as deemed necessary by the instructor. During the workout phase, the target HRR reserve will maintained by averaging increases and decreases in intensity/HR with a target to maintain within a 10% offset from the HRR goal during the workout phase [33, 34].

To ensure high compliance in session attendance, the instructor will hold weekly one-on-one meetings with participants to provide personalized feedback and encouragement. Participants' heart

rate data will also be reviewed during these meetings. Additionally, the study coordinator will remind participants of their scheduled sessions one day in advance through phone calls. Attendance in sessions will be closely monitored, and records of attended exercise sessions will be maintained. Participants who miss sessions will be contacted via phone calls to encourage attendance.

Any adverse events occurring during or after HIIT sessions will be documented, with medical advice sought if necessary. All participants will be instructed to adhere to their usual dietary habits for the entire study duration. These habits will be monitored biweekly by a registered dietician using the Automated Self-Administered 24-Hour Dietary Assessment Tool (ASA24) [37], administered via phone calls three times per week (including two weekdays and one weekend day). Control group participants, in addition, will be advised to maintain their routine physical activity levels, which will be assessed biweekly using the short form of the International Physical Activity Questionnaire (IPAQ) through phone calls [38].

Procedures

The details about the measurements, study tools, and timelines are outlined in Table 1.

Study Feasibility

Table 2 shows the study feasibility metrics. Continuous data collection on feasibility parameters, such as response rate, screening yield, enrollment rate, time to enrollment, intervention compliance, resource utilization (cost and staff time), and retention rate, will be conducted throughout the study.

Intervention Acceptability

The intervention acceptability will be assessed by administring the Theoretical Framework of Acceptability (TFA) questionnaire [33] among intervention participants after completing the

intervention. This questionnaire includes various constructs, including affective attitude, burden, ethicality, perceived effectiveness, intervention coherence, self-efficacy, opportunity costs, and general acceptability. Participants will rate these constructs on a 1 to 5-point scale, where 1 represents "strongly disagree" and 5 represents "strongly agree". We will calculate the total mean score of TFA items to evaluate the overall level of intervention acceptability, with higher scores indicating greater acceptability among participants.

Continuous Glucose Monitoring

All participants, regardless of their assigned treatment, will be fitted with a continuous glucose monitoring (CGM) device on their abdominal area upon enrollment. The CGM device, Dexcom G6 Pro CGM system (DexCom, Inc., San Diego, CA), will be used in blinded mode to minimize bias and ensure that it does not influence the study outcomes. These devices will be worn for 10 days preceding the intervention, throughout the 8-week intervention period, and for 10 days post-intervention. Participants will receive training on replacing the device every 10 days, following the instructions outlined in the manual [39]. This CGM system will record glucose levels in the fasting state, and before and after HIIT sessions. With 288 glucose measurements per day over several days, we will also obtain additional granularity on the effects of HIIT on glucose patterns that otherwise would be missed with single point-specific blood glucose assessments. The adequacy of CGM data will be evaluated using the following criteria: a minimum of 80% of the potential 288 glucose values per day should be present for at least three consecutive days, commencing from the day following sensor insertion [40].

Clinical Measures

Data on health behaviors, physical and biochemical measurements will be collected at both baseline and 8 weeks.

a. Health Behaviors

Physical activity levels will be assessed using the short form of the IPAQ [38] and dietary intake with the ASA24 questionnaire [37]. Data on smoking and alcohol use will be obtained using questions adapted from the World Health Organization STEPwise approach to NCD risk factor surveillance [41] and National Health and Nutrition Examination Survey questionnaires [42].

b. Physical Measures

Height will be measured using a stadiometer (Welch Ally—Scale-Tronix, NY, USA) with an accuracy of 0.1 cm. Weight will be assessed using a digital weighing scale (Welch Ally—Scale-Tronix, NY, USA) with a precision to the nearest 0.1 kg. Waist and hip circumferences will be measured using an inelastic measuring tape (BaumGartens, GA, USA) with a precision of 0.1 cm. Body composition measures, including fat mass, muscle mass, fat-free mass, visceral adipose tissue mass, and fat percent, will be obtained using Dual-Energy X-ray Absorptiometry (DXA) (enCORE V18, GE Healthcare, USA).

c. Biochemical Measures

A GCRC nursing staff will administer an OGTT following a standardized protocol [43]. Participants will undergo an overnight fast lasting at least 8 hours, with the testing session scheduled between 7:00 a.m. and 9:00 a.m. Venous blood samples will be collected at 0, and 30 and 120 minutes after ingesting a 75-gram oral glucose load dissolved in 250 to 300 ml of water, consumed over 5 minutes. Additionally, blood samples for insulin will be obtained at 0 and 30 minutes after glucose load ingestion, and for alanine aminotransferase (a surrogate marker of liver fat) at 0 minutes. Blood samples will be processed at the GCRC lab and transported in ice boxes to the Emory Medical Laboratory (EML) for analysis. EML is a fully accredited and licensed clinical laboratory, actively

participating in the College of American Pathologists Laboratory Accreditation Program. Additionally, it holds Clinical Laboratory Improvement Amendments certification through the Centers for Medicare and Medicaid Services. EML is also duly licensed by the state of Georgia. Glucose levels will be assessed through enzymatic assays, insulin levels via immunoassays, and alanine aminotransferase using the calorimetric assay. All these analyses will utilize kits provided by Beckman Coulter Inc., CA, USA, and will be performed on a Beckman Coulter analyzer.

d. Indices of ß-cell Function and Insulin Resistance

Table 3 provides details on the indices of ß-cell function and insulin resistance derived from glucose and insulin levels. Early-phase insulin secretion will be assessed using the insulinogenic index (IGI) [44], while total ß-cell function with be evaluated with the oral disposition index (DIo) [45] and homeostatic model assessment of ß-cell function (HOMA-B) [46]. Whole-body insulin resistance will be determined using the Matsuda index [47] and homeostatic model assessment of insulin resistance (HOMA-IR) [46], while tissue-specific insulin resistance will be assessed with the hepatic insulin resistance index (HIRI) [48] and muscle insulin sensitivity index (MISI) [48].

Outcomes

The primary outcomes consist of feasibility metrics and the total mean TFA score for intervention acceptability. Secondary outcomes include between-group changes in: 1) CGM metrics, such as the proportion of time spent in the time in range (TIR) overnight (60 to <110 mg/dl) and TIR during a 24-hour period (60-140 mg/dl) [49], glycemic variability, and mean glucose levels during the fasting state, and before and after exercise sessions; 2) Fasting glucose and insulin levels, weight, waist and hip circumferences, and body composition; and 3) Indices of ß-cell function and insulin resistance.

Data Management

The study coordinator will enter questionnaire data, as well as physical and biochemical measurements directly into Emory University's REDCap database [27]. This database will feature validation checks to ensure data accuracy, along with skip patterns facilitated by branching logic functions. The principal investigator (S.T.) will constantly review the data for any errors, promptly flagging any errors for correction by the study coordinator. Upon completion of data entry and cleaning, a master copy of the dataset will be generated and securely stored within the REDCap database. CGM raw data (in CSV file format per participant) will be downloaded from the Dexcom Clarity software and uploaded to REDCap. Access to these datasets will be limited to the study coordinator and the PI for confidentiality and data security purposes.

Statistical Analysis

Assuming a Cohen's d of 0.3 to <0.7 (medium standardized effect size) [24, 50] for fasting plasma glucose in the planned main trial, with an alpha of 5% and a power of 90%, a sample size of 15 participants per treatment group is deemed necessary for this pilot study. Factoring in a 10% loss to follow-up in each group, the total sample size was estimated to be 34 participants (17 per group). **Objective 1 (Feasibility and Intervention Acceptability):** Continuous variables will be summarized using either mean and standard deviation or median and interquartile range, depending on their distribution, which will be visually assessed through histograms. Categorical variables will be presented as counts (n) and percentages (%). **Objective 2 (Efficacy):** The analyses will adhere to the "intention-to-treat" principle. Baseline differences between study groups will be compared using parametric t-tests (or non-parametric Wilcoxon rank-sum tests) for continuous variables and Chi-square tests for categorical variables. Variables showing significant differences at baseline will be included as covariates in regression models. Data on fasting glucose and insulin levels, indices of ß-cell function and insulin resistance, and physical measures at 8 weeks will be compared between study groups using regression models, adjusting for baseline values. The correlation between

changes in fasting glucose and the indices from baseline to 8 weeks will be assessed using either Pearson's or Spearman's correlation coefficients, depending on the nature of the data distribution.

The coefficient of variation (CV) for glycemic variability of CGM data will be calculated as follows: CV=(standard deviation/mean)*100 [51]. A higher CV indicates greater glycemic variability, while a lower CV suggests more stable glucose levels over the monitoring period. Regression models will be used to compare CGM metrics between study groups in three distinct phases: 10 days before commencing the intervention, throughout the intervention, and 10 days post-intervention. Statistical significance will be considered with a two-sided p-value less than 0.05 with no adjustments for the multiplicity of comparisons. All analyses will be conducted using Stata version 18.0 (Stata Corp LLC, Texas, USA).

Challenges and Mitigation Strategies

The potential challenges that could be enountered at various stages of the study and the corresponding mitigation strategies are outlined in Table 4.

Ethics Approval

The study was approved by the Institutional Review Board (IRB) of Emory University, Atlanta, USA (IRB ID: MOD001-STUDY00005855). Written informed consent will be obtained from all participants before they participate in the study.

Results

Table 5 shows the study timeline. The study is scheduled to commence recruitment in June 2024, aiming for completion by the end of November 2024. We plan to publish the study findings by mid-2025.

Discussion

This study represents one of the first efforts to assess the feasibility and acceptability of implementing a HIIT intervention among individuals with i-IFG. Additionally, it aims to provide preliminary estimates regarding the efficacy of HIIT on the pathophysiology and glucose metabolism of i-IFG.

Our study has some limitations. We will be assessing the pathophysiological abnormalities in i-IFG based on indices derived from the OGTT and fasting insulin levels. Nevertheless, the estimates of these indices have demonstrated strong correlation with those obtained from the gold standard methods, including the intravenous glucose tolerance test and glycemic clamps [52-54]. Furthermore, our reliance on a single OGTT may be subject to day-to-day variability in glucose tolerance status. However, stringent adherence to a standardized protocol for conducting the OGTT [43] should help minimise this variability to a considerable extent.

In conclusion, the results of this study are expected to guide the design and implementation of an RCT to assess the efficacy of HIIT intervention in reducing diabetes incidence and achieving remission in individuals with i-IFG.

Data Availability

Not applicable.

Acknowledgments

This study was supported by the Georgia CTSA's Pilot Program, funded by the Robert W. Woodruff Health Science Center at Emory University and the National Center for Advancing Translational

Sciences of the National Institutes of Health (NIH) under Award Number UL1TR002378. S.T. was partially supported by a grant (#75D30120P0742) from the Centers for Disease Control and Prevention (CDC) Atlanta. R.B. was partly funded by the NIHR Applied Research Collaboration (ARC) West Midlands. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Robert W. Woodruff Health Science Center or the NIH. The funder had no role in the conceptualization, design, data collection, analysis, decision to publish, or preparation of the manuscript.

Authors' Contributions

Conceptualization, S.T., L.S., F.L., M.L.MS., M.D.S., F.J.P., J.N.; methodology, S.T., T.R.Z., L.S., F.L., M.L.MS., M.D.S., F.J.P., J.N.; writing—original draft preparation, S.T., A.V.; writing—review and editing, T.R.Z., L.S., F.L., M.L.MS., M.D.S., R.B., M.P., F.E.F., S.K., R.J.T., J.S., F.J.P., J.N.; project administration, T.S., T.R.Z., F.J.P., J.N.; funding acquisition, S.T. All authors have read and agreed to the published version of the article.

Conflicts of Interest

None declared.

Abbreviations

ADA	American Diabetes Association
ASA24	Automated Self-Administered 24-Hour Dietary Assessment Tool
BMI	body mass index
CGM	continuous glucose monitoring
CV	coefficient of variation

DI_O	oral disposition index
EML	Emory Medical Laboratory
GCRC	Georgia Clinical Research Center
HIIT	high-intensity interval training
HIRI	hepatic insulin resistance index
HOMA-B	homeostatic model assessment of ß-cell function
HOMA-IR	homeostatic model assessment of insulin resistance
HR	heart rate
HRR	heart rate reserve
i-IFG	isolated impaired fasting glucose
i-IGT	isolated impaired glucose tolerance
IGI	insulinogenic index
IPAQ	International Physical Activity Questionnaire
DXA	Dual-Energy X-ray Absorptiometry
IRB	Institutional Review Board
MISI	muscle insulin sensitivity index
OGTT	oral glucose tolerance test
RCT	randomized controlled trial
TFA	Theoretical Framework of Acceptability
TIR	time in range

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Figure legends

Figure 1. Potential pathways through which HIIT sessions may address the pathophysiological abnormalities and fasting hyperglycemia in individuals with isolated impaired fasting glucose. HIIT, high-intensity interval training.

Figure 2. Study flowchart.

Table 1. Measurements, study tools, and study timeline.

Variables	Components	Study tools	Baseline	8 weeks
Feasibility	Response rate, screening yield, intervention compliance, resource utilization, and retention rate	REDCap database	✔	✔
Intervention acceptability	Questions about affective attitude, burden, ethicality, perceived effectiveness, intervention coherence, self-efficacy, opportunity costs, and general acceptability	TFA questionnaire [55]	--	✔
Socio-demographics	Age, sex, marital status, education, and occupation	WHO STEPS [41] and NHANES questionnaires [42]	✔	--
Eligibility criteria	Inclusion and exclusion criteria[a]	• IPAQ [38] • ADA risk test [30]	✔	--
Behavioral measures	Dietary habits	ASA24 dietary assessment tool [37]	Dietary habits will be assessed bi-weekly throughout the study duration	
	Physical activity	IPAQ [38]	Physical activity of control participants will be assessed bi-weekly throughout the study duration	
	Smoking	WHO STEPS [41] and NHANES questionnaires [42]	✔	✔
	Alcohol consumption	WHO STEPS [41] and NHANES questionnaires [42]	✔	✔
Physical measures	Height	Stadiometer	✔	--
	Weight	Digital weighing scale	✔	✔
	Waist circumference	Inelastic measuring tape	✔	✔
	Hip circumference	Inelastic measuring tape	✔	✔

	Body composition	Bioimpedance analysis	✔	✔
Biochemical measures	OGTT (0, 30, and 120 minutes)	Enzymatic assays	✔	✔
	Insulin levels at 0 and 30 minutes	Immunoassays	✔	✔
	Alanine aminotransferase at 0 minutes	Calorimetic assay	✔	✔
Continuous glucose monitoring (CGM)	Proportion of time spent in the time in range (TIR) overnight (60 to <110 mg/dl) and TIR during the 24-hour period (60-140 mg/dl),[49] glycemic variability, and mean glucose levels during the fasting state, and before and after exercise sessions.	Dexcon G6 Pro	All participants will be fitted with the CGM device upon enrollment, and they will be trained to replace the device every 10 days until 10 days post-intervention	

ADA, American Diabetes Association; STEPS, STEPwise approach to NCD risk factor surveillance; NHANES, National Health and Nutrition Examination Survey; IPAQ, International Physical Activity Questionnaire; ASA24 Automated Self-Administered 24-Hour Recall; TFA, Theoretical Framework of Acceptability; OGTT, oral glucose tolerance test; DXA, dual-energy x-ray absorptiometry. **Inclusion criteria: a**ged 35-65 years, overweight (body mass index (BMI) ≥25 to <29 kg/m² or ≥23 to <29 kg/m² if Asian descent) or obese (BMI ≥30 kg/m²) [28], physically inactive (<150 minutes per week of moderate-intensity physical activity or <75 minutes per week of vigorous-intensity physical activity) [29], and a diagnosis of prediabetes or score ≥5 on the American Diabetes Association (ADA) risk test [30]. **Exclusion criteria:** diagnosis of diabetes, diagnosis of other chronic illnesses (e.g., cardiovascular disease), current smoker, currently enrolled in weight loss programs, currently enrolled in any regular exercise programs, currently following a specific diet (e.g., ketogenic diet, Mediterranean diet), currently taking weight-loss medications or drugs known to influence glucose tolerance (steroids and antipsychotics), ever underwent bariatric surgery, plans to relocate outside the study area during the study period, pregnant or planning to become pregnant during the study period, or breastfeeding.

Table 2. Study's feasibility metrics.

Parameters	**Calculations**
Response rate	No. of individuals responded to the invitation/No. of individuals invited
Screening yield	No. of individuals diagnosed with i-IFG/No. of individuals screened
Enrolment rate	No. of individuals enrolled/No. of individuals diagnosed with i-IFG
Time to enrollment	Average time taken from sending the invitation to enrolling one participant in the trial
Intervention compliance	No. of HIIT sessions attended/Total no. of HIIT sessions
Resource utilization	**Program costs:** Includes screening cost, cost of procedures, intervention cost, participant incentives, and other costs. **Staff time:** Time spent screening and recruiting participants, time spent delivering the intervention, time spent making phone calls to participants, time spent implementing the study procedures, and time spent for baseline and follow-up assessments.
Retention rate	No. of participants attended follow-up visits/No. of participants enrolled

i-IFG, isolated impaired fasting glucose; HIIT, high-intensity interval training.

Table 3. Indices of ß-cell function and insulin resistance.

ß-cell function or IR	Components	Indices	Formula
ß-cell function	Early-phase insulin secretion	IGI [44]	$(I_{30}-I_0)/(G_{30}-G_0)$
	ß-cell function	• DI_O [45] • HOMA-B [46]	• $([\Delta I_{0-30}/\Delta G_{0-30}] \times [1/I_0])$ • $(20 \times I_0)/(G_0 - 3.5)$ - I_0 in µU/l - G_0 in mmol/l
Insulin resistance	Whole-body insulin sensitivity	Matsuda index [47]	$10{,}000 /\sqrt{((G_0 \times I_0) \times (G_{mean} \times I_{mean}))}$
	Insulin resistance	HOMA-IR [46]	$(I_0 \times G_0)/22.5$ - I_0 in µU/L - G_0 in mmol/l
	Hepatic insulin resistance	HIRI [48]	$(G_0-G_{30}[AUC] \times I_{0-30}[AUC])$ - G_0 in mg/dl - I_0 in µU/ml
	Muscle insulin resistance	MISI [48]	$(dG/dt)/\bar{I}$ - dG/dt in mmol/l/min - $\bar{I}$ in pmol/l

IR, insulin resistance; IGI, Insulinogenic index; DI_O, Oral Disposition Index; HOMA-B, Homeostatic Model Assessment of ß-cell function; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; HIRI, Hepatic Insulin Resistance Index; MISI, Muscle Insulin Sensitivity Index. I_{30} is mean insulin at 30 minutes during the oral glucose tolerance test (OGTT), I_0 is mean insulin at 0 minutes during the OGTT, G_{30} is mean glucose at 30 minutes during the OGTT, G_0 is mean glucose at 0 minutes during the OGTT, G_{mean} is mean glucose during the 2-hr OGTT, I_{mean} is mean insulin during the 2-hr OGTT, AUC is area under the curve during the first 30 min of the OGTT, dG/dt is the slope of the regression line from the peak of the plasma glucose curve to its nadir, $\bar{I}$ is the mean insulin concentration over the 2-hr duration of the OGTT.

Table 4. Potential challenges and proposed mitigation strategies.

Study stage	Challenges	Mitigation strategies
Identifying potential participants	Insufficient number of potentially eligible individuals	We will use multiple sources, including two large patient databases and physical referrals, to identify potential participants.
Screening	Low yield of screening	The two-step screening procedure was carefully designed, drawing upon insights from our previous research and existing literature, to target individuals who are likely to have i-IFG.
Intervention	Low HIIT compliance	• The study coordinator will remind participants of their scheduled exercise sessions through phone calls. Additionally, the coordinator will regularly review the attendance log, providing motivation and support to participants with low attendance levels. • The exercise instructor will hold weekly one-on-one meetings with participants to review their progress and provide motivation, specifically targeting those with low attendance levels.
Procedures	Periodic data gaps with CGM whenever the receiver is located more than 5 feet	The CGM data will be assessed for adequacy based on the following criteria: Data points must be present for at least 80% of the possible 288 glucose values per day for at least 3 days, starting on the day after sensor insertion.
Follow-up	Low retention rate	<u>Compensation for time and parking:</u> • Participants will receive a $50 gift card upon completion of the study. • Parking fees at study sites will be covered. <u>Building Rapport:</u> Study staff will create a warm and supportive environment during study visits, fostering a sense of trust and comfort. <u>Ongoing Support:</u> The study coordinator will provide continuous support through

		regular phone calls. This proactive approach ensures that participants feel connected to the study outside of scheduled visits. The study coordinator will address any concerns, answer queries, and offer encouragement, reinforcing a sense of partnership between participants and the research team.

i-IFG, isolated impaired fasting glucose; HIIT, high-intensity interval training; CGM, continuous glucose monitoring.

Table 5. Study timeline.

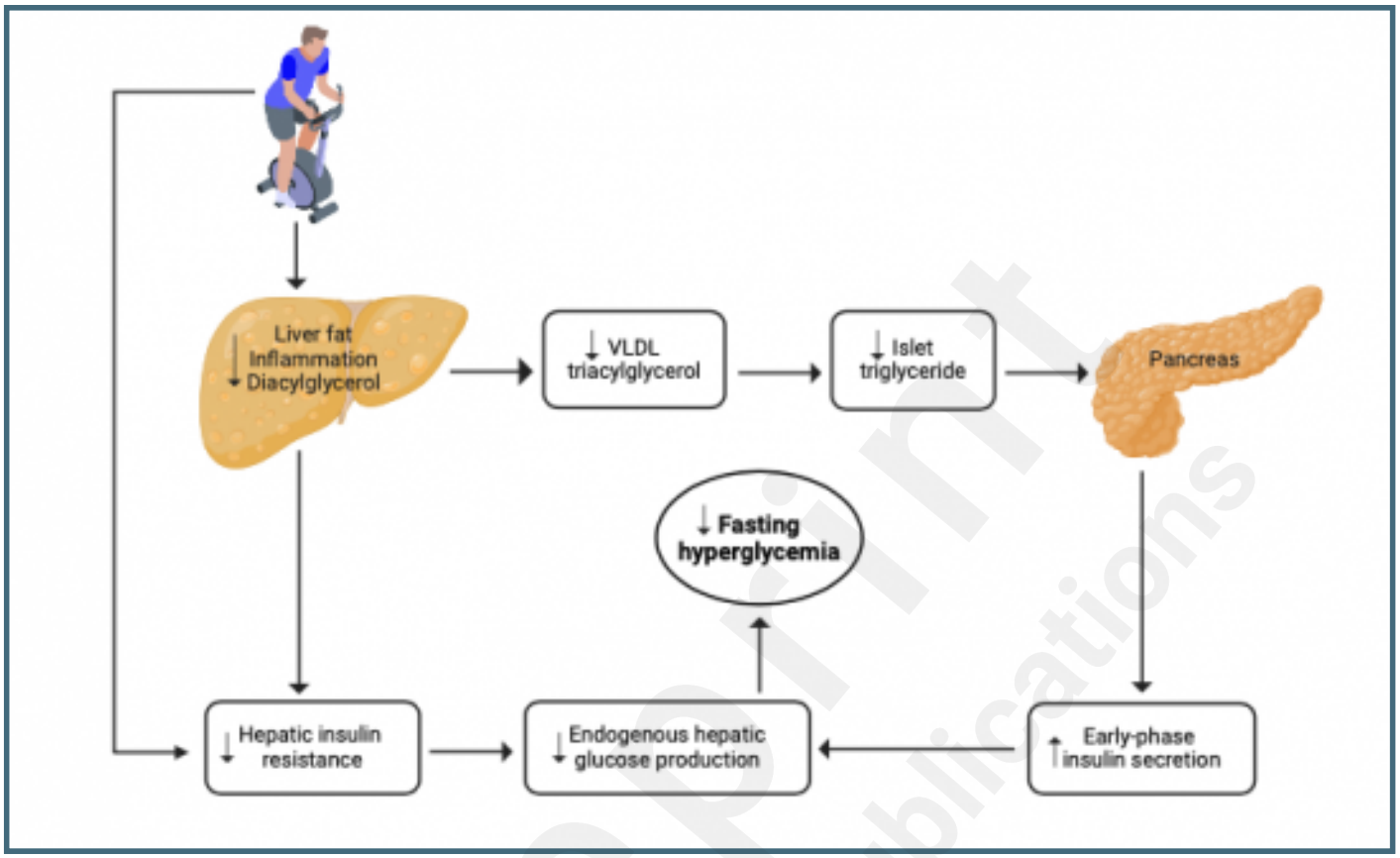
	2024							2025			
	June	**July**	**Aug**	**Sep**	**Oct**	**Nov**	**Dec**	**Jan**	**Feb**	**Mar**	**Apr**
Screening & recruitment											
Baseline assessments											
HIIT intervention											
8-week assessments											
Data analysis											
Study report & Submission for publication											
Conferences & scientific meetings											

HIIT, high-intensity interval training.

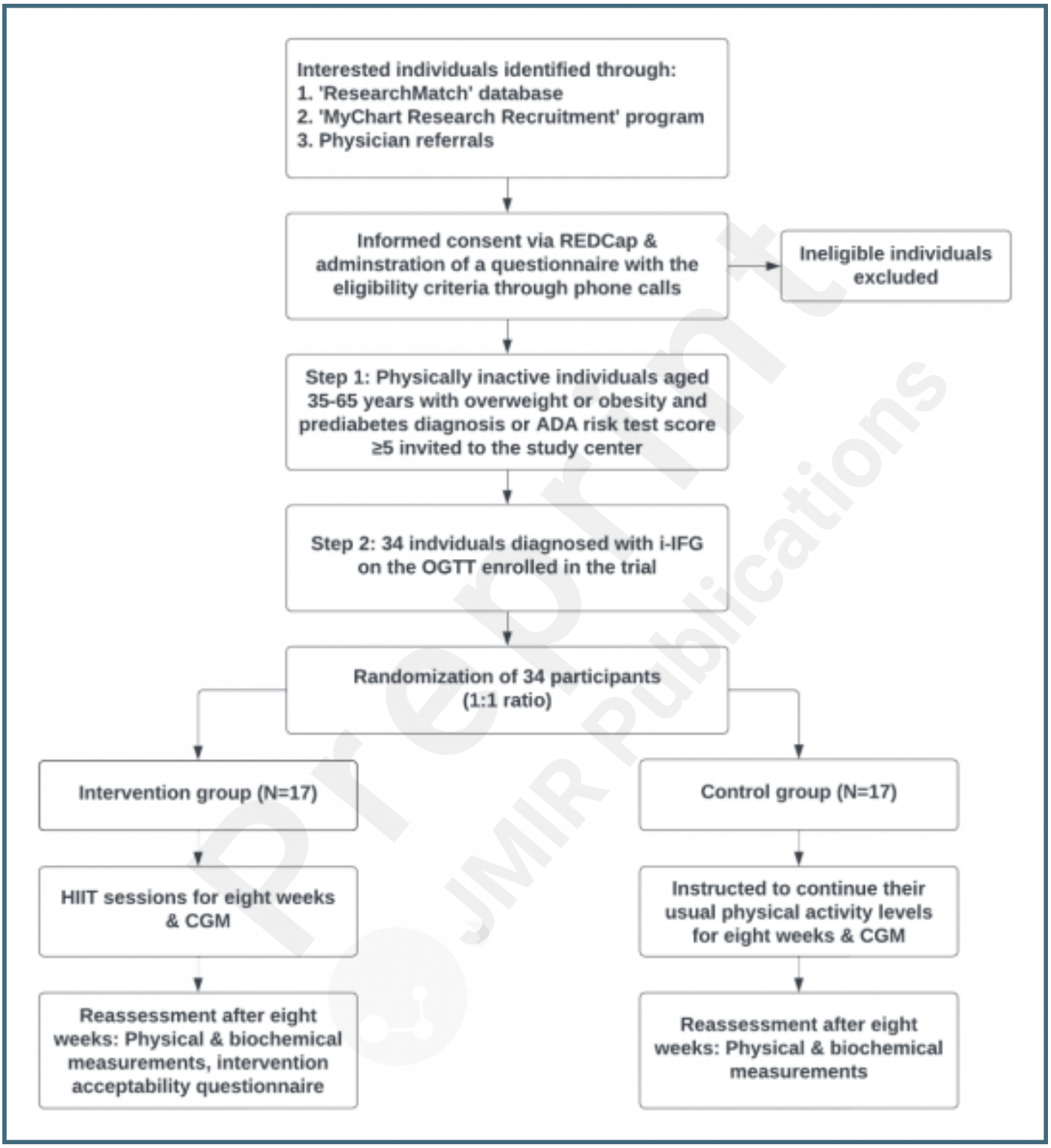
Supplementary Files

Figures

Potential pathways through which HIIT sessions may address the pathophysiological abnormalities and fasting hyperglycemia in individuals with isolated impaired fasting glucose.



Study flowchart.



Multimedia Appendixes

Peer review report.
URL: http://asset.jmir.pub/assets/7681eff50924372c4d91f881200d9aea.pdf