The SmartRX trial: Acute effectS of manipulating stRength eXercise volume on insulin sensitivity in overweight/obese adults: a protocol for a randomized controlled, crossover, clinical trial

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Research Article

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**Title**

The SmartRX trial: Acute effects of manipulating strength exercise volume on insulin sensitivity in overweight/obese adults: a protocol for a randomized controlled, crossover, clinical trial

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**Abstract**

**Background:** Type 2 diabetes mellitus is a disease in which insulin action on sensitive tissues is impaired, and even an acute bout of strength exercise can cause positive changes on insulin sensitivity. Current guidelines for strength exercise prescription suggest that 8 to 30 sets should be performed, although it is not known how such variations in volume impact insulin action. Additionally, this means an almost 4-fold difference in time commitment, which might directly impact an individual's motivation and perceived capacity to exercise. This study will assess the effects of different strength exercise volumes on insulin sensitivity.

**Methods:** Fourteen overweight/obese individuals of both sexes who are over 35 years old will undergo 3 experimental sessions in a random order, with a minimum washout period of 4 days between them, after being thoroughly familiarized with the procedures: Session 1: high-volume (7 exercises, 3 sets per exercise, 21 total sets); Session 2: low-volume (7 exercises, 1 set per exercise, 7 total sets); Session 3: control session, where no exercise will be performed. Psychological assessment (affect, enjoyment, and self-efficacy) will be performed after the sessions. All sessions will be held at night, and the next morning, an oral glucose tolerance test will be performed in a local laboratory, from which indexes of insulin sensitivity will be derived.

**Discussion:** We believe this study will aid in strength exercise prescription for those individuals who claim not to have time to exercise and to those who perceive high-volume strength exercise intimidating to adhere to.

**Trial registration:**

Clinical trial registry number: ReBEC #RBR-3vj5dc5 (https://ensaiosclinicos.gov.br/rg/RBR-3vj5dc5)

World Health Organization Universal Trial Number (UTN): U1111-1287-9212

Open Science Framework (OSF): https://osf.io/4gu87/
### Keywords
resistance exercise, strength training, exercise volume, glucose tolerance, oral glucose tolerance test, obesity, overweight, insulin resistance.

### Administrative information
Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see [http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/](http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/)).

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<tr>
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| Trial registration {2a and 2b}. | Clinical trial registry number: ReBEC #RBR-3vj5dc5 ([https://ensaiosclinicos.gov.br/rg/RBR-3vj5dc5](https://ensaiosclinicos.gov.br/rg/RBR-3vj5dc5))
World Health Organization Universal Trial Number (UTN): U1111-1287-9212 (supplement file)
Open Science Framework (OSF): https://osf.io/4gu87/ |
| Protocol version {3} | Version 3 of Dec 8th 2023 |
| Funding {4} | This study is supported by the National Council for Scientific and Technological Development (CNPQ: Grant#407975/2018-7 and #402091/2021-3) and by the Minas Gerais State Agency for Research and Development (FAPEMIG: Grant# APQ-00008-22). |
| Author details {5a} | LFRS, MFDP, FG, FCM: Department of Physical Education, Federal University of the Jequitinhonha and Mucuri Valleys – Diamantina, MG – Brazil
BCCG: Laboratory of Exercise Biology and Immunometabolism, Centro Integrado de Pós-Graduação e Pesquisa em Saúde, Programa Multicêntrico de Pós-Graduação em Ciências Fisiológicas, |
### Name and contact information for the trial sponsor {5b}

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<td>F de Castro Magalhaes (PI)</td>
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<td><a href="mailto:fcm@unm.edu">fcm@unm.edu</a></td>
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### Role of sponsor {5c}

This is an investigator initiated clinical trial. The funders played no role in this study's design, and will not play any roles in study conduct, interpretation of data, or reporting of results.

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### Introduction

#### Background and rationale {6a}

Diabetes Mellitus (DM) is a chronic condition in which blood glucose levels remain high in the face of insufficient insulin production and/or the tissues cannot make efficient use of it [1]. If maintained for a long period, hyperglycemia can lead to severe and life-threatening disorders, such as cardiovascular disease, nerve damage (neuropathy), kidney damage (nephropathy), amputation of limbs, vision loss and even blindness [1]. The number of people affected by DM has been growing exponentially, and by 2017, this disease was already the ninth leading cause of death in the entire world population [2], and in 2021 it was responsible for 12.2% of global deaths in people aged 20-79 [1]. DM is related to high financial costs [3], and in Brazil, the total expenditure on DM in 2014 was more than BRL 26 billion (~US$ 5 bi) [4]. Approximately 90-95% of DM cases are type 2 (DM2) [5], which is related to impaired insulin sensitivity, in the majority of cases induced by adiposity [6]. Therefore, therapies that act on insulin sensitivity in overweight/obese individuals are urgently needed.

The beneficial effects of strength training on insulin sensitivity have been increasingly recognized. Notably, several studies point to the beneficial effects of a single acute bout of strength exercise on improving insulin sensitivity [7]. Moreover, exercise training effects on improved insulin...
sensitivity may be lost in as little as 6 days after the last exercise session in DM2 patients[8],
suggesting the positive effects of exercise on glycemic control can be largely attributed to the acute
improvements observed in the hours-days after each exercise bout[9]. Thus, understanding the
strength exercise prescription that elicits acute improvements in insulin action is of great clinical value.

Notwithstanding, a closer inspection of the literature reveals some controversy on studies that
have assessed the effect a strength exercise session on insulin sensitivity. For example, Koopman et
al [10] reported that a strength exercise session improved insulin sensitivity in healthy young men,
consistent with previous research [11–13]. The benefits of strength exercise on insulin sensitivity have
also been observed in older [14], obese [15], in insulin-resistant subjects, prediabetics and DM2
patients [16]. For instance, Van Dijk et al [17] studied glucose intolerant individuals, individuals with
DM2 treated with exogenous insulin and individuals with DM2 treated with oral hypoglycemic drugs
after a session of strength exercise and reported decreased average concentrations of glucose over
24 hours, and reduced prevalence of hyperglycemia in all groups. On the other hand, some studies
did not demonstrate positive effects of a strength exercise session on insulin sensitivity. Chapman et
al [18] reported no change in post-strength exercise glucose or insulin during an intravenous glucose
tolerance test in sedentary postmenopausal women. A lack of a positive effect on insulin sensitivity
after strength exercise was also observed in strength-trained men [19], healthy individuals [20], obese
women [21], and individuals with prediabetics and DM2 [22, 23]. Taken together, the literature
pertaining to the acute effects of a strength exercise session on insulin sensitivity is somewhat
conflicting.

Variables related to the prescription of strength exercise may help explain the inconsistency
observed in improving insulin sensitivity. For instance, Brown et al [24] identified prescription features
that seemed related to improvements in insulin sensitivity, although the literature was not
systematically reviewed, nor was a metanalysis conducted in that study. Nevertheless, it was
suggested that concentric muscular failure (characterized as the inability to continue the set due to
failure in the concentric moment of the movement of a given repetition), multi-joint (as opposed to
single-joint), and higher number of sets per exercise (which means higher exercise volume) were
variables associated with improvements in insulin sensitivity after a strength exercise session. In
support of the later, the suggestion that improved insulin sensitivity follows a high-volume session is
corroborated by results from a recent systematic review and metanalysis that reported that strength
exercise sessions with 21 sets or more shows a greater improvement in glycemic control compared to
sessions with fewer than 21 sets [25].

Despite the indication that high-volume would result in better insulin sensitivity, current
recommendations suggest that a strength exercise program could be composed of 8 to 10 exercises
and 1 to 3 sets for each exercise [26], which results in a wide range of exercise volumes during a
given session. It must be stressed, however, that very few studies directly investigated how session
volume impacts on insulin sensitivity. Reed et al [27] studied the effects of 10 vs 30 sets performed in
a circuit style on normoglycemic women and found a reduction of the area under the glucose curve
only after the high-volume session. Unfortunately, the prescription of strength exercise in circuit
prevents inferences for traditional strength exercise, and the study’s protocol was biased toward the
high-volume, as effort in every set was presumably further away from concentric failure in the low- vs the high-volume condition. Furthermore, Black et al [28] evaluated the effect of 8 vs 32 sets performed with high and moderate load, and observed improvements in insulin sensitivity in all protocols, with low-volume protocols showing lower effect. In that study, the degree of effort in each set is not reported and arguably different among conditions. These few existing studies in the literature, as well as their clear methodological limitations, show the need for more research on the effects of strength exercise volume on insulin sensitivity.

Another important point regarding the prescription of strength exercise volume on insulin sensitivity are the factors that prevent people from regularly engaging in exercise training. When asked about non-adherence to an exercise protocol, the most frequent justification is lack of time [29]. In addition, low self-efficacy (self-perception of the inability to accomplish something) is also one of the reasons why people do not exercise frequently, and the lower the person's training status, the lower self-efficacy they have [30]. Additionally, other physiological responses such as enjoyment experienced in response to exercise are important factors for long-term adherence [31, 32]. Therefore, investigating the effect of low- and high-volume strength exercise – which leads to low and high time commitment, respectively [33], and can lead to different self-efficacy and enjoyment – on insulin sensitivity can be beneficial to motivate people who claim not to have time to perform strength exercises and for those who feel that they are not able to or do not enjoy performing high-volume strength exercise.

Objectives {7}

Primary objective

The primary objective will be to investigate whether the volume of strength exercise affects insulin sensitivity indexes in overweight/obese individuals.

Secondary objective

Assess the effect of strength exercise session volume on affect, enjoyment, and self-efficacy in overweight/obese individuals.

Trial design {8}

This study will be a randomized controlled, crossover, 3-way, clinical trial. Participants will undergo a health history questionnaire, anthropometric measures, a period of familiarization and strength assessment. After at least 5 days, they will carry out 3 experimental sessions, performed at random, separated by at least 4 (but no more than 28) washout days, as it has been shown that the acute effect of exercise on improved insulin action lasts up to 2 days [34]. In case the experimental sessions are scheduled 21 to 28 days apart, participants will be required to perform a familiarization session 2 weeks after the preceding (and 1 to 2 weeks before the following) experimental session to avoid defamiliarization. To avoid the variation in insulin sensitivity across the menstrual cycle [35–41], in case premenopausal women are included in the sample, they will be assessed in the follicular phase (days 1-14) [16, 27, 42–44] of their menstrual cycle. Two of the sessions will be performed with
strength exercises: high-volume session: 3 sets per exercise; low-volume session: 1 set per exercise; and a control session: no exercise. In the exercise sessions, 7 exercises will be performed for the major muscle groups (1 – hex bar squat; 2 – bench press; 3 – leg press; 4 – lat pulldown; 5 – leg extension; 6 – shoulder press; 7 – leg curl; [Figure 1]), totaling 7 sets in the low-volume session and 21 sets in the high-volume session [25]. The sessions will be held at night, between 8:00 pm and 9:00 pm, and the next morning between 7:00 am and 8:00 am (between 10 and 11 hours after the session), an oral glucose tolerance test (OGTT) will be performed in a local clinical laboratory. Participants will respond to scales of affect, enjoyment, and self-efficacy after the exercise session. All sessions will be supervised by a certified fitness professional. The experimental design is illustrated in Figure 2.
Figure 2. Illustration of the experimental protocol timeline. BMI: body mass index; PACES: physical activity enjoyment scale; OGTT: oral glucose tolerance test; IS: insulin sensitivity.
Methods: Participants, interventions and outcomes

Study setting {9}

This study will be based at the Federal University of the Jequitinhonha and Mucuri Valleys (Diamantina-MG, Brazil) which will provide the equipment and space (DXA, strength training room, strength training equipment, etc.) necessary for conducting the research.

Eligibility criteria {10}

Insulin resistance has been related to increased lipotoxicity, a consequence of an increase in adiposity [45]. Thus, the inclusion criteria are overweight/obese individuals of both sexes (body mass index – BMI > 25 kg/m²), aged over 35 years, with central obesity (waist circumference > 102 cm in men and > 88 cm in women), with stable body mass (±3 kg) in the last 3 months and able to perform physical activity [46]. Exclusion criteria are individuals with signs, symptoms or presence of diabetes or any other metabolic disease, cardiovascular disease, cerebrovascular disease, kidney disease, respiratory disease, and osteoarticular disease [46]. In addition, those who report using any medication that may influence the expected results (including oral contraceptives [47]) and use of anabolic steroids or being pregnant will be excluded. Furthermore, participants who describe dietary supplement intake known to affect exercise performance, such as caffeine, beta-alanine, creatine, and sodium bicarbonate [48] will be excluded.

Who will take informed consent? {26a}

After being thoroughly informed of the study’s risks and benefits, and before initiating participation, subjects will sign an "Informed Consent Form" (model available upon request), previously approved by the local institutional review board.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable, no samples collected.

Interventions

Explanation for the choice of comparators {6b}

Control session – In this session, all procedures (including pre-session instructions) will be identical to the high-volume session, with the exception of performing the strength exercises. However, to simulate all other procedures, participants will follow all instructions and, in the gym, will wear the same clothes, sit on the equipment for the same amount of time as the high-volume session, without any
repetitions being performed. Subjective measures and OMNI will also be responded by the participants mimicking the exercise sessions.

**Intervention description {11a}**

**Pre-participation screening and anthropometric measurements**

Participants will answer a health questionnaire based on the most recent recommendations of the American College of Sports Medicine [46] that will assess possible risks of performing the exercise protocol. Then, they will be submitted to the measurement of body mass and height on an analog scale, with a stadiometer attached, to calculate the BMI. Subsequently, the waist circumference of the participants will be measured. Then, the body composition will be evaluated by means of dual-energy X-ray absorptiometry (DXA, Lunar, iDXA Advanced). Participants will be accommodated in the device, following the manufacturer's instructions for analysis of fat mass, fat-free mass, and visceral fat mass.

**Familiarization**

Familiarization will be carried out on 5 different days in each of the 7 strength exercises, performing 8 repetitions per set and 3 sets per exercise. On the first day, the participant will be instructed to lift a light load, in which performing 8 repetitions is considered “somewhat easy” or between “3” and “4” according to the OMNI-RES scale [49]. In the second session, a load considered “somewhat hard” or between “5” and “7” should be lifted. In the third session, the load will be considered “hard”, or between “7” and “9”. In the 4th session, they should lift loads between “hard” and “extremely hard” or between “9” and “10”, mimicking the effort expected in the strength test itself. The interval between sets will be 90 to 120 seconds. After being familiarized with the exercises and effort, a fifth familiarization session to the strength tests will be performed during which the test itself will be mimicked (see below in Strength tests). In all sessions, the correct technique of performing the exercises (range of motion, duration of concentric:eccentric phases (~1:2 sec; aka tempo) will be carefully observed, and corrections will be made. Furthermore, in every session, participants will be familiarized with the subjective measurements (affect, enjoyment, and self-efficacy, see below). All sessions will be supervised by a certified fitness professional. The interval between familiarization days will be at least 48 but no more than 168 hours (2 to 7 days).

**Strength tests**

At least 72 hours after the last familiarization session, participants will perform 8-repetition maximum (RM) tests on each of the 7 exercises. The aim is to find the maximum load lifted for 8 repetitions. After an initial 5 minutes warm-up walking on a treadmill (~3-4 km/h), and 1 set with low-load (12 reps, ~40-50% 1RM, ~3-4 OMNI), the participant will be instructed to perform 8 repetitions, and the load will gradually increase with each set performed until the participant is able to perform only 8 repetitions (with full range of motion and tempo ~1:2 sec). The rest period between attempts will be between 120 and 180 seconds [50]. All tests will be performed under the supervision of the same person, and the results will serve as a basis for prescribing the load during the exercise sessions.

**Dietary control**
In the first laboratory visit (anthropometric measurements), participants will be instructed by a certified nutritionist on how to log their diet in a notebook on 3 nonconsecutive days of the week, one of the days being on the weekend [51]. Using the data collected from the participants, daily caloric intake in kilocalories (kcals) and kcals consumed from lipids, protein and carbohydrates will be analyzed using nutritional software (Dietbox Software, Brazil). Thereafter, a food plan will be given to the participants who will follow exactly the same food plan during the day before and the day of the experimental sessions. This food plan will not change the composition and amounts of the daily basis food consumption of the participants, but they will be instructed to consume the same meals and the same amounts of food at the same time of the day during the experimental protocol days, including a pre-session meal composed of 65% carbohydrates, 15% proteins, and 20% lipids one hour before reporting to the gym (~6:30 pm). Frequent text messages will be sent to participants to ensure they followed instructions. Adherence to dietary instructions will be verified by assessing their food record. Immediately after the experimental sessions, a standard snack (65% carbohydrates, 15% proteins, and 20% lipids) will be offered, which will be ingested between 9:00 and 9:30 pm at the gym where the sessions will take place, with calories determined from the individual daily needs, plus the estimated net energy expenditure of the session [52]. Participants will be instructed not to consume food after the offered snack and must fast until the morning of the next day to perform the OGTT in a local laboratory.

**Interventions**

Participants will be instructed not to perform moderate/high intensity physical activity during the 48 hours that precede the experimental sessions. Frequent text messages will be sent to participants to ensure they follow instructions. Adherence to physical activity instructions will be verified before each session by asking the participants.

**High-volume session** – All sessions will be held at the university facilities and will always be accompanied by a certified fitness professional. Participants will report to the gym at 7:30 pm, where they will remain at rest, only receiving guidance on the exercises to be performed and will respond to the pre-session affect scale (see below in **Subjective measurements**), as suggested by Alves et al [53]. The experimental session will start at 8:00 pm and will be as follows: an initial 5 minutes warm-up walking on a treadmill (~3-4 km/h), followed by 7 strength exercises that recruit the major muscle groups, performed in the order presented below: 1 – hex bar squat; 2 – bench press; 3 – leg press; 4 – lat pulldown; 5 – leg extension; 6 – shoulder press; 7 – leg curl. Participants will perform 3 sets with the previously determined 8RM load, with as many repetitions per set as they tolerate (until concentric muscular failure – determined as the inability to maintain full range of motion or the inability to maintain time [~1:2 sec] for 2 consecutive repetitions, or by voluntary fatigue of the participant), with a rest of 120 s between sets and between exercises. At the end of each set, they will respond to the OMNI-RES scale to ensure that they have reached maximum effort (9 or 10 on the scale). The number of repetitions performed in each set will be recorded to calculate the total exercise volume-load [54]. Based on pilot studies, sometimes the participant might not be able to complete the first rep of a given set, especially for latter exercises (e.g. leg extension and leg curl). In case that happens, if the participant is unable to complete the first rep of a given set, we will not consider that set, will reduce the load by 5-10%, and give them 1 minute to rest after which another attempt will be made. If
even after this the participant is unable to complete the first rep of the set, we will consider that the
can be 0, and will move on to the next exercise, or finish the session (if this
during the last exercise, e.g. leg curl). Also based on pilot studies, we anticipate this session
will end between approximately 8:45 and 8:55 pm. Then, participants will remain sedentary, answer
the affect, enjoyment, and self-efficacy scales (see below in Subjective measurements), and then
ingest the standard meal described above between 9:00 and 9:30 pm, after which they will be sent
home, and requested not to ingest anything else. After an overnight fast, they will report to a clinical
analysis laboratory the next day in the morning (between 07:00 and 08:00 am) to perform the OGTT.
Thus, the interval between the end of the session and the OGTT will be ~10 to 11 hours.

Low-volume session – In this session, all procedures will be identical to session 1, with the
exception of the number of sets performed; in this case, only 1 set will be performed in each of the 7
strength exercises. This session will last ~15-20 min. To avoid variations in the time between the end
of the session and the OGTT, this session will start between 8:35-8:40 pm so that it ends at the same
time as the high-volume session.

Criteria for discontinuing or modifying allocated interventions {11b}
Subjects’ participation will be discontinued in case of withdraw of the consent, or in case the interval
between sessions is higher than 28 days for any reason. We will report reasons for withdrawal and
discuss the reasons qualitatively.

Strategies to improve adherence to interventions {11c}
Frequent text messages will be sent to participants to ensure they follow instructions. Adherence to
physical activity instructions will be verified before each session by asking the participants.

Relevant concomitant care permitted or prohibited during the trial {11d}
Participants will be instructed not to perform moderate/high intensity physical activity during the 48
hours that precede the experimental sessions.

Provisions for post-trial care {30}
Participants will be reimbursed for expenses incurred due to the research and resulting from it. At any
time if they suffer any damage, unarguably resulting from this research, they will be entitled to
compensation, full and immediate assistance, free of charge for as long as necessary.

Outcomes {12}
Primary outcomes – OGTT-derived indexes
After ~9-10 hours of overnight fasting and ~10-11 hours after each session, participants will
report to a local clinical laboratory, and a blood sample will be collected (minute 0). Then, they will
ingest 75 grams of glucose in 300 ml of water, and blood samples will be collected every 30 minutes
until 120 minutes after glucose ingestion, totaling 5 withdrawals (minute 0, minute 30, minute 60, minute 90, and minute 120). Plasma concentrations of glucose, insulin, and C-peptide (a marker of beta-cell insulin production) will be analyzed in each sample.

**Secondary outcomes**

- **Lipid profile.** Fasting blood samples will be analyzed for the lipid profile (total cholesterol and fractions and triglycerides).

- **Subjective measurements.** To verify affect, the scale described by Hardy and Rejeski [55] and validated to Portuguese by Alves et al [53] will be used. This scale will be answered by the participants before and after the experimental session [53]. To assess enjoyment the physical activity enjoyment scale (PACES) described by Kendzierski and DeCarlo [56] and validated in Portuguese by Alves et al [53] will be used. To assess self-efficacy, a scale proposed by McAuley et al [57] will be used, modified for the context of the present study.

**Participant timeline {13}**

The protocol description followed the SPIRIT [58] and the TIDieR [59] guidelines (figure 3).
<table>
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<tr>
<th>TIMEPOINT**</th>
<th>Enrolment</th>
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<th>Allocation</th>
<th>Interventions</th>
<th>Post Intervention</th>
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OGTT: oral glucose tolerance test

*Sessions order is randomized with >3-day washout period
Sample size {14}
The sample size was calculated from the literature [10, 14, 15, 17, 18, 22, 24, 27, 28] using the G*Power program (Heinrich-Heine-Universität Düsseldorf, Germany, version 3.1.9.6), inserting the parameters for a one-way ANOVA, effect size of 0.6, probability of error type alpha of 0.05 and power (probability of error type 1 – beta) of 0.9. With these parameters, 14 individuals will be needed (actual power of 0.93). Due to the usual sample loss of 25-40%, we will initially recruit 20 participants.

Recruitment {15}
Participants will be from the local community (Diamantina, MG – Brazil) and the project will be publicized through social media, posters at strategic points in the city, and word of mouth. After showing interest, participants will receive information by the researchers (LFRS or FCM) about the objectives of the work, possible discomforts, risks and benefits before volunteering.

Assignment of interventions: allocation

Sequence generation {16a}
The order in which the experimental sessions will be held will be randomized with the aid of the website https://www.randomizer.org.

Concealment mechanism {16b}
The random orders generated by the program will be printed and inserted inside opaque, sequentially numbered envelopes, which will later be sealed. After completing the strength tests, the envelope will be opened, and the sequence of experimental sessions that will be followed will be revealed.

Implementation {16c}
A research collaborator not directly involved in data collection.

Assignment of interventions: Blinding

Who will be blinded {17a}
Employees from the local clinical laboratory responsible for blood harvesting, processing, and analysis will be blinded to allocation. For that, participants will be instructed not to reveal details about the protocol to the clinical laboratory personnel. Moreover, the researcher responsible for data and statistical analyses will remain blind to allocation until completion of analysis. Allocation will only be revealed after statistics are run.
In case there are doubts about data entry (missing values, or values outside the reference range), the researcher responsible for data analysis will contact the collaborator outside the research team responsible for double entry of the data to check accuracy.

**Procedure for unblinding if needed** {17b}
Due to characteristics inherent to this trial (exercise), blinding of participants and researchers involved in data collection is not possible.

**Data collection and management**

**Plans for assessment and collection of outcomes** {18a}
With the insulin and glucose results from minute 0 (fasting values), insulin resistance will be calculated from the model of insulin resistance homeostasis (HOMA-IR) using the formula glucose (mmol) x insulin (µU/mL) ÷ 22.5 [60], and insulin sensitivity using the quantitative insulin sensitivity check index [61]. Insulin sensitivity indexes will be derived from the OGTT data [62], such as the oral glucose insulin sensitivity index [63], the Matsuda insulin sensitivity index [64] and Cederholm's index [65], muscle insulin sensitivity index [66, 67], glucose-stimulated insulin sensitivity index [21], oral disposition index [68, 69], Gutt index [70], Avignon et al. [71], Belfiore et al. index [72], Stumvoll et al. index [73], and McAuley et al. index [74]. In addition, the area under the glucose, insulin, and C-peptide curves will be calculated using the trapezoidal method [75].

**Plans to promote participant retention and complete follow-up** {18b}
In order to promote participant retention, frequent text messages will be sent as reminders to follow the instructions, and to show up in the scheduled sessions. Also, in case the participant misses a session, all effort will be made to reschedule as long as it is within 28 days of the previous session. Dropout reason will be recorded and reported in the manuscript.

**Data management** {19}
A collaborator outside the research team will double entry data coded for allocation into a computer in separate spreadsheets so that the researcher responsible for data analysis can assess data without having access to information about the allocation.

**Confidentiality** {27}
To ensure confidentiality, all study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access controlled by the principal investigator (FCM). All laboratory specimens, reports, data collection, process, and administrative forms will be identified by a coded ID number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such informed consent forms, will be stored separately from study records identified by code number. No personal information from participants will be released outside the study.
Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use (33)
Not applicable, no samples collected for this purpose.

Statistical methods

Statistical methods for primary and secondary outcomes (20a)
Data will be expressed as the mean and standard deviation, with a confidence interval of 95%. For the analysis of data normality, we will perform the Shapiro-Wilk test. For normally distributed data, analysis of variance will be used with one source of variation (experimental situation). If a significant main effect is observed, post hoc Tukey test will be used. For non-parametric data, the Kruskal-Wallis test will be used, or Friedman’s test, when necessary. The effect size will be calculated and interpreted as follows: 0.2 = low effect, 0.5 = medium effect, and greater than 0.8 = high effect [76, 77]. The significance level will be 5%. The Prisma program (GraphPad Software, San Diego, CA-USA – version 8.4.0) will be used to analyze the results. The trial will be reported following the CONSORT guidelines [78, 79].

Interim analyses (21b)
There will be no interim analysis.

Methods for additional analyses (e.g. subgroup analyses) (20b)
Not applicable, no analysis will be conducted for this purpose.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data (20c)
The statistical analysis will be conducted following the principles of intention-to-treat analysis [80]. Thus, data from subjects will be assessed as randomized, regardless of whether they received the randomized treatment, meaning that even if they fail to follow the physical activity and diet pre- and post-session instructions, or fail to complete the sessions as required (e.g. fail to achieve 9-10 in the OMNI scale), or fail to perform the OGTT at the schedule time [so-called non-adheres], their data will be included in the analyses. Furthermore, we will also analyze the data “per protocol” [81], meaning that participants who deviate from instructions will be excluded from final analyses. Differences in results stemming from intention-to-treat and per protocol analyses will be discussed accordingly. The available variables will also be compared between participants who withdraw from the study and those who remain. Incomplete datasets
(e.g. participant who complete 1 or 2 of the 3 sessions) will be analyzed via sensitivity analysis of augmented data sets. Dropouts will be included in the analysis by modern imputation methods for missing data [82].

Plans to give access to the full protocol, participant level-data and statistical code {31c}
Full access to the complete dataset will be permitted only to LFRS and to FCM.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}
Not applicable, there will be no steering committee.

Composition of the data monitoring committee, its role and reporting structure {21a}
Not applicable, there will be no steering committee.

Adverse event reporting and harms {22}
Adverse events related or nonrelated to the research protocol experienced by participants during study (e.g. skeletomuscular injury, having a cold, etc.) will be carefully recorded and reported in the final manuscript.

Frequency and plans for auditing trial conduct {23}
Not applicable, there will be no auditing.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}
Any modifications to the protocol will be submitted to the ethics committee, followed by an updating of the trial registry.

Dissemination plans {31a}
The results stemming from this trial will be published in journals of the field regardless of the magnitude or direction of the outcomes.

Discussion
Potential impact and significance of the study
An acute bout of strength exercise has been shown to effectively improve insulin action and glucose metabolism [24]. However, current recommendations for the prescription of strength exercise suggest that 8
to 30 sets could be performed [26], which means a ~4-fold difference in exercise volume and thus time commitment. Furthermore, high-volume strength exercise might discourage individuals with low self-efficacy, which might diminish adherence to a training program. Therefore, assessing the effects of low- vs high-volume strength exercise on insulin action and glucose metabolism bears clinical relevance because if low-volume strength exercise elicits improvement in these parameters, individuals might be more motivated and feel more confident in performing low-volume strength exercise.

**Strengths and weaknesses**

**Strengths.** This study will be a randomized clinical trial. Additionally, to reduce the risk of bias, the researcher who will perform the stats will be blinded to the treatment. Furthermore, we will employ principles of intention-to-treat analysis [80], and we will assess the characteristics of those participants who do not complete the trial and compare them to those who do complete the trial. The strength exercises selection was based on studies that suggested using at least 21 sets per session [25], performing multi-joint exercises that recruit large muscle mass, carrying the sets to or close to concentric muscular failure, and allowing 120 seconds recovery between sets and exercises [24]. Additionally, we will have a prolonged period of familiarization to ensure that participants are performing the exercises correctly, and a certified fitness professional will be present at every session. Finally, we will ask participants to follow the diet prescribed by a certified nutritionist and we will verify whether participants followed the prescribed diet by assessing their food logs. Moreover, we will provide a standard, individualized, energy expenditure-adjusted meal after the sessions to ensure that energy and carbohydrate replenishment are not confounding factors on post-exercise insulin sensitivity [83, 84]. Finally, although the OGTT might not be the gold-standard tool to assess insulin sensitivity compared to the euglycemic-hyperinsulinemic clamp (EHC), ingesting 75 grams of glucose it is considered to be a more physiological stimulus compared the supraphysiological insulin levels during EHC [85]. Moreover, the insulin sensitivity indexes that will be calculated from OGTT in the present study show high correlation (r=0.61 and 0.96) [86] with EHC results. Also, OGTT is considered reliable and consistent for estimating insulin sensitivity over consecutive days [87]. Last, but not the least, the majority of studies that assessed the acute effects of a strength exercise session on insulin sensitivity employed OGTT as the assessment tool [12, 16, 27, 42, 88–95].

**Weaknesses.** This study cannot be completed in a double-blind manner, as the participants and the researchers who will be present during the sessions will be aware of the treatment (high- or low-volume or control session). However, the professionals at the clinical lab who will collect and analyze the blood will be blinded to treatment, as well as the researcher who will perform the stats. We will include overweight/obese men and women over 35 years old, so our results might not be readily translated to other clinical populations, such as younger, healthy individuals or DM2 patients. Furthermore, individuals with potentially different levels of insulin resistance might be included in this study, and greater exercise-induced improvement in insulin resistance has been observed in individuals with higher levels of baseline insulin resistance [27, 96]. Thus, this factor can also increase results variability. Finally, participants might not follow the dietary and physical activity instructions the day before and the day of the sessions, which might also be confounding factors when interpreting our results. However, we will stress the importance of following the physical activity instructions by sending frequent text messages, and adherence to instructions will be
verified when they report to the gym. Finally, we will ask them to report what they ate to the nutritionist, which we believe increases adherence to diet prescription.

**Trial status**

The protocol version is #3, Dec 8th, 2023. Recruitment is to start Jan, 2024. Anticipated recruitment completion is April, 2024.

**Abbreviations**

- Body mass index (BMI)
- Diabetes Mellitus (DM)
- Euglycemic-hyperinsulinemic clamp (EHC)
- Insulin sensitivity (IS)
- Kilocalories (kcals)
- Model of insulin resistance homeostasis (HOMA-IR)
- Oral glucose tolerance test (OGTT)
- Repetition maximum (RM)
- Type 2 Diabetes Mellitus (DM2)

**Declarations**

**Acknowledgements**

We thank the Federal University of the Jequitinhonha and Mucuri Valleys (Diamantina-MG, Brazil) which will provide the equipment and space (DXA, strength training room, strength training equipment, etc.) necessary for conducting the research. We acknowledge the funding agencies that supported this study (National Council for Scientific and Technological Development (CNPQ: Grant#407975/2018-7 and # 402091/2021-3) and by the Minas Gerais State Agency for Research and Development (FAPEMIG: Grant# APQ-00008-22).

**Authors’ contributions {31b}**

uis Filipe Rocha Silva, Bruna Caroline Chaves Garcia, Elizabethe Adriana Esteves, Valmor Tricoli, and Flávio de Castro Magalhães contributed to the concept and design of the study, established the hypothesis,
and wrote the first draft of the manuscript. Marco Fabrício Dias-Peixoto, Fernando Gripp, Fabiano Trigueiro Amorim and Zachary A Mang performed critical revisions of the manuscript. All authors approved the final version of the manuscript.

**Funding {4}**

This study is supported by the National Council for Scientific and Technological Development (CNPQ: Grant#407975/2018-7 and # 402091/2021-3) and by the Minas Gerais State Agency for Research and Development (FAPEMIG: Grant# APQ-00008-22). The funders played no role in this study's design, and will not play any roles in study conduct, interpretation of data, or reporting of results.

**Availability of data and materials {29}**

The datasets used and/or analyzed during the current study will be made available from the corresponding author upon reasonable request.

**Ethics approval and consent to participate {24}**

This study was approved by the local institutional review board (the Research Ethics Committee of the Federal University of the Jequitinhonha and Mucuri Valleys - certificate number CAAE 63190422.0.0000.5108). The present study was prospectively registered in a clinical trial registry (ReBEC #RBR-3vj5dc5 https://ensaiosclinicos.gov.br/rg/RBR-3vj5dc5).

**Consent for publication {32}**

This manuscript does not contain individual personal data from patients.

**Competing interests {28}**

None declared.

**Authors’ information (optional)***

* Address all correspondence to Dr de Castro Magalhaes: fcm@unm.edu

**References**

64. Matsuda M, DeFronzo RA (1999) Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 22:1462–1470
Supplement file

### WHO Trial Registration Data Set

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<td><strong>Contact for Public Queries</strong></td>
<td>Dr Magalhães: <a href="mailto:fcm@unm.edu">fcm@unm.edu</a></td>
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<tr>
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