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Protocol for the INTENSITY study: Improving iNdividual glycemic response with exercise inTENSITY

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Protocol for the INTENSITY study: Improving iNdividual glycemic response with exercise inTENSITY

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Trial Registration

This trial has been registered on ClinicalTrails.gov (NCT03787836)

Study Protocol

Version 3.0, dated May 8th, 2019

Study Sponsors

Sponsor: New Brunswick Health Research Foundation

Address: 10 Knowledge Park Dr. Suite 100, Fredericton NB, Canada, E3C 2M7.

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Abstract

Introduction: Exercise is recommended to improve glycemic control. Yet, individual changes in glycemic control following exercise can vary greatly, meaning while some significantly improve others, coined 'non-responders', do not. Increasing the intensity of exercise may 'rescue' non-responders and help generate a response to training. This trial will identify non-responders to changes in glycated hemoglobin (HbA1c) across inactive individuals living with prediabetes or type 2 diabetes mellitus (T2DM) following an aerobic exercise program and evaluate if increasing training intensity will elicit beneficial changes to 'rescue' previously categorized non-responders.

Methods and analysis: This study will recruit 60 participants for a two-phase aerobic exercise training program. Participants will be assigned to a control or intervention group. Control participants will maintain their current lifestyle habits. During Phase One, intervention participants will complete 16 weeks of aerobic exercise at an intensity of 4.5 metabolic equivalents (METs) for 150 minutes per week. Participants will then be categorized as responders or non-responders based on the change in HbA1c. For Phase Two, participants will be blocked based on responder status and randomly allocated to a maintained intensity, or increased intensity group for 12 weeks. The maintained group will continue to train at 4.5 METs, while the increased intensity group will train at 6.0 METs for 150 minutes per week.

Ethics and dissemination: Results will be presented at scientific meetings and submitted to peer-reviewed journals. Publications and presentations related to the study will be authorized and reviewed by all investigators. Findings from this study will be used to provide support for future randomized control trials. All experimental procedures have been approved by the Research Ethics Board at the University of New Brunswick (REB: 2018-168).

Trial registration: This trial has been registered on ClinicalTrails.gov (NCT03787836).

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Article Summary

Strengths and Limitations

- Participants will be allocated, not randomized, to control and intervention groups for Phase One, as data from the control group is required to estimate variance and allow for the accurate categorization of intervention participants prior to subsequent randomization to exercise intensity branches in Phase Two.
- Multiple measurements of the primary outcome are taken at each timepoint to increase reliability.
- An absolute measure of exercise intensity will be prescribed to equalize energy expenditure across all participants.

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Introduction

Organizations around the globe provide standardized exercise recommendations to reduce the onset of chronic disease and premature mortality.[1–5] However, observed changes following a typical exercise program are often heterogenous. This heterogeneity can result in individuals not experiencing the desired benefits of standard exercise training, and being labelled as 'exercise non-responders'. Attempts to quantify the observed heterogeneity, known as interindividual variation, and/or estimate the prevalence of non-responders have recently proliferated.[6–15]

Research designed to identify non-responders has primarily focused on cardiorespiratory fitness in apparently healthy adults. Moreover, attempts to categorize youth[6,15] and adult[9,11,13,14] participants as responders or non-responders based on cardiometabolic outcomes have not often included a time-matched control group in their analysis. Opting to use single-group study designs or reliability data to set response thresholds and categorize participants, produces response rates which reflect the number of participants who improved beyond an estimate of random or measurement error[10,16,17]. Alternatively, including a time-matched control group allows an estimate of within-subject variation to be considered when setting a response threshold or calculating individual confidence intervals, encapsulating additional variance and accounting for its impact when making categorizations.[10,18,19]

Labeling individuals who do not experience the intended benefits following an exercise program as non-responders can be problematic for several reasons, including the substantial influence a subjectively chosen threshold has on response categorizations, the high likelihood that a non-responder experienced a beneficial change in a secondary outcome, and the specificity of a response categorization to the provided intervention.[10,11,20,21] Accordingly, adapting exercise protocols for individuals initially categorized as non-responders may garner beneficial changes in

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the primary outcome, and thereby 'rescue', those individuals from their non-responder status.[22] Montero and Lundby (2017) highlighted the potential effectiveness of such efforts, using a 120-minute increase in weekly exercise volume to rescue a group of 21 apparently healthy, young adult, male non-responders from their original categorization.[12] Less is known, however, about the ability of adapting exercise training intensity to rescue non-responders. One study from Ross et al., (2015) allocated 121 sedentary adults living with obesity to one of three groups for 24 weeks of exercise training: (1) low-volume, low-intensity; (2) high-volume, low-intensity; or (3) high-volume, high-intensity.[8] The authors found doubling the training volume (group 1 vs. 2) led to a 50% decrease in non-response, whereas increasing the intensity and volume (group 3) only produced responders. While these findings suggest an increase in exercise intensity can increase the overall proportion of responders, it remains unknown if this would translate to specific improvements in those previously categorized as non-responders. Moreover, no such work has been conducted with those living with prediabetes or T2DM or using an indicator of glycemic control as the primary outcome.

The INTENSITY study is a two-phase, quasi-experimental trial. The objectives are to:

1. Identify the number of exercise non-responders, based on the observed changes in HbA1c, across individuals living with prediabetes or T2DM following 16 weeks of continuous aerobic exercise training.
2. Explore if increasing the intensity and/or increasing the duration of exercise training by 12 weeks will 'rescue' previously identified non-responders by garnering improvements in HbA1c.

For the purpose of this analysis, an exercise responder will be defined as any individual who has experienced a decrease in HbA1c beyond the minimal clinically important difference (MCID)

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following participation in the provided exercise trail, while accounting for the variation-induced changes in HbA1c experienced by the time-matched control group. We hypothesize that a significant proportion of participants will be categorized as non-responders following participation in the exercise program, and increasing the intensity of exercise training will rescue the previously identified non-responders by producing beneficial changes in HbA1c.

Methods and analysis

Study setting

The INTENSITY trial will be conducted at the University of New Brunswick in Fredericton, New Brunswick, Canada. This location was chosen due to the available equipment, ease of access for participants, availability of a private exercise facility for the delivery of the training protocol, and the relatively high rates of T2DM throughout the province.[23]

Eligibility criteria

Inclusion criteria:

1. Community-dwelling adults aged 19 years or older.
2. Currently living with prediabetes or T2DM as diagnosed by a physician and confirmed by an HbA1c value of 5.7% or above, as verified by duplicate testing.
3. Not currently partaking in a self-reported regular physical activity regimen, defined as consistent participation in running or jogging activity, attending physical activity or exercise classes on a weekly basis, or averaging 10,000 steps per day or more over the course of 7 days.

Exclusion criteria:

1. Currently diagnosed as having, or being treated for, low iron concentrations or anemia.
2. Diagnosed with any red blood cell altering condition.

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3. Currently living with any cardiovascular disease which would impact the ability to safely participate in exercise training.
4. Currently prescribed any medication which would impact the ability to use a heart rate monitor to accurately track exercise intensity.

Recruitment

Participants will be recruited from the city of Fredericton, New Brunswick, Canada, and the surrounding area using advertisements placed in participating grocery stores, pharmacies, health care centers, physician offices, and on social media. The research team will also use internal newsletters and electronic communication platforms to inform staff and students at the University of New Brunswick and St. Thomas University of the study. Partnerships with the local branches of Diabetes Canada and government-funded diabetes education and support programs will allow for research staff to attend meetings and distribute advertisements to clients.

Patient and Public Involvement

Prior to designing the study, 65 patients living with T2DM in Fredericton, New Brunswick and the surrounding area who previously engaged in an exercise-based lifestyle intervention program were consulted by the research team to help ensure relevance of the research purpose to this population, and provide effective dissemination input. As a results, findings will be provided to study participants on an individual basis via their requested means of communication, and the research team will host a public event to discuss the findings, what they mean, and how they may be implemented by interested stakeholders.

Interventions

Participation in the INTENSITY trial will take place across two distinct phases (Figure 1).

Phase One

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Eligible participants will be assigned to one of a control or intervention group. Allocation will be based on the time of recruitment, with the first participants assigned to the control condition until group capacity is reached. All subsequent participants will be assigned to the intervention. Allocation was chosen in favour of randomization during Phase One, as data from the control group is required to estimate measurement variance and allow for the accurate categorization of intervention participants prior to randomization in Phase Two.

Participants allocated to the control group will receive no exercise advice or instruction. Control participants will be instructed to maintain current lifestyle habits, contacted monthly to ensure continued enrollment and answer pertinent questions, and asked to return for mid-point testing in 16 weeks. Participants allocated to the intervention group will be scheduled to begin the first phase of the training protocol within one week of completing all baseline testing. The Phase One training protocol will last for 16 weeks, requiring participants to exercise at an intensity of 4.5 metabolic equivalents (METs) on a treadmill. An absolute measure of intensity was chosen in favour of a relative measure of intensity to equalize energy expenditure across all participants. All exercise will be supervised by research staff and take place in a private exercise facility located on the University of New Brunswick campus. To maximize attendance exercise sessions will be scheduled on a weekly basis. Participants will be eased into the program using a four-week progression, completing 80 minutes of exercise in week one, 100 minutes in week two, 120 minutes in week three, and 135 minutes in week four. For each of the remaining twelve weeks participants will complete 150 minutes of exercise. Each participant will choose the number of weekly sessions needed to complete the required time, as long as the total number of sessions is greater than one. Participants will be allowed to choose the speed and grade of the treadmill during the exercise time, as long as the prescribed intensity is achieved and maintained for the duration

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of each session. The supervising research staff will instruct participants to increase or decrease exercise intensity by increasing or decreasing the speed and/or grade of the treadmill, as necessary. At the start of every training session participants will be given five minutes to warmup and achieve the targeted intensity. Warmup time during each session will not count towards the total exercise time for the week. To account for improvements in cardiorespiratory fitness and ensure participants train at the appropriate intensity, each participant will be re-evaluated every four weeks. Based on the observed changes in HbA1c following the 16 weeks of exercise training, each participant in the intervention group will be categorized as a responder, non-responder, or uncertain responder.

Phase Two

Participants in the control group will again be instructed to maintain their current lifestyle habits, contacted monthly to answer any pertinent questions, and asked to return for follow-up testing in 12 weeks. Participants in the intervention group will be blocked based on their responder status and randomly allocated to either a maintained exercise group, or an increased intensity group. Participants in the maintained exercise group will continue the supervised, treadmill-based aerobic exercise training for 150 minutes per week at an intensity of 4.5 METs, for 12 weeks. Participants in the increased intensity group will increase the intensity of their supervised, treadmill-based aerobic exercise to 6.0 METs, for 150 minutes per week. Participant scheduling, freedom to choose treadmill speed and slope, and supervision will follow the same methods as applied during Phase One. Likewise, cardiorespiratory fitness will be re-evaluated every four weeks.

Deviations from protocol

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Research staff will emphasize that each participant receives the same dose of exercise (time and energy expenditure), as differences throughout the intervention group can have negative repercussions on the SD_{IR}.[24] Accordingly, enrollment will be discontinued if a participant is unable to achieve the required time allotment for three consecutive weeks, or for a total of four weeks during either Phase One or Phase Two. If a participant is absent from the trial for a full week (due to illness, vacation, family emergency, etc.), an additional week will be added at the end of the trial for that participant. A maximum of three weeks throughout the totality of the trial may be added for a single participant. Enrollment will also be discontinued if a participant experiences any musculoskeletal injury or other medical event which prevents or limits safe participation in exercise for three consecutive weeks, or if the participant receives medical advice to stop participation.

Data collection and management

Participant files will be de-identified, and each participant will be assigned a unique identifier at the time of first contact with the research staff. All participants will meet with the research staff for the sole purpose of data collection six times across three timepoints: twice at the time of enrollment for baseline evaluation, twice between Phase One and Phase Two for mid-point follow up and to allow for randomization, and twice following Phase Two for post-testing (Table 1). Additionally, participants' heart rate, chosen treadmill speed, and chosen treadmill slope will be recorded in five-minute segments throughout the duration of every exercise training session. All data will be collected in written form, and subsequently transferred to electronic files. Physical versions of all files will be stored locally, in a secure room at the University of New Brunswick. Digital files will be housed on a secure server operated by the University of New Brunswick.

Outcomes and instrumentation

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Primary outcome

The primary outcome of the INTENSITY trail is HbA1c, analyzed using a DCA Vantage Analyzer (Siemens, Germany). To increase reliability HbA1c will be measured twice at each timepoint, separated by less than seven days, with the mean value used in all analyses. The potential influence of measurement error will be estimated by calculating the Typical Error (TE; see below).

Secondary outcomes

At baseline research staff will record participant demographics, family history of cardiovascular and cardiometabolic disease, and current medication use. Participants will then complete the Physical Activity and Sedentary Behaviour Questionnaire to assess current physical activity and sedentary behaviours (Canadian Society for Exercise Physiology, 2013), and will be sent home with a Piezo Rx pedometer (StepsCount, Deep River, ON, Canada) to provide an objective indication of daily physical activity. Research staff will instruct each participant to wear the pedometer for seven consecutive days, excluding sleep time, and to remove the pedometer prior to any activity with the potential to submerge the device in water.

At each timepoint physiological and anthropometric measurements will occur over the span of two days, separated by less than one week. Participant height, systolic and diastolic blood pressure, and waist circumference will be measured by a member of the research team in accordance with Canadian Society for Exercise Physiology protocols.[25] Body mass, fat mass, and fat free mass will be estimated using the BODPOD (COSMED; Rome, Italy) following a 12-hour overnight fast. The BODPOD is a highly valid and reliable method for assessing body composition.[26,27] All cardiorespiratory fitness (VO_2peak) evaluations will be supervised by TH, using a modified version of the Balke and Ware treadmill test.[28] Participants will walk at 3.4 miles

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per hour (mph) at 0% grade on a treadmill (9500HR [Life Fitness, Illinois, USA]). After two minutes the grade will be increased to 5.0%, and progressively increase by 1.0% every minute thereafter until 15.0% is achieved. If the participant is not fatigued, the grade will be maintained, and the speed increased by 0.5 mph each minute until volitional fatigue. Gas exchange and heart rate will be continuously gathered using a TrueOne 2400 Metabolic Cart (ParvoMedics, Salt Lake City, UT, USA) and Polar FT1 heart rate monitor (Polar, Kempele, Finland), respectively. VO_2peak will be identified as the highest achieved 15-second average VO_2. Following the treadmill test, participant METs and heart rate values will be reviewed by TH, and the heart rate associated with an intensity of 4.5 or 6.0 METs (in line with the current exercise prescription) will be identified. The identified heart rate value will be used to prescribe and monitor participant intensity during subsequent training sessions, until cardiorespiratory fitness is re-evaluated. Should the exact MET value not be observed during the test, the next closest value below the desired MET value (i.e. 4.4 or 5.9 METS) will be used. The same research staff member (TH) will be present at each assessment to reduce the potential for inter-rater differences to skew results.

Cardiorespiratory fitness re-evaluation

Every four weeks throughout each Phase, a staff member will re-evaluate each participant to ensure adaptations in cardiorespiratory fitness are accounted for. Replicating a typical exercise session, participants will warm-up and workout while gas exchange and heart rate are recorded using a TrueOne 2400 Metabolic Cart (Parvomedics, Salt Lake City, UT, USA) and Polar FT1 heart rate monitor (Polar, Kempele, Finland), respectively. The participant will remain in control of the treadmill grade and speed and instructed to increase intensity as needed until the desired MET value (4.5 or 6.0 METs) is achieved and maintained for a period of one minute, as observed by the supervising staff member. Exercise accumulated during the re-evaluation will count towards

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the required weekly training time. The target heart rate identified during the fitness re-evaluation will be used for all subsequent training sessions, until the next re-evaluation is completed. The same research staff member (TH) will review the results of every re-evaluation to ensure consistency throughout the trial. A submaximal re-evaluation protocol was chosen in place of repeated administration of the maximal testing protocol to avoid the potential influence of repeated maximal tests on the outcomes, and to maximize participant comfort and compliance.

Exercise monitoring

To ensure participants are exercising at the appropriate intensity, research staff will monitor and record participant heart rate in five-minute intervals using the Polar Team2 (Polar, Kempele, Finland) heart rate monitoring system, treadmill speed and treadmill slope. The supervising research staff member will ensure each participant's heart rate throughout each training session remains within ± 2.5% of heart rate associated with the assigned MET value (as identified during the cardiorespiratory fitness test or subsequent re-evaluation).

Blinding

Participants and all research staff who assess, train, or otherwise interact with participants will be blinded to all follow-up measures of HbA1c, as well as the participant responder categorization. To maintain blinding, research staff who do not normally interact with participants will be responsible for the collection and recording of HbA1c results, determining individual participant responder status, and completing the randomization process. Group allocation for Phase Two will then be told to TH, who will disseminate the required training protocol to other research staff and participants.

Randomization

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Randomization of intervention participants will occur after the follow-up assessment prior to Phase Two. Randomization will occur in blocks of five based on participant response status (responder vs. non-responder and uncertain responder), using a random number generator. The Phase Two arm will be communicated to TH by member of the Cardiometabolic Exercise & Lifestyle Laboratory staff not related to the project.

Statistical analysis

The sample size calculation was based on the anticipated change in the primary outcome measure, HbA1c, following Phase One of the trial. A meta-analysis conducted by Umpierre et al., (2011)[29] indicates supervised aerobic exercise training of 12 weeks or longer is associated with a 0.73% reduction in HbA1c, which is anticipated here. Given a desired power of 80% and alpha of 0.05, a generalized linear model with a linear auto-regression structure (to account for the duplicate measures of HbA1c) was used to calculate the necessary sample size. A sample of 42 participants was identified to detect significant changes in HbA1c. Provided an anticipated 20% drop-out rate, 50 participants will be recruited to participate in the intervention group. An additional 10 participants will be recruited for allocation to the time-matched control group.

Objective 1: Identify the number of exercise non-responders, based on the observed changes in HbA1c, across individuals living with prediabetes or T2DM following 16 weeks of continuous aerobic exercise training. Individuals will be categorized as responders if the observed change can confidently be assumed to be beyond the MCID, while accounting for the variation-induced changes experienced by the time-matched control group. Accordingly, individual 90% confidence intervals (CI) for each participant will be calculated using the equation outlined by Swinton et al. (2018)[19]:

$$\text{Individual CI} = (\text{Observed score}_{\text{MID}} - \text{Observed score}_{\text{BASELINE}}) \pm (\text{CI multiplier} \times \text{SD}_{\text{CON}}).$$

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Here, the SD_{CON} allows for potential variation introduced in the absence of the intervention to be considered when constructing each CI. As the sample size of the control group may influence the certainty of the CI, the CI multiplier will be adjusted for a control sample size of 10 individuals (CI multiplier = 1.83)[19]. The individual CIs will be evaluated against a threshold of clinical relevance. In line with the Federal Drug Agency and the European Medicines Agency, an MCID of 0.3% for HbA1c will be used.[30,31] Participants whose lower bound of the 90% CI lays above the MCID threshold will be categorized as responders. Participants whose upper bound of the 90% CI lays below the MCID will be categorized as non-responders. Participants whose 90% CI partially crosses the MCID will be categorized as uncertain. For randomization, participants categorized as uncertain will be grouped with non-responders.

Objective 2: Explore if increasing the intensity and/or increasing the duration of exercise training will 'rescue' previously identified non-responders by garnering improvements in HbA1c. Following the completion of Phase Two, the categorization procedure conducted during Objective 2 will be repeated for all previously identified uncertain and non-responders, with important adjustments made to the CI equation. The SD_{CON} will be re-calculated with the standard deviation of the pre-post difference scores from the control group using HbA1c measurements taken at midpoint and follow-up post testing. This will allow for the CIs to represent the potential the variation-induced changes experienced by the time-matched control group across the second, 12-week period for Objective 3.

Accordingly, the individual 90% CIs will be calculated using the equation outlined by Swinton et al. (2018):

$$\text{Individual CI} = (\text{Observed score}_{POST} - \text{Observed score}_{MID}) \pm (\text{CI multiplier} \times [SD_{CON}]).$$

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Individual CIs will again be evaluated against the MCID response threshold of 0.3%, and participants re-categorized as previously described. The raw number of participants who were previously categorized as a non-responder or uncertain responder that are categorized as responders after completing Phase Two will be reported.

Ethics and dissemination

All experimental procedures have been approved by the Research Ethics Board at the University of New Brunswick (REB: 2018-168). Any substantial protocol amendments will be sent to the Research Ethics Board for review and approval prior to implementation.

Informed Consent

At the time of first contact with a member of the research staff, interested individuals will be provided with information about the study and have their eligibility confirmed. Eligible individuals will be provided with a digital copy of the consent form prior to the first meeting. At the initial meeting, all eligible individuals will be provided with adequate time to review a physical copy of the consent form, ask any questions, and consider their participation. If the individual decides to become a participant, they will be asked to provide written consent, which will be countersigned by the research staff. All participants are free to withdraw from the study at any time.

Dissemination

Results will be presented at scientific meetings and submitted to peer-reviewed journals. All publications and presentations related to the study will be authorized and reviewed by all investigators. Findings from this study will be used to develop and provide support for future randomized control trials. All study participants will have the option at the time of consent to

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request a copy of the study findings at the time of completion. A summary of the findings will be provided to all participants who indicate a desire to receive it.

Trial status

The study is currently recruiting and enrolling participants. The first participant was recruited in May 2019, and recruitment is expected to be complete in November 2020. The expected completion date of the project, including all follow-up appointments, is June 2021.

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Contributor Statement

Dr. Martin Sénéchal is the primary investigator. Dr. Danielle Bouchard, Dr. Brendon Gurd and Travis Hrubeniuk contributed to the study design and analysis methods. Travis Hrubeniuk will coordinate study implementation and data collection. All authors contributed to the completion and approved the final version of this manuscript. The study sponsor had no input to the design, implementation, interpretation, or any decision making of this study. The authors would also like to thank the patient advisers who contributed to the study.

Competing Interests

The authors have no competing interests to report.

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Data Sharing Statement

No data are available for sharing.

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Table 1. Measurement timeline

	Weeks								
	1		**2 – 17**	**18**			**19 – 31**	**32**	
Visit	**1**	**2**	**Phase One**	**3**	**4**		**Phase Two**	**5**	**6**
Demographics & Family History	**X**		**16 weeks exercise training** **(Approximately 3-5 visits per week)** **Submaximal fitness re-evaluation every 4 weeks**			**Randomization**	**12 weeks exercise training** **(Approximately 3-5 visits per week)** **Submaximal fitness re-evaluation every 4 weeks**		
Medication Use	**X**							**X**	
Anthropometrics & Blood Pressure	**X**			**X**				**X**	
Glycemic Control	**X**	**X**		**X**	**X**			**X**	**X**
Cardiorespiratory Fitness	**X**			**X**				**X**	
Physical Activity & Sedentary Behaviour	**X**							**X**	

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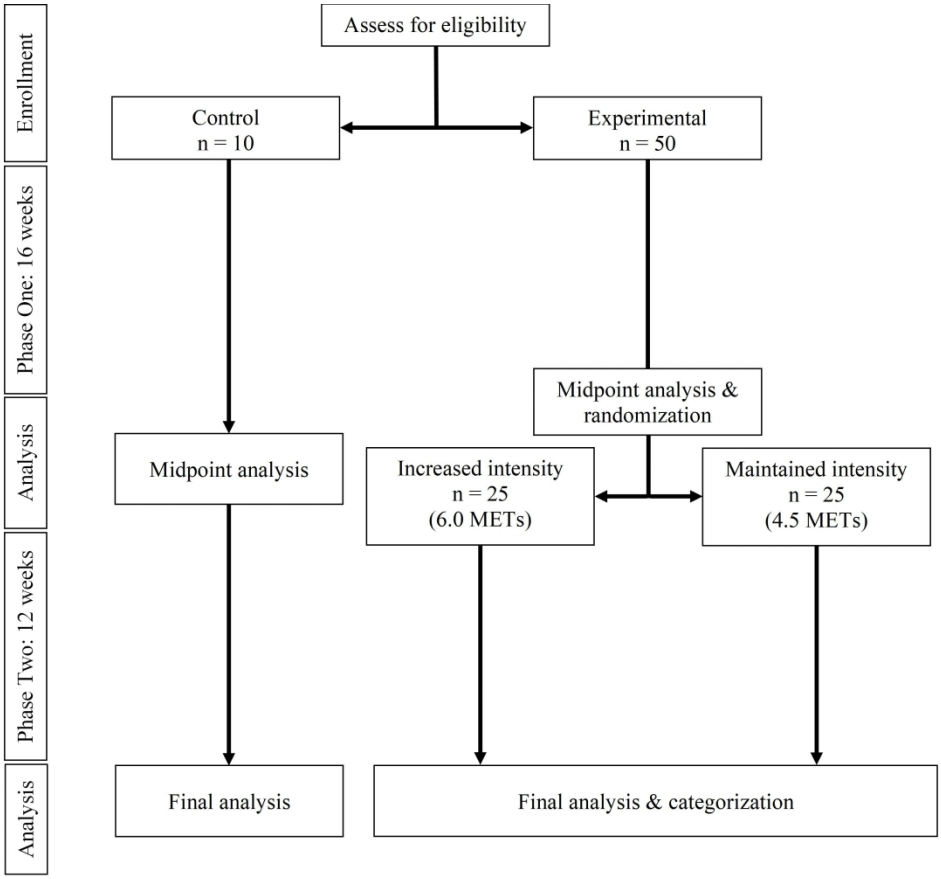

Figure 1. Participant flowchart (METs, metabolic equivalent tasks).

302x268mm (300 x 300 DPI)

BMJ Open

Can non-responders be 'rescued' by increasing exercise intensity? A quasi-experimental trial of individual responses among humans living with prediabetes or type 2 diabetes mellitus in Canada.

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Keywords:	DIABETES & ENDOCRINOLOGY, SPORTS MEDICINE, General diabetes < DIABETES & ENDOCRINOLOGY

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Can non-responders be 'rescued' by increasing exercise intensity? A quasi-experimental trial of individual responses among humans living with prediabetes or type 2 diabetes mellitus in Canada.

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Trial Registration

This trial has been registered on ClinicalTrails.gov (NCT03787836)

Study Protocol

Version 3.0, dated May 8th, 2019

Study Sponsors

Sponsor: New Brunswick Health Research Foundation

Address: 10 Knowledge Park Dr. Suite 100, Fredericton NB, Canada, E3C 2M7.

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Abstract

Introduction: Exercise is recommended to improve glycemic control. Yet, individual changes in glycemic control following exercise can vary greatly, meaning while some significantly improve others, coined 'non-responders', do not. Increasing the intensity of exercise may 'rescue' non-responders and help generate a response to training. This trial will identify non-responders to changes in glycated hemoglobin (HbA1c) across inactive individuals living with prediabetes or type 2 diabetes mellitus (T2DM) following an aerobic exercise program and evaluate if increasing training intensity will elicit beneficial changes to 'rescue' previously categorized non-responders.

Methods and analysis: This study will recruit 60 participants for a two-phase aerobic exercise training program. Participants will be allocated to a control group or assigned to an intervention group. Control participants will maintain their current lifestyle habits. During Phase One, intervention participants will complete 16 weeks of aerobic exercise at an intensity of 4.5 metabolic equivalents (METs) for 150 minutes per week. Participants will then be categorized as responders or non-responders based on the change in HbA1c. For Phase Two, participants will be blocked based on responder status and randomly allocated to a maintained intensity, or increased intensity group for 12 weeks. The maintained group will continue to train at 4.5 METs, while the increased intensity group will train at 6.0 METs for 150 minutes per week.

Ethics and dissemination: Results will be presented at scientific meetings and submitted to peer-reviewed journals. Publications and presentations related to the study will be authorized and reviewed by all investigators. Findings from this study will be used to provide support for future randomized control trials. All experimental procedures have been approved by the Research Ethics Board at the University of New Brunswick (REB: 2018-168).

Trial registration: This trial has been registered on ClinicalTrails.gov (NCT03787836).

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Article Summary

Strengths and Limitations

- Participants will be allocated, not randomized, to control and intervention groups for Phase One, as data from the control group is required to estimate variance and allow for the accurate categorization of intervention participants prior to subsequent randomization to exercise intensity branches in Phase Two.
- In line with recommendations from numerous governing bodies and policy makers, the physical activity intervention will have participants complete 150 minutes of aerobic physical activity per week.
- Multiple measurements of the primary outcome are taken at each timepoint to increase reliability.
- An absolute measure of exercise intensity will be prescribed to equalize energy expenditure across all participants.

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Introduction

Organizations around the globe provide standardized exercise recommendations to reduce the onset of chronic disease and premature mortality.[1–5] However, observed changes following a typical exercise program are often heterogenous. This heterogeneity can result in individuals not experiencing the desired benefits of standard exercise training, and being labelled as 'exercise non-responders'. Attempts to quantify the observed heterogeneity, known as interindividual variation, and/or estimate the prevalence of non-responders have recently proliferated.[6–15]

Research designed to identify non-responders has primarily focused on cardiorespiratory fitness in apparently healthy adults. Moreover, attempts to categorize youth[6,15] and adult[9,11,13,14] participants as responders or non-responders based on cardiometabolic outcomes have not often included a time-matched control group in their analysis. Opting to use single-group study designs or reliability data to set response thresholds and categorize participants, produces response rates which reflect the number of participants who improved beyond an estimate of random or measurement error[10,16,17]. Alternatively, including a time-matched control group allows an estimate of within-subject variation to be considered when setting a response threshold or calculating individual confidence intervals, encapsulating additional variance and accounting for its impact when making categorizations.[10,18,19]

Labeling individuals who do not experience the intended benefits following an exercise program as non-responders can be problematic for several reasons, including the substantial influence a subjectively chosen threshold has on response categorizations, the high likelihood that a non-responder experienced a beneficial change in a secondary outcome, and the specificity of a response categorization to the provided intervention.[10,11,20,21] Accordingly, adapting exercise protocols for individuals initially categorized as non-responders may garner beneficial changes in

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the primary outcome, and thereby 'rescue', those individuals from their non-responder status.[22] Montero and Lundby (2017) highlighted the potential effectiveness of such efforts, using a 120-minute increase in weekly exercise volume to rescue a group of 21 apparently healthy, young adult, male non-responders from their original categorization.[12] Less is known, however, about the ability of adapting exercise training intensity to rescue non-responders. One study from Ross et al., (2015) allocated 121 sedentary adults living with obesity to one of three groups for 24 weeks of exercise training: (1) low-volume, low-intensity; (2) high-volume, low-intensity; or (3) high-volume, high-intensity.[8] The authors found doubling the training volume (group 1 vs. 2) led to a 50% decrease in non-response, whereas increasing the intensity and volume (group 3) only produced responders. While these findings suggest an increase in exercise intensity can increase the overall proportion of responders, it remains unknown if this would translate to specific improvements in those previously categorized as non-responders. Moreover, no such work has been conducted with those living with prediabetes or T2DM or using an indicator of glycemic control as the primary outcome.

The INTENSITY study is a two-phase, quasi-experimental trial. The objectives are to:

1. Identify the number of exercise non-responders, based on the observed changes in HbA1c, across individuals living with prediabetes or T2DM following 16 weeks of continuous aerobic exercise training.
2. Explore if increasing the intensity and/or increasing the duration of exercise training by 12 weeks will 'rescue' previously identified non-responders by garnering improvements in HbA1c.

For the purpose of this analysis, an exercise responder will be defined as any individual who has experienced a decrease in HbA1c beyond the minimal clinically important difference (MCID)

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following participation in the provided exercise trail, while accounting for the variation-induced changes in HbA1c experienced by the time-matched control group. We hypothesize that a significant proportion of participants will be categorized as non-responders following participation in the exercise program, and increasing the intensity of exercise training will rescue the previously identified non-responders by producing beneficial changes in HbA1c.

Methods and analysis

Study setting

The INTENSITY trial will be conducted at the University of New Brunswick in Fredericton, New Brunswick, Canada. This location was chosen due to the available equipment, ease of access for participants, availability of a private exercise facility for the delivery of the training protocol, and the relatively high rates of T2DM throughout the province.[23]

Eligibility criteria

Inclusion criteria:

1. Community-dwelling adults aged 19 years or older.
2. Currently living with prediabetes or T2DM as diagnosed by a physician and confirmed by an HbA1c value of 5.7% or above, as verified by duplicate testing.
3. Not currently partaking in a self-reported regular physical activity regimen, defined as consistent participation in running or jogging activity, attending physical activity or exercise classes on a weekly basis, or averaging 10,000 steps per day or more over the course of 7 days.

Exclusion criteria:

1. Self-reported diagnosis of low iron concentrations, anemia, or being treated for these conditions.

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2. Diagnosed with any red blood cell altering condition.
3. Currently living with any cardiovascular disease which would impact the ability to safely participate in exercise training.
4. Currently prescribed any medication which would impact the ability to use a heart rate monitor to accurately track exercise intensity.

Recruitment

Participants will be recruited from the city of Fredericton, New Brunswick, Canada, and the surrounding area using advertisements placed in participating grocery stores, pharmacies, health care centers, physician offices, and on social media. The research team will also use internal newsletters and electronic communication platforms to inform staff and students at the University of New Brunswick and St. Thomas University of the study. Partnerships with the local branches of Diabetes Canada and government-funded diabetes education and support programs will allow for research staff to attend meetings and distribute advertisements to clients.

Patient and Public Involvement

Prior to designing the study, 65 patients living with T2DM in Fredericton, New Brunswick and the surrounding area who previously engaged in an exercise-based lifestyle intervention program were consulted by the research team to help ensure relevance of the research purpose to this population, and provide effective dissemination input. As a results, findings will be provided to study participants on an individual basis via their requested means of communication, and the research team will host a public event to discuss the findings, what they mean, and how they may be implemented by interested stakeholders.

Interventions

Participation in the INTENSITY trial will take place across two distinct phases (Figure 1).

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Phase One

Eligible participants will be assigned to one of a control or intervention group. Allocation will be based on the time of recruitment, with the first participants assigned to the control condition until group capacity is reached. All subsequent participants will be assigned to the intervention. Allocation was chosen in favour of randomization during Phase One, as data from the control group is required to estimate measurement variance and allow for the accurate categorization of intervention participants prior to randomization in Phase Two.

Participants allocated to the control group will receive no exercise advice or instruction. Control participants will be instructed to maintain current lifestyle habits, contacted monthly to ensure continued enrollment and answer pertinent questions, and asked to return for mid-point testing in 16 weeks. Participants allocated to the intervention group will be scheduled to begin the first phase of the training protocol within one week of completing all baseline testing. The Phase One training protocol will last for 16 weeks, requiring participants to exercise at an intensity of 4.5 metabolic equivalents (METs) on a treadmill. An absolute measure of intensity was chosen in favour of a relative measure of intensity to equalize energy expenditure across all participants. All exercise will be supervised by research staff and take place in a private exercise facility located on the University of New Brunswick campus. To maximize attendance exercise sessions will be scheduled on a weekly basis. Participants will be eased into the program using a four-week progression, completing 80 minutes of exercise in week one, 100 minutes in week two, 120 minutes in week three, and 135 minutes in week four. For each of the remaining twelve weeks participants will complete 150 minutes of exercise. Each participant will choose the number of weekly sessions needed to complete the required time, as long as the total number of sessions is greater than one. Participants will be allowed to choose the speed and grade of the treadmill during

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the exercise time, as long as the prescribed intensity is achieved and maintained for the duration of each session. The supervising research staff will instruct participants to increase or decrease exercise intensity by increasing or decreasing the speed and/or grade of the treadmill, as necessary. At the start of every training session participants will be given five minutes to warmup and achieve the targeted intensity. Warmup time during each session will not count towards the total exercise time for the week. To account for improvements in cardiorespiratory fitness and ensure participants train at the appropriate intensity, each participant will be re-evaluated every four weeks.

Categorization of Exercise Responders and Non-Responders

Based on the observed changes in HbA1c following the 16 weeks of exercise training, each participant in the intervention group will be categorized as a responder, non-responder, or uncertain responder. Individual 90% confidence intervals (CI) around the observed change in HbA1c will be calculated for each participant, with participants whose lower bound of the 90% CI lays above the selected response threshold categorized as responders, and those whose upper bound of the 90% CI lays below the response threshold categorized as non-responders. As the CI for some participants may cross the threshold for response, it may not be possible to confidently categorize all participants as either a responder or non-responder. Therefore, those participants whose 90% CI partially crosses the response threshold will be categorized as uncertain responders. For the purpose of randomization in Phase Two, participants categorized as uncertain will be grouped with non-responders.

Phase Two

Participants in the control group will again be instructed to maintain their current lifestyle habits, contacted monthly to answer any pertinent questions, and asked to return for follow-up

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testing in 12 weeks. Participants in the intervention group will be blocked based on their responder status and randomly allocated to either a maintained exercise group, or an increased intensity group. Participants in the maintained exercise group will continue the supervised, treadmill-based aerobic exercise training for 150 minutes per week at an intensity of 4.5 METs, for 12 weeks. Participants in the increased intensity group will increase the intensity of their supervised, treadmill-based aerobic exercise to 6.0 METs, for 150 minutes per week. Participant scheduling, freedom to choose treadmill speed and slope, and supervision will follow the same methods as applied during Phase One. Likewise, cardiorespiratory fitness will be re-evaluated every four weeks.

Deviations from protocol

Research staff will emphasize that each participant receives the same dose of exercise (time and energy expenditure), as differences throughout the intervention group can have negative repercussions on the SD_{IR}.[24] Accordingly, enrollment will be discontinued if a participant is unable to achieve the required time allotment for three consecutive weeks, or for a total of four weeks during either Phase One or Phase Two. If a participant is absent from the trial for a full week (due to illness, vacation, family emergency, etc.), an additional week will be added at the end of the trial for that participant for each week missed. A maximum of three weeks throughout the totality of the trial may be added for a single participant, at which point the participant will be excluded from further participation. The reason provided for missing a week of training will be documented and available for interpretation when conducting the final analysis. Enrollment will also be discontinued if a participant experiences any musculoskeletal injury or other medical event which prevents or limits safe participation in exercise for three consecutive weeks, or if the participant receives medical advice to stop participation. Data from these participants will be kept

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to allow for baseline comparisons. Likewise, if the injury or medical event takes place during Phase Two, the participant's Phase One data will be included in the analysis, and the reason for exclusion clearly indicated.

Data collection and management

Participant files will be de-identified, and each participant will be assigned a unique identifier at the time of first contact with the research staff. All participants will meet with the research staff for the sole purpose of data collection six times across three timepoints: twice at the time of enrollment for baseline evaluation, twice between Phase One and Phase Two for mid-point follow up and to allow for randomization, and twice following Phase Two for post-testing (Table 1). Additionally, participants' heart rate, chosen treadmill speed, and chosen treadmill slope will be recorded in five-minute segments throughout the duration of every exercise training session. All data will be collected in written form, and subsequently transferred to electronic files. Physical versions of all files will be stored locally, in a secure room at the University of New Brunswick. Digital files will be housed on a secure server operated by the University of New Brunswick.

Outcomes and instrumentation

Primary outcome

The primary outcome of the INTENSITY trail is HbA1c, analyzed using a DCA Vantage Analyzer (Siemens, Germany). A finger prick will be conduced using a Safe-T Pro Plus single use lancet (Accu-Chek, Roche Diagnostics, Switzerland) to allow for the collection of 1 microlitre of whole blood. The sample will then be loaded into the DCA Vantage Analyzer, where a rapid assessment of HbA1c is conducted, providing results in approximately six minutes. The DCA Vantage Analyzer has been shown to provide accurate, valid measures of HbA1c when compared to laboratory measurements.[25–27] To further increase reliability HbA1c will be measured twice at

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each timepoint, separated by less than seven days, with the mean value used in all analyses. The potential influence of measurement error will be estimated by calculating the Typical Error (TE; see below).

Secondary outcomes

At baseline research staff will record participant demographics, family history of cardiovascular and cardiometabolic disease, and current medication use. Participants will be monitored by the research staff throughout the study and required to report any changes in medication use. These changes will be confirmed at each testing time point. To confirm current physical activity patterns and ensure eligibility, participants will then complete the Physical Activity and Sedentary Behaviour Questionnaire to assess current physical activity and sedentary behaviours (Canadian Society for Exercise Physiology, 2013), and will be sent home with a Piezo Rx pedometer (StepsCount, Deep River, ON, Canada). Research staff will instruct each participant to wear the pedometer for seven consecutive days, excluding sleep time, and to remove the pedometer prior to any activity with the potential to submerge the device in water. If the pedometer is lost or not worn, participants will be required to wear the device for another seven days.

At each timepoint physiological and anthropometric measurements will occur over the span of two days, separated by less than one week. Participant height, systolic and diastolic blood pressure, and waist circumference will be measured by a member of the research team in accordance with Canadian Society for Exercise Physiology protocols.[28] Body mass, fat mass, and fat free mass will be estimated using the BODPOD (COSMED; Rome, Italy) following a 12-hour overnight fast. The BODPOD is a highly valid and reliable method for assessing body composition.[29,30] All cardiorespiratory fitness (VO_2peak) evaluations will be supervised by TH. The original Balke and Ware treadmill test protocol[31] has been amended for this study, to fit

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within the restrictions of the available equipment. Participants will walk at 3.4 miles per hour (mph) at 0% grade on a treadmill (9500HR [Life Fitness, Illinois, USA]). After two minutes the grade will be increased to 5.0%, and progressively increase by 1.0% every minute thereafter until 15.0% is achieved. If the participant is not fatigued, the grade will be maintained, and the speed increased by 0.5 mph each minute until volitional fatigue. Gas exchange and heart rate will be continuously gathered using a TrueOne 2400 Metabolic Cart (ParvoMedics, Salt Lake City, UT, USA) and Polar FT1 heart rate monitor (Polar, Kempele, Finland), respectively. VO_2peak will be identified as the highest achieved 15-second average VO_2. Following the treadmill test, participant METs and heart rate values will be reviewed by TH, and the heart rate associated with an intensity of 4.5 or 6.0 METs (in line with the current exercise prescription) will be identified. The identified heart rate value will be used to prescribe and monitor participant intensity during subsequent training sessions, until cardiorespiratory fitness is re-evaluated. Should the exact MET value not be observed during the test, the next closest value below the desired MET value (i.e. 4.4 or 5.9 METS) will be used. The same research staff member (TH) will be present at each assessment to reduce the potential for inter-rater differences to skew results.

Cardiorespiratory fitness re-evaluation

Every four weeks throughout each Phase, a staff member will re-evaluate each participant to ensure adaptations in cardiorespiratory fitness are accounted for. Replicating a typical exercise session, participants will warm-up and workout while gas exchange and heart rate are recorded using a TrueOne 2400 Metabolic Cart (Parvomedics, Salt Lake City, UT, USA) and Polar FT1 heart rate monitor (Polar, Kempele, Finland), respectively. The participant will remain in control of the treadmill grade and speed and instructed to increase intensity as needed until the desired MET value (4.5 or 6.0 METs) is achieved and maintained for a period of one minute, as observed

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by the supervising staff member. Exercise accumulated during the re-evaluation will count towards the required weekly training time. The target heart rate identified during the fitness re-evaluation will be used for all subsequent training sessions, until the next re-evaluation is completed. The same research staff member (TH) will review the results of every re-evaluation to ensure consistency throughout the trial. A submaximal re-evaluation protocol was chosen in place of repeated administration of the maximal testing protocol to avoid the potential influence of repeated maximal tests on the outcomes, and to maximize participant comfort and compliance.

Exercise monitoring

To ensure participants are exercising at the appropriate intensity, research staff will monitor and record participant heart rate in five-minute intervals using the Polar Team2 (Polar, Kempele, Finland) heart rate monitoring system, treadmill speed and treadmill slope. The supervising research staff member will ensure each participant's heart rate throughout each training session remains within ± 2.5% of heart rate associated with the assigned MET value (as identified during the cardiorespiratory fitness test or subsequent re-evaluation).

Blinding

Participants and all research staff who assess, train, or otherwise interact with participants will be blinded to all follow-up measures of HbA1c, as well as the participant responder categorization. To maintain blinding, research staff who do not normally interact with participants will be responsible for the collection and recording of HbA1c results, determining individual participant responder status, and completing the randomization process. Group allocation for Phase Two will then be told to TH, who will disseminate the required training protocol to other research staff and participants.

Randomization

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Randomization of intervention participants will occur after the follow-up assessment prior to Phase Two. A member of the Cardiometabolic Exercise & Lifestyle Laboratory (C_{ELLAB}) staff not related to the project will collect the HbA1c values following Phase One, calculate the participant's change score, and determine the response categorization, which will be communicated via email to DRB, who has no contact with participants. The response categorization will be entered into a random number generator (SPSS version 22.0) to decide the Phase Two arm allocation. Randomization will occur in blocks of 10 (five per group) based on participant response status (responder vs. non-responder and uncertain responder). Blocks of five for each group were chosen for the randomization procedure due to the inability to predict the proportion of participants which would be categorized as responders or non-responders/uncertain responders, as a method to reduce potential biases and maximize the likelihood of achieving balance between the maintained intensity and increased intensity groups. The Phase Two arm for the participant will be communicated to TH via email by the member of the C_{ELLAB} staff.

Statistical analysis

The sample size calculation was based on the anticipated change in the primary outcome measure, HbA1c, following Phase One of the trial. A meta-analysis conducted by Umpierre et al., (2011)[32] indicates supervised aerobic exercise training of 12 weeks or longer is associated with a 0.73% reduction in HbA1c, which is anticipated here. Given a desired power of 80% and alpha of 0.05, a generalized linear model with a linear auto-regression structure (to account for the duplicate measures of HbA1c) was used to calculate the necessary sample size. A sample of 42 participants was identified to detect significant changes in HbA1c in Phase One of the trial. Provided an anticipated 20% drop-out rate, 50 participants will be recruited to participate in the intervention group. All participants who complete Phase One are anticipated to continue and

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complete Phase Two. An additional 10 participants will be recruited for allocation to the time-matched control group.

Objective 1: Identify the number of exercise non-responders, based on the observed changes in HbA1c, across individuals living with prediabetes or T2DM following 16 weeks of continuous aerobic exercise training. Individuals will be categorized as responders if the observed change can confidently be assumed to be beyond the MCID, while accounting for the variation-induced changes experienced by the time-matched control group. Accordingly, individual 90% CI for each participant will be calculated using the equation outlined by Swinton et al. (2018)[19]:

Individual CI = (Observed $score_{MID}$ – Observed $score_{BASELINE}$) ± (CI multiplier x SD_{CON}).

Here, the SD_{CON} allows for potential variation introduced in the absence of the intervention to be considered when constructing each CI. As the sample size of the control group may influence the certainty of the CI, the CI multiplier will be adjusted for a control sample size of 10 individuals (CI multiplier = 1.83)[19]. The individual CIs will be evaluated against a threshold of clinical relevance. In line with the Federal Drug Agency and the European Medicines Agency, an MCID of 0.3% for HbA1c will be used.[33,34]

Objective 2: Explore if increasing the intensity and/or increasing the duration of exercise training will 'rescue' previously identified non-responders by garnering improvements in HbA1c. Following the completion of Phase Two, the categorization procedure conducted during Objective 2 will be repeated for all previously identified uncertain and non-responders, with important adjustments made to the CI equation. The SD_{CON} will be re-calculated with the standard deviation of the pre-post difference scores from the control group using HbA1c measurements taken at midpoint and follow-up post testing. This will allow for the CIs to represent the potential the

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variation-induced changes experienced by the time-matched control group across the second, 12-week period for Objective 3.

Accordingly, the individual 90% CIs will be calculated using the equation outlined by Swinton et al. (2018):

Individual CI = (Observed $score_{POST}$ – Observed $score_{MID}$) ± (CI multiplier x [SD_{CON}]).

Individual CIs will again be evaluated against the MCID response threshold of 0.3%, and participants re-categorized as previously described. The raw number of participants who were previously categorized as a non-responder or uncertain responder that are categorized as responders after completing Phase Two will be reported.

Ethics and dissemination

All experimental procedures have been approved by the Research Ethics Board at the University of New Brunswick (REB: 2018-168). Any substantial protocol amendments will be sent to the Research Ethics Board for review and approval prior to implementation.

Informed Consent

At the time of first contact with a member of the research staff, interested individuals will be provided with information about the study and have their eligibility confirmed. Eligible individuals will be provided with a digital copy of the consent form prior to the first meeting. At the initial meeting, all eligible individuals will be provided with adequate time to review a physical copy of the consent form (Supplementary File 1), ask any questions, and consider their participation. If the individual decides to become a participant, they will be asked to provide written consent, which will be countersigned by the research staff. All participants are free to withdraw from the study at any time.

Dissemination

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Results will be presented at scientific meetings and submitted to peer-reviewed journals. All publications and presentations related to the study will be authorized and reviewed by all investigators. Findings from this study will be used to develop and provide support for future randomized control trials. All study participants will have the option at the time of consent to request a copy of the study findings at the time of completion. A summary of the findings will be provided to all participants who indicate a desire to receive it.

Trial status

The study is currently recruiting and enrolling participants. The first participant was recruited in May 2019, and recruitment is expected to be complete in November 2020. The expected completion date of the project, including all follow-up appointments, is June 2021.

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Contributor Statement

Dr. Martin Sénéchal is the primary investigator. Dr. Danielle Bouchard, Dr. Brendon Gurd and Travis Hrubeniuk contributed to the study design and analysis methods. Travis Hrubeniuk will coordinate study implementation and data collection. All authors contributed to the completion and approved the final version of this manuscript. The study sponsor had no input to the design, implementation, interpretation, or any decision making of this study. The authors would also like to thank the patient advisers who contributed to the study.

Competing Interests

The authors have no competing interests to report.

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Access to Data

Following trial completion, only those investigators listed as author above, and necessary research staff will have access to the dataset.

Data Sharing Statement

No data are available for sharing.

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Table 1. Measurement timeline

	Weeks								
	1		**2 – 17**	**18**			**19 – 31**	**32**	
Visit	**1**	**2**	**Phase One**	**3**	**4**		**Phase Two**	**5**	**6**
Demographics & Family History	**X**		**16 weeks exercise training** **(Approximately 3-5 visits per week)** **Submaximal fitness re-evaluation every 4 weeks**			**Randomization**	**12 weeks exercise training** **(Approximately 3-5 visits per week)** **Submaximal fitness re-evaluation every 4 weeks**		
Medication Use	**X**							**X**	
Anthropometrics & Blood Pressure	**X**			**X**				**X**	
Glycemic Control	**X**	**X**		**X**	**X**			**X**	**X**
Cardiorespiratory Fitness	**X**			**X**				**X**	
Physical Activity & Sedentary Behaviour	**X**							**X**	

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Figure Captions

Figure 1. Participant Flowchart

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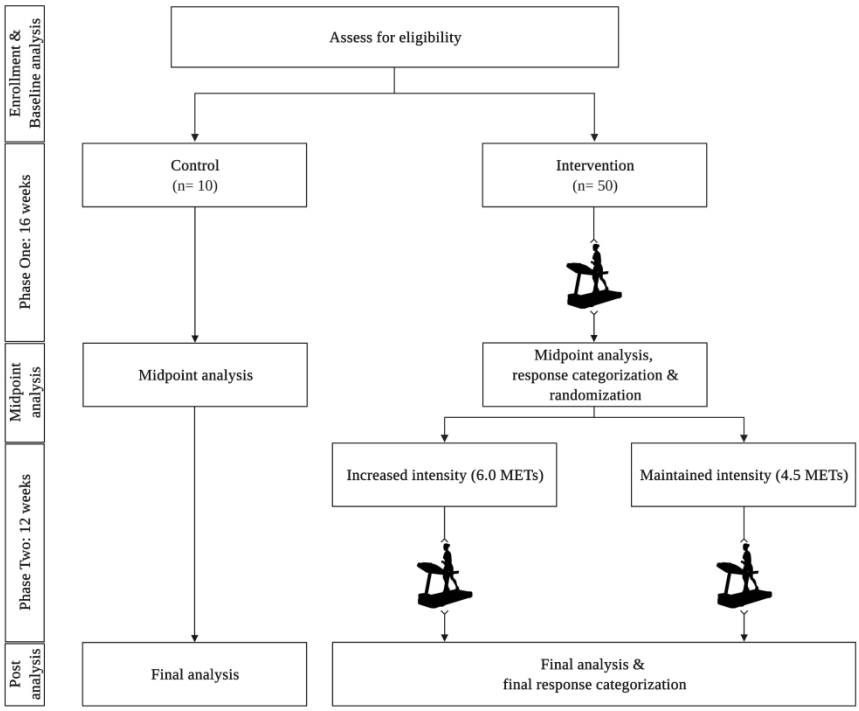

Figure 1. Participant Flowchart

PARTICIPANT INFORMATION AND CONSENT FORM

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INTRODUCTION

You are being asked to participate in this research study. Please take time to review this consent form and discuss any questions you may have with the study staff before agreeing to participate in the described experimental research. You may discuss it with your regular doctor, friends, and/or family

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before you make your final decision. This consent form may contain words that you do not understand. Please ask the Principal Investigator, Co-Investigators, or study staff to explain any words or information you do not clearly understand.

BACKGROUND OF STUDY

The prevalence of Type-2 diabetes has increased worldwide, and New Brunswick is no exception. It is understood that exercise can be an effective way to control blood glucose and prevent the progression towards Type-2 diabetes. However, research suggests there is large interindividual variation in the blood glucose response to any exercise program. This is believed to result in a number of people who do not benefit from exercise, known as non-responders. Emerging evidence proposes that altering an exercise program and providing a sufficient exercise stimulus can improve the number of people who respond to exercise, leading to a reduction in the number of non-responders. While this is encouraging, to date there have been no attempts to reduce the number of non-responders across a population of individuals living with prediabetes or Type-2 diabetes, or to observe if there are long-term health implications associated with responding (or not responding) to exercise.

This study is being conducted based on previous studies that indicated an increase in exercise intensity can lead to a higher proportion of exercise responders (In other words, more people benefiting from exercise). In addition, no research has looked at the effects of maintaining the original exercise prescription and comparing it to a higher intensity exercise prescription. We suspect that; 1) a meaningful number of participants will not improve their blood glucose following the original 16-week exercise prescription, 2) the non-responder participants who increase the intensity of the exercise prescription during the next 12-weeks will see an greater improvement in their blood glucose levels compared to the non-responders who continue with the original program, and 3) responding to the exercise program will lead to health benefits 1-year following the cessation of the exercise programs.

OBJECTIVES OF THE STUDY

The purpose of this study is to find out 1) how common non-response to a standard exercise program is amongst individuals living with prediabetes or Type-2 diabetes, 2) if increasing the intensity of the exercise program can lead to more responders than simply maintaining current exercise, and 3) if there are long-term benefits associated with responding.

WHY WERE YOU ASKED TO PARTICIPATE IN THIS STUDY?

You are being asked to take part in this study because you are above 19 years of age, currently have blood glucose levels that indicate you may be living with prediabetes or Type-2 diabetes and are not currently engaged in a structured exercise program. A total of 60 participants will be in this study.

Participation Timeline:

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Week	1		2 – 17	18		19 – 31	32		84
Visit	1	2	3 – 50	51	52	53 – 88	89	90	91
Questionnaires	X		16 weeks exercise training (Approximately 3-5 visits each week totaling 150 minutes) Submaximal fitness testing every 4 weeks			12 weeks exercise training (Approximately 3 visits each week totaling 150 minutes) Submaximal fitness testing every 4 weeks			X
Height, Weight, Waist Circumference, Body Composition	X			X			X		X
Physical Activity & Dietary Assessment	X						X		X
Bloodwork	X	X		X	X		X	X	X
Fitness Test	X	X		X	X		X	X	X
Feces collection	X			X			X		

STUDY PROCEDURES

Listed below are the tests and procedures involved in participating in this study:

1. Medical History

You will be asked a series of questions regarding your health and any current mediations being taken.

2. Physical Activity, Dietary Recall, Screen Time and Sedentary Behaviour, Self-Regulation Eating and Addiction Questionnaires

You will be asked to complete a series of questionnaires outlining your current level of physical activity and sedentary behaviour, the total amount of screen time you engage in, and your dietary habits. In addition, questionnaires about your self-regulation and potential eating addiction will be completed.

3. Gender Role and Mental Health Questionnaires

You will be asked to fill out questionnaires meant to help us adequately understand your perceived gender role and understand your current mental health status.

4. Body Measurements

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We will measure your body weight, height, and take a measurement of your waist circumference.

5. Body Composition

We will look at the amount of muscle and fat in your body using a Bod Pod. In order to do that, you will be asked to wear a bathing suit and swim cap while sitting in a device called the Bod Pod. The Bod Pod resembles an egg-shaped chamber with a window for you to look out of. Air will move into the enclosed space where you sit and you may feel a slight change in air pressure. While enclosed in this chamber, if you begin to feel uncomfortable, you can press a button located by your knee to open the door. The Bod Pod measures the airflow and the changes in the airflow that occur while your body is in the chamber. You are to sit quietly while the first measurements of airflow are conducted. This takes about 30 seconds, at which time the technician will open and close the Bod Pod door to repeat the measurement again. The whole test takes approximately 5 minutes. The test is performed in a private room. To accurately complete this test, it is required that you do not eat or drink any beverage for at least 4 hours, or smoke for at least 2 hours before the test starts.

6. Blood Work at UNB

A registered nurse will take a draw of your blood (equating to approximately 6 tablespoons) for our analysis purposes. Specifically, we will analyze the concentrations of glucose, insulin, and a protein named irisin, present in your blood. To complete this test, it is required that you fast overnight.

7. Fitness Test

At the CELLAB we will measure your heart and lung fitness levels. This test takes approximately 8 to 12 minutes. The exercise test will be performed on a treadmill. We will measure your heart rate and blood pressure during the test. Heart rate will be measured with a small black band around your chest, and blood pressure is measured with a cuff on your arm. We will also measure your breathing during the exercise test. To do this, you will be required to wear a mouth piece or mask to properly throughout the test. To start, you will be asked to walk at an easy pace with no incline. We will then progressively increase the slope 1% every minute. You will decide when to stop the test; the study staff will encourage you to continue as long as you can. To accurately complete this test, it is required that you do not consume caffeine, eat, or smoke within 3 hours, or exercise within 12 hours of the test.

8. Physical Activity and Dietary Assessment

You will leave the CELLAB with a pedometer to wear for seven days following the first visit. The pedometer is a small device that you will be asked to wear on your left hip to track your daily physical activity levels. This device must be returned upon completion. You will also receive physical activity log to fill out for one week, asking you to take record of how may steps you took each day, alongside any additional physical

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activity you complete. Finally, you will receive a dietary log to be completed every day for one week. On this log you will need to record any food and/or beverage you consume every day for one week.

9. Exercise Training

Following visit 1 and 2, you will be randomized into one of two groups. The first group will not be provided any exercise intervention to complete from week 2 to 17, or from week 19 to 31. However, various prizes will be awarded to those participants who successfully show up to all testing sessions (week 1, week 18, week 32). Once this group has completed the final testing, they will be offered to opportunity to partake in the exercise offered to the second group.

The second group will be prescribed moderate intensity aerobic exercise from weeks 2 to 17. During the first week of exercise, you will be required to complete 80 minutes of moderate intensity aerobic exercise. The duration of exercise will slightly increase in each subsequent week for the first four weeks of exercise training (week 2 – 5). From week 6 – 17 you will complete 150 minutes of moderate intensity aerobic exercise per week. The CELLAB will be open at various times throughout the week, providing you with ample opportunity to complete the required exercise. Optimally, participants will come three times per week, with each session consisting of 50 minutes of exercise. The minimum number of sessions that can be used to complete the 150 minutes of exercise is **two**. Every four weeks you will complete a submaximal treadmill walking test (as described below) to allow the study group to adjust the intensity of your training to your potentially improved fitness level.

After testing visits 51 and 52 (during week 18), participants in the second group will be randomized into two exercise programs. **You will not be informed if you are a responder or a non-responder until the study is completed.** Participants in the first exercise program will continue their current exercise prescription for 12 weeks (week 19 – 31). Participants randomized to the second exercise program will still complete 150 minutes of exercise per week, however they will do so at a slightly higher intensity (moderate to vigorous). Submaximal treadmill walking tests will again be completed every four weeks to allow the study group to adjust exercise Intensity as necessary.

10. Submaximal Fitness Tests

Every four weeks throughout the exercise training you will complete a submaximal treadmill walking test. We will measure your heart rate and your breathing during the test. Heart rate will be measured with a small black band around your chest. Measuring your breathing will required to wear a mouth piece or mask while walking on the treadmill for 4 minutes at a pre-determined grade and speed.

11. Feces collection

You will be asked to provide a fecal sample at baseline, after the initial 16 weeks of exercise and at post-testing. Therefore, a total of 3 time-points will be recorded. Although this type of measurement is usually unpleasant, we have taken every means available to make this as easy as possible for you. A fecal sample collection kit will be provided by our research team. The research staff will provide you with detailed instructions as well as an instructional online video. The fecal sample will be collected by you, in your

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home, and then brought back to the lab within 2 days. The sample will be stored appropriately in a -80°C freezer. This procedure does not have any risk associated with It, other than the potential discomfort associated with the collection (which will happen in the comfort of your home). The collection of fecal samples will provide further insight into exercise responders vs. non-responders (using glycemic control), following an exercise intervention.

STUDY VISITS

Visit 1 & 2 (within 1 week of each other)
Location: UNB CELLAB

- Review and sign the Informed Consent (Visit 1 only)
- Medical History (Visit 1 only)
- Questionnaires (Visit 1 only)
- Weight, height, hip, and waist measurement
- Body Composition
- Bloodwork
- Fitness Test
- Physical Activity & Dietary Assessment & Questionnaires

Each visit takes about 2 hours

Visits 3 – 50 (Group 2 participants only)
Location: UNB CELLAB Gym

- Exercise Training
- Submaximal Treadmill Walking Test (Every 4 weeks)

Visit 51 & 52 (within 1 week of each other)
Location: UNB CELLAB

- Weight, height, hip, and waist measurement
- Body Composition
- Bloodwork
- Fitness Test

Each visit takes about 2 hours

Visits 53 – 88 (Group 2 participants only)
Location: UNB CELLAB Gym

- Exercise Training
- Submaximal Treadmill Walking Test (Every 4 weeks)

Visit 89 & 90 (within 1 week of each other)

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Location: UNB CELLAB

- Weight, height, hip, and waist measurement
- Body Composition
- Bloodwork
- Fitness Test
- Physical Activity & Dietary Assessment & Questionnaires
  Each visit takes about 2 hours

Visit 91 (One year later)
Location: UNB CELLAB

- Medical History (Visit 1 only)
- Questionnaires (Visit 1 only)
- Weight, height, hip, and waist measurement
- Body Composition
- Bloodwork
- Fitness Test
- Physical Activity & Dietary Assessment & Questionnaires
  Each visit takes about 2 hours

POTENTIAL RISKS AND DISCOMFORT

Study personnel are trained to respond to any emergency and a registered nurse and will be on site during the necessary procedures.

Physical Activity and Dietary Assessment: There are no risks associated with wearing a pedometer. It is possible that the pedometer makes you feel uncomfortable, but that is unlikely.

Body Composition: During the Bod Pod testing, it is possible that you might experience some light-headedness or dizziness. It is also possible that if you are claustrophobic, that you may begin to have a feeling of being shut-in. A button at your knee while you are inside of the Bod Pod, will allow you to have the door of the Bod Pod open *immediately*. A window on the Bod Pod also will allow you and the technician to see and communicate with one another. There is no physical danger involved in these measurements. Room air is continuously circulated through the Bod Pod compartment when it is closed. The compartment does not lock and the person inside can exit at any time. Your parent/legal guardian will be present at all time during this test with someone from our research staff. The test is performed behind a medical curtain to maintain privacy and ensure nobody see you.

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Exercise Training: When people exercise for the first time in a long while, there is the possibility of an increased risk of muscle or joint injuries. However, all exercise will be performed in the presence of a trainer who will know exactly what to do in case a physical injury, or any additional concern, occurs. Also, the selected training methods, duration, and Intensity in this program were carefully chosen to minimize injury risk and optimize the benefits for each participant. The research staff is educated in proper exercise prescription for individuals living with diabetes, and will follow the 2018 Diabetes Canada Guidelines for exercise in order to ensure each participant is properly monitored, prepared, and advised as recommended throughout the exercise training program. It is possible that the heart rate monitor worn throughout each session will make you feel uncomfortable, but we have a variety of models that may be used, and discomfort is unlikely.

Bloodwork: Some people experience slight discomfort, bleeding and/or bruising during the collection of blood samples. Sometimes people feel dizzy or faint. An infection in your arm can develop if the testing site is not clean, so the nurse will clean your arm with alcohol before taking blood. Every effort will be made to reduce any risks and discomfort. We have a registered nurse that will do all the blood collection.

Fitness Tests: There is a possibility of certain changes occurring during the exercise test. Serious complications of exercise testing occur in approximately 1 in 10,000 tests in adults. Such complications may include abnormal blood pressure, fainting, heart rate disorder and, in rare instances, heart attack, stroke and death. Exercise testing may also cause slight injury to muscles and joints, routine discomforts that will go away within three days after the test. Every effort will be made to minimize these risks by reviewing information about your health and fitness before the test and by closely monitoring how your body responds to the exercise. We will reduce these risks by closely monitoring your condition throughout the exercise test. If you experience any abnormal response to the exercise, the session will be stopped.

What Are the Potential Benefits of the Study?

Benefit to you: By participating in the study, you will receive information about your health and physical activity level. In addition, you will be provided with a personal trainer and regular access to a fitness facility at no cost to you, which would not be possible during a regular doctor's visit. It is very likely that engaging in this study will improve your health. Participants will likely learn what kind of exercise they can do to continue obtaining health benefits once the project is complete, and better understand why they are getting healthier.

Benefit to other people: The main benefit of participating in this study is the knowledge we will gain about how the body responds to exercise, and if it is possible to improve the number of responders among individuals living with prediabetes or Type-2 diabetes.

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What Are the Costs of the Study?

There are no costs to you for participating in this study. This study will cover all costs, which include clinic and professional fees, along with the diagnostic and laboratory tests. A parking pass will be provided so you do not have to pay for parking.

Is the Study Confidential?

Information gathered in this research study may be published or presented in public forums, however your name and other identifying information will not be used or revealed. Medical records that contain your identity will be treated as confidential. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law.

The Research Ethics Board at the University of New Brunswick may also review your research-related records for quality assurance purposes.

Only your consent form will have information that relates to your identification number (ID) number and this will be kept in a locked cabinet within a locked room located at the University of New Brunswick. All other study documents related to you will bear only your assigned ID number. These records will be kept in a locked secure area and only those identified will have access to those records. No information revealing any personal information, such as your name, phone number or address, will leave the University of New Brunswick. All data collected will be entered into computers, however all data will be password protected and data files will not include any identifying information, only the subject ID number. All your data will be kept for 7 years and then will be destroyed.

Do I Have the Right to Change My Mind?

Your decision to take part in this study is totally up to you. You may refuse to participate or you may quit at any time. Your decision to participate or withdraw from the study will not affect your regular medical care. The investigators reserve the right to end your participation in the study for any reason.

If you are enrolled and subsequently withdraws from the study, any information or biological samples supplied up to that point remains in the possession of the research team and will be retained as data for research purposes.

What Else Should I Know?

- Any results from this study cannot be used for diagnosis.

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- You may request a copy of any images and the blood tests.
- At your request, a summary of the test results can be provided to your primary care physician.
- Your primary care physician will not know whether you have agreed to participate in this study or not unless you request that a summary of the test results be provided to him or her. You may request that the test results be provided to your physician at the end of the study.
- The investigators have no financial interest in the outcome of the study.
- All the blood samples will be kept for a maximum of 7 years in a locked freezer in our exercise physiology lab, which is a restricted access room. The samples will be kept anonymous; no linkage or genetic tests are anticipated with these samples. They will be destroyed safely according to standard biohazard procedures.

If, in the opinion of the researchers, it is believed that you need further medical follow-up based on standard results you will be advised of this.

This project has been reviewed by the UNB Research Ethics Board and is on file as REB 2018-168

Potential Changes to Study Protocols due to COVID 19

Given the potential for the current COVID-19 pandemic to close University of New Brunswick facilities, or restrict face to face data collection, the study protocol will need to change. Below we outline two scenarios.

Scenario 1: Intervention not possible in CELLAB

Should face to face data collection be approved, but the University of New Brunswick restrict access to on campus facilities, exercise will instead take place at a location of your choice such as your home or a public space. The study timeline, purpose and objectives, and randomization will remain unchanged.

You will still be required to complete the weekly time allotment at the prescribed exercise intensity. Likewise, you will be able to select the time and number of sessions completed each week. However, you will be asked to place the heart rate monitor on yourself. Moreover, you will be asked to use provided steps (or a staircase in your home) and while under supervision by a research staff member via video calling software, complete the training session. You will be asked to report your heart rate every 5 minutes, and the research staff will inform you when you need to increase the intensity.

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Scenario 2: Intervention and testing not possible in CELLAB

In addition to perform the exercise in at a location of your choice, the testing will be limited as well. If allow by Public Health and accepted by you, a research assistant will come into your home and performed testing to respect the study timelines.

4. Body measurements

Height and weight will be taken with portable equipment

5. Body Composition

The BODPOD will no longer be used to estimate body composition. In its place, a handheld Omron HBF-306C bioelectrical impedance analyzer will be temporarily provided. Prior to the test, you will be asked to avoid consuming any food or liquids for 4 hours prior to the test, and to use the bathroom within 30 minutes of the analysis. You will then stand straight up, and hold the monitor with your arms fully extended. The device will then complete its measurement, taking approximately 30 seconds.

6. Blood Work at UNB

All tests completed using a blood draw will be dropped from the study besides HbA1c, that will be collected through a finger prick. You will be provided instructions as to how to safely conduct a finger prick, in line with the procedures followed for daily glucose measurements. You will be provided with a small collection tube, which will be used to collect 1 µL of blood from the finger prick. The collection tube will then be taken by the research staff to conduct the analysis, and all materials disposed of in line with proper biohazard and sharps waste disposal procedures.

7. Fitness Test

In place of the maximal fitness test, a predicted aerobic fitness test will be completed. Specifically, the modified Canadian Aerobic Fitness Test (mCAFT) will be used. You will be provided with a heart rate monitor, the mCAFT music, and sanitized, standardized set of steps. You will also be provided the link to a video showing how to properly put on a heart rate monitor, and how to make sure it is working, as well as clear instructions on how to complete the test. While supervised by a research staff member over an online video chatting software, you will listen to the music and follow the audio cues to step up and down the provided steps at the required cadence, completing 3-minute stages until cut off by the research staff member. You will be asked to report their heart rate between each stage. A predictive equation will then be used to estimate the participant's maximal aerobic fitness.

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10. Submaximal Fitness Test

Instead of completing the submaximal treadmill walking tests, every four weeks you will be asked to repeat the mCAFT test, as outlined previously.

How Can I Get More Information?

To receive additional **information** about this study from the researchers:

- Martin Sénéchal, Ph.D., CEP (506) 451-6889

For questions about your **rights as a research subject**, you may contact:

- Wayne Albert, Dean of the Faculty of Kinesiology (506) 453-4575
- Steven R. Turner Chair of UNB Research Ethic Board (506) 458-7433

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Signatures

- I have received a copy of this consent form and I have read it. I understand the nature of the study, including the potential risks and benefits. I have had adequate time to consider the information. My questions about the study have been answered.
- I will be given a copy of this document, after signing it.
- By signing this document, I am not waiving any of my legal rights and I understand that I can stop being in the study at any time.
- **I hereby agree to participate in the study outlined throughout this document.** My consent has been given freely.
- I wish to be contacted for future studies. (Additional consent will be required and I will be free to decline participation in any further studies at the time of contact.)

  YES ❑ **NO** ❑

I wish to receive a report of the results of this study when available. ❑

Consent of the Participant (Print)	Signature	Date

Person Obtaining Consent

To the best of my knowledge, the information that I have provided in response to any questions fairly represents the project. I am committed to conducting this study in compliance with all the ethical standards that apply to projects that involve human subjects.

Name (Print)	Signature	Date

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **Completed: Line 1 - 3**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **Completed – Line 25**
	2b	All items from the World Health Organization Trial Registration Data Set **Not applicable**
Protocol version	3	Date and version identifier **Completed – Line 27**
Funding	4	Sources and types of financial, material, and other support **Included in online submission as per journal instructions**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **Completed – Lines 5 – 9 & 403 - 408**
	5b	Name and contact information for the trial sponsor **Completed – Lines 27 - 35**
	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 **Not applicable**
	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) **Not applicable**
Introduction		

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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 **Completed – Lines 76 - 125**
	6b	Explanation for choice of comparators **Completed – Lines 76 - 125**
Objectives	7	Specific objectives or hypotheses **Completed – Lines 112 – 118**
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) **Competed – Line 112**
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 **Completed – Lines 128 - 131**
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) **Completed – Lines 133 - 148**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **Completed – Lines 166 – 219**
	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) **Completed – Lines 221 – 234**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **Completed – Lines 183 - 191**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **Not applicable**

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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 **Completed – Lines 247 - 314**
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) **Completed – See attached figure**
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 **Completed – Lines 339 - 349**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **Completed – Lines 150 – 156**
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 **Completed – Lines 324 - 337**
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 **Completed – Lines 324 - 337**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **Completed – Lines 327 - 328**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **Completed – Lines 316 - 322**

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	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **Unblinding is not necessary for this trial.**

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 **Completed – Lines 247 - 314**
	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 **Completed – Lines 232 - 234**
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 **Completed – Lines 236 - 245**
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 **Completed – Lines 350 - 379**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **Not applicable**
	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) **Not applicable due to the nature of our analyses.**

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 **Not in place for this trial**

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	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 **Not in place for this trial**
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 **Not applicable**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **Not in place for this trial**

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **Completed – Lines 378 - 380**
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) **Completed – Lines 378 - 380**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **Completed – Lines 382 - 389**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **Not applicable**
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 **Completed – Lines 233 - 237**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **Completed – Line 410**
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 **Completed – Lines 416 - 417**

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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 **Not applicable**
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 **Completed – Lines 391 - 396**
	31b	Authorship eligibility guidelines and any intended use of professional writers **Not applicable (no plans for professional authors, all authors and contributions are listed above)**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **Not applicable**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **Included**
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 **Not applicable**

*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.

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