# Statistical analysis plan (SAP)

# Type 1 interferon induced changes to exercise adaptations in systemic lupus erythematosus patients

Version: 0.1

Version date: April 22, 2024

Trial registration: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

Trial registration number: NCT05478018

Ethical committee: Capital Region of Denmark

Approval number: **H-21039032**

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## BACKGROUND AND RATIONAL

Systemic lupus erythematosus (SLE) is a rare chronic autoimmune disease with a varied phenotype and a predisposition for women of childbearing age1. Systemic involvement of skin, joints and internal organs are based on a complex interaction between distinct immunopathogenic pathways including overexpression of interferons (IFN) 2,3. Disease manifestations comprise flares interspaced by periods of inactive disease, cumulative accrual of organ damage and constitutive symptoms such as pain and fatigue3–7.

Patients with SLE also suffer from reduced exercise capacity with lower improvement in maximal oxygen uptake (V̇O2max) and fatigue severity scores (FSS) following moderate continuous exercise training (MCT) compared to healthy controls7–9.

High-intensity interval-training (HIIT) is a broad category of aerobic exercise programs. High intensity typically refers to exercising above a certain heart rate, ranging from 75% to 95% of the maximal heart rate (HRmax)10,11. Interval training refers to interspacing these high intensity intervals with durations ranging from 15 seconds to 5 minutes with lower intensity buffers. Multiple sets of these intervals will then compromise a total exercise duration of one session ranging from 20 to 180 minutes11,12. These individual HIIT sessions are then repeated 2-5 times weekly10–12.

Compared to MCT, HIIT has proven particularly effective at increasing V̇O2max and alleviating fatigue in several other populations than SLE-patients, including healthy13,14, middle-aged15, and elderly women16,17, heart failure patients10,12, as well as pre- and perioperative cancer patients11,18. As of now, no randomised controlled studies have investigated the impact of HIIT on fatigue or V̇O2max in SLE.

The fatigue and exercise impairment reported by patients with SLE remains unexplained but may reflect aberrations in immune function and physical adaptations to exercise19. Pathway analyses indicate a central role of IFN driven immune activation in SLE20. In this respect, overexpression of type I IFNs (IFN-I) is of particular interest; often reported as a composite score reflecting whole blood mRNA expression of IFN regulated genes, denoted as the IFN gene signature (IFNGS)21.

Among the various effects of IFN-I is suppression of interleukin 6 (IL-6) signalling; in ex vivo studies, IFN-I has been found to attenuate IL-6 -induced phosphorylation of transducer and activator of transcription 3 (STAT3) leading to an abrogation of IL-6 activated intracellular pathways. Furthermore, IFN-I induces transcription of the suppressor of cytokine signalling 3 (SOCS3) gene further inhibiting IL-6 signaling22,23.   
IL-6 is a cytokine with both pro- and anti-inflammatory effects, it has multiple sources including contracting skeletal muscle24. IL-6 in humans can cause lipolysis 25, increase glucose uptake and glycogen storage in skeletal muscle26, and it may supress production of proinflammatory cytokines such as TNF and IL-1β 27,28. Furthermore, it has been shown that IL-6 is required for exercise induced loss of visceral adipose tissue in overweight adults29.

Based on these observations, this study hypothesises that in patients with SLE followed in routine care, a high IFNGS, predicts poorer improvement in aerobic capacity and fatigue following a 12- week HIIT intervention.

## OBJECTIVES

### Primary aim:

The primary aim is to investigate if increasing IFN-I activity determined by IFNGS negatively influences any effect of a 12-week supervised HIIT vs. no intervention on aerobic exercise capacity by V̇O2max or fatigue by FSS in patients with SLE.

### Secondary aims:

The secondary aim is to investigate if IFNGS negatively influences any effects of 12-week HIIT on measures of SLE disease activity and health related quality of life.

### Primary objective:

Investigate the effect of HIIT relative to the no exercise control comparator on changes in aerobic capacity and fatigue following a 12 week intervention.

Furthermore, to investigate the effect modulation of IFNGS on this effect.

### Key secondary objective:

Examining the effects of physical activity on SLE-disease activity and health related quality of life, and investigating any effect modulation of IFNGS on this effect.

### Other objectives:

Examine the effect of 12 weeks of HIIT on the pulmonary function of SLE patients. Considering effect modulation by IFNGS.

Examine the effects of exercise on the cardiac adaptations of SLE patients. Considering effect modulation by IFNGS.

Examine the effects of exercise on metabolic markers of SLE patients. Considering effect modulation by IFNGS.

Examine the effects of exercise on body composition in SLE paitents. Considering effect modulation by IFNGS.

Examine the effect of 12 weeks of HIIT on the transcriptome related to IFN-I, IFN-II, TNF, and IL-6 in SLE patients.

## HYPOTHESES

### Primary Hypotheses

12 weeks of HIIT exercise will increase aerobic capacity as compared to no intervention control.

This effect can be modulated by IFNGS.

12 weeks of HIIT exercise will decrease fatigue scores, as compared to no intervention control.

This effect can be modulated by IFNGS.

The hierarchy of the hypotheses and subsequent claims for the primary outcome are as follows;

1. HIIT is superior to no intervention control at improving aerobic capacity. Superiority is claimed if the difference is statistically significant and favors the HIIT intervention.
   1. The effect of HIIT on aerobic capacity is modulated by IFNGS, such that a higher IFNGS results in lower benefits of HIIT.
2. HIIT is superior to no intervention control at alleviating fatigue. Superiority is claimed if the difference is statistically significant and favors the HIIT intervention.
   1. The effect of HIIT on fatigue is modulated by IFNGS, such that a higher IFNGS results in less decrease of initial fatigue from HIIT.

### Secondary Hypotheses

The hierarchy of thesecondary hypotheses and subsequent claims are as follows;

1. HIIT is superior to no intervention control at reducing SLE symptoms.
   1. This effect is modulated by IFNGS.
2. HIIT is superior to no intervention control at improving health related quality of life.
   1. This effect is modulated by IFNGS.

### Exploratory Hypotheses

The hierarchy of the exploratory hypotheses and subsequent claims are as follows;

1. HIIT is superior to no intervention control at reducing pain in SLE patients.
   1. This effect is modulated by IFNGS.
2. HIIT is superior to no intervention control at increasing the lean mass of SLE patients.
   1. This effect is modulated by IFNGS.
3. HIIT is superior to no intervention control at decreasing total adipose tissue.
   1. This effect is modulated by IFNGS.
4. HIIT is superior to no intervention control at decreasing the waist-to-height ratio.
   1. This effect is modulated by IFNGS.
5. HIIT is superior to no intervention control at inducing cardiac remodeling
   1. The effect of HIIT on aerobic capacity is modulated by IFNGS, such that a higher IFNGS results in lower benefits of HIIT.
6. HIIT is superior to no intervention control at alleviating fatigue.

## TRIAL DESIGN, DATA COLLECTION AND OUTCOMES ASSESSMENT

The study protocol, detailing the hypotheses, methods, recruitment and conduct of the study has been published in a non-peer reviewed openly accessible preprint database30. In brief, the study is a randomized control trial, consisting of 2 arms, labeled exercise and control. Participants are stratified for sex and randomly allocated 1:1 to exercise or control. At [www.clinicaltrials.gov](http://www.clinicaltrials.gov) the study is identified by NCT05478018. Prior to commencement the scientific ethics committee of the capital region of Denmark approved to trial with identifier H-21039032. The trial primarily took place at Centre for Physical Activity on Rigshospitalet, Ole Maaløes Vej 24, in Copenhagen, Denmark. Recruitment took place primarily at the center for vasculitis and spine diseases on Rigshospitalet in Blegdamsvej 9, Copenhagen, Denmark. 82-Rb-Pet-CT scans were conducted at the department of clinical physiology at Rigshospitalet, Blegdamsvej 9, Copenhagen, Denmark.

The exercise group underwent 12 weeks of thrice weekly 45 minute HIIT exercise sessions, with 4 intervals of 4 minutes of high intensity exercise, defined as a heart rate above 85% of the maximal heart rate interspaced with 3 minute active breaks of pedaling against light resistance (less than 20% wattmax).

As noted above the hypothesis was that these 12 weeks would improve aerobic capacity and fatigue in SLE patients. But it would improve more in patients with lower IFNGS.

Participants flow through the project with a screening visit, where aerobic capacity is assessed, a baseline visit with most of the outcomes, and a baseline-acute bout session consisting of one exercise bout and the measurements of the autonomic nerve system. A subgroup of patients will then undergo a 82-Rb-rest-stress-PET-CT evaluating cardiac adaptation. Patients are then randomized to exercise or control. Whereafter they will undergo a followup visit, another acute bout (termed the follow-up acute bout) and at last if they did one at baseline, they will do a repeat 82-Rb-rest-stress-PET-CT.

## OUTCOMES

### Primary outcomes

#### Domain: Aerobic Capacity

Timeframe: -2, 0 to 12 weeks

Measurement: Maximal volume of inspired oxygen per minute per kilogram of body weight of the participant (VO2Max).

* Measured during a maximal exercise bout. Maximal defined as two out of three of the following:
  + Plateau in volume of inspired oxygen per minute. So that increase in workload results in no increase in inspired oxygen.
  + Ratio between volume of inspired oxygen and expired carbondioxide more than 1.1
  + Exertion by BORG scale 18, 19 or 20.

If the bout is considered a maximal bout, the VO2max will be defined as the highest 30 second average oxygen uptake per minute per kilogram of bodyweight. (in ml/min/kg)

* Volumes of gases measured by indirect calorimetry.
* Heart rate during the bout is measured by PolarFlow™

#### Domain: Fatigue – Patient reported

Timeframe: 0 to 12 weeks

Measurement:

* Patient reported outcome measure (PROM).
* Krupp’s Fatigue severity scale31, as the average of all 9 domains (0-7).
* This scale has been verified for use in Danish SLE patients32.

### Key Secondary Outcome

#### Domain: Physician evaluated changes in measures of SLE

Timeframe: 0 to 12 weeks

Measurement: Y2K updated SLE disease activity (SLEDAI-2K) with the SELENA modifications33.

### Other secondary outcomes

#### Domain: Patient reported outcome quality of life.

Timeframe: 0 to 12 weeks

Measurement:

* Short Form (SF)-36 Health Survey (0-100)34 - Possible scores range from 0 to 100, with higher scores representing better health status.

#### Domain: Type 1 Interferon gene signature

Timeframe: 0 to 12 weeks

Measurement: Pax-gene tubes withdrawn from fasting participants at baseline.

* Analyzed by Nanostring for genes related to IFN-signaling.35
* Normalized to housekeeping genes
* Calculating a standardized z-score compared to the expression from 9 healthy controls

### Exploratory outcomes

#### Domain: Physician evaluated changes in disease activity

Timeframe: 0 to 12 weeks

Measurement:

* Itemized Physician evaluated changes in measures of SLE on a scale from 0-22 that account for partial improvements in condition. Evaluated by the Systemic Lupus Erythematosus Disease Activity Index 2000 Responder Index-50 (SRI-50)36.
* Disease activity as evaluated by a physician familiar with SLE diagnosis based on physical examination and patient history on a scale of 0 to 100, higher score indicating more active disease.

#### Domain: Patient reported outcome measures

Timeframe: 0 to 12 weeks

Measurements:

* Total fatigue as assessed by the participant on a visual analog scale from 0-100, higher scores equal less fatigue.
* Total pain on a visual analog scale of 0-100, higher scores equal more pain (worse).
* Quick systemic lupus activity questionnaire (Q-SLAQ) as reported by the Q-SLAQ questionnaire (translated to Danish by author MLA)37. Possible scores range from 0 to 33, with higher scores representing more active SLE (worse)
* SLE activity on a visual analog scale of 0-10 higher scores equal more active disease (worse).

#### Domain: Kidney disease

Timeframe: 0 to 12 weeks

Measurements:

* Measured by proteinuria.
* Measured by plasma-creatinine.

#### Domain: Body Composition

Timeframe: 0 to 12 weeks

Measurements:

By DEXA scan:

* Total adipose tissue by weight/percentage.
* Android adipose tissue by weight/percentage.
* Gyneoid adipose tissue by weight/percentage.
* Total lean mass by weight.
* Bone Mass density by weight per area.

By tape measure

* Waist to height ratio

#### Domain: Lung Function

Timeframe: 0 to 12 weeks

Measurements:

By dynamic spirometry

* Forced Expiratory Volume at 1 second (FEV1) as volume / percentage of expected.
* Forced vital capacity as volume / percentage of expected.
* Forced expiratory volume by forced vital capacity – ratio between volumes / percentages.
* Total lung capacity – volume / percentage of expected.
* Residual Lung volume – volume / percentage of expected.
* Alveolar volume – volume / percentage of expected.
* Diffusing capacity for carbon mono-oxide – volume / percentage of expexted.
* Carbon mono-oxide transfer coefficient – diffusing capacity per liter of lung volume – ratio / percentage of expected

#### Domain: Metabolic adaptations

Timeframe: 0 to 12 weeks

Measurements: Measured during an OGTT at 0, 15, 30, 60, 90, and 120 minutes following consumption of 83g of glucose in 250mL of water.

* Plasma concentration of glucose.
* Plasma concentration of insulin.
* Plasma concentration of pro-insulin c-peptide.
* Overall changes in the curves will be compared.
* Matsuda Index will be calculated
* AUC will be calculated

Measurements: Measured following an overnight fast, at the 0 minute mark of the OGTT

* Plasma concentration of total cholesterol
* Plasma concentration of triglycerides
* Plasma concentration of LDL-cholesterol
* Plasma concentration of VLDL-cholesterol
* Plasma concentration of HDL-cholesterol

#### Domain: Peripheral Capillary adaptations

Timeframe: 0 to 12 weeks

Measurements: Measured by nailfold capillaroscopy by a trained physician, twice before and twice after intervention. Analyzed for:

* Capillary density - score of 1-4, higher scores equal fewer capillaries
* Average capillary width – in µm
* Average capillary length – in µm
* Count of avascular areas - score of 1-4, higher scores indicate more avascular areas
* Capillary disorganization - score of 1-4, higher scores indicate more disorganization
* Microhemmorhages – count per finger
* Bushy capillaries – average number per millimeter
* Mega capillaries – average number per millimeter
* Meandering capillaries – average number per millimeter
* Tortuous capillaries – average number per millimeter
* Other findings – physicians comment

#### Domain: Cardiac adaptations

Timeframe: 0 to 12 weeks

Measurements:

Measured bedside:

* Systolic blood pressure at rest
* Diastolic blood pressure at rest
* Heart rate at rest

Measured by echocardiography by a trained physician

* Left ventricular end-diastolic volume
* Left atrial end-diastolic volume
* Global longitudinal strain
* Stroke volume
* Left ventricular ejection fraction
* Left ventricular mass
* Coronary perfusion reserve

Measured by 82Rb-rest-stress-Pet-CT on a subset of patients (30-40 depending on patient opt-in), stress will be conducting with low-dose adenosine:

* Coronary perfusion reserve
* Myocardial flow reserve
* Ventricular volumes at rest and stress
* Atrial volumes at rest and stress
* Ventricular and atrial ejection fractions at rest and stress
* Splenic response ratio
* Splenic stress-to-rest intensity ratio
* Heart rate at rest and stress
* Rate pressure product
* Systolic blood pressure at rest and stress
* Cardiovascular resistance at rest and stress

#### Domain: Free-living physical activity

Timeframe: 0 to 12 weeks

Measurements:

* Free-living physical activity measured using axial accelerometer-based physical activity monitors (AX3; Axivity, Newcastle upon Tyne, UK) for a 5 day period

#### Domain: Acute exercise bout

Timeframe: 0 to 12 weeks

Description: Subjects arrive fasted and then undergo a 45minute exercise sessions consisting of 4 intervals of 4 minutes and interspaced with active rest, starting with a 10 minute warmup and ending with a 10 minute cooldown, peripheral blood will be sampled 9 times at the following timepoints (in minutes): -5 (before going on the bike), 0 (on the bike before first pedaling), 10 (after warmup), 14 (after first interval), 35 (after last interval), 45 (after cooldown), 60 (resting for 15 minutes after getting off the bike), 90 (resting for 45 minutes after getting off the bike), and 105 (resting for 60 minutes after getting off the bike)

Measurements: concentration in peripheral blood:

* High Sensitivity C-Reactive Protein
* Interleukin-6
* Soluble Interleukin-6 receptor
* Interleukin-1
* Interleukin-10
* Interferon α
* Interferon γ
* Hemoglobin
* Thrombocytes
* Sodium
* Potassiumn
* Chloride
* Hematocrit
* Ferritin
* Leukocyte Differential count

Measurements: Subject adaptations to exercise

* Heart rate (continuous throughout session)
* Resistance in high intensity intervals
* Subject exhaustion by Borg Scale (6-20 higher scores equal more exhaustion) during, warmup, each interval and following cooldown.

#### Domain: Pro- and anti-inflammatory related mRNA expression

Timeframe: 0 to 12 weeks

Description: as with the secondary outcome, mRNA segments of genes related to the following signaling pathways will be measured using Nanostring™

Measurements:

* Expression related to IFN-β
* Expression related to IFN Gamma
* Expression related to TNF
* Expression related to IL-6

#### Domain: Dietary changes

Timeframe: 0-2 to 12-14 weeks

Description: Subjects will be tasked to fill in dietary diaries for three consecutive representative days at baseline and followup. Using standard calculations energy intake and macronutrients will be calculated from this diary.

Measurements:

* Energy intake (kJ/day)
* Carbohydrate intake (g/day)
* Lipid intake (g/day)
* Protein intake (g/day)
* Other intake (categorical)

#### Domain: Changes to muscles

Timeframe: 0 to 12 weeks

Description: A subset of volunteering subjects who will undergo muscle biopsy can deliver baseline and followup muscular biopsies

Measurements:

* Muscle Biopsy transcriptomic analysis of genes related to TNF, IL-6, IFN alpha, beta and Gamma signalling.
* NF-κB p65 DNA binding activity (ELISA), phosphorylated and total JNK, phosphorylated AMPK (p-AMPK) total AMPK (Western blotting).
* NF-κB p65 DNA binding activity (ELISA) & NF-κB binding activity (Western blotting).
* Phosphorylated and total c-Jun N-terminal kinase
* AMP-activated protein kinase

#### Domain: Autonomic Nerve Function testing

Timeframe: 0-2 to 12-14 weeks

Description: By Vagus™, a device measuring heart rate and heart rate variability will measure:

Measurements:

* Resting heart rate
* Ratio between minimal and maximal heart rate when the subject is:
  + Rising from supine
  + Controlled breathing exercises
  + Doing the Valsalva maneuver

## STUDY POPULATION, ANALYSIS SET AND STATISTICAL PRINCIPLES

Eligibility criteria have been previously published 30. The

## STATISTICAL METHODS

The primary analysis will be performed using a linear mixed effect model with an unstructured covariance matrix. The primary model will be aerobic capacity by time and treatment:time interaction

Analysis will be done in an updated version of R38. The LMMstar package39 will be used for the primary analysis, the LME4 package40 will be used as a comparator, but assuming the results are similar only the LMMstar results will be published. The code will be available on Github (<https://github.com/Malte-Lund/Lupex-Statistics> )

## DEVIATIONS FROM THE ORIGINAL PROTOCOL

## IMPLEMENTATION OF THE SAP

## EXPECTED WRITING COMMITTEE

Malte Lund Adamsen, Simon Jønck, Marie Louise L Petersen, Clara Egelund, Iben Rasmussen, Mark Lyngbæk, Julie Lyng Forman, Anna A. Lützen, Kanwal Zahid Siddiqi, Helga Ellingsgaard, Phillip Hasbak, Louise Diederichsen, Regitse H Christensen, Ronan M. G. Berg, Bente K. Pedersen, Pil Højgaard, Søren Jacobsen

Acknowledgements

We would like to thank the patient panel (in alphabetical order, last names omitted to preserve anonymity): Anne-Maren, Ea, Mette, Rasmus

## EXPECTED OUTLINE OF THE REPORT

The study report will be aimed at a clinical journal, thus the report will contain 3500-4000 words and 4 to 6 main figures and tables depending on the journal.

## OVERVIEW OF CONTENT (Unformatted tables with specific variables are placed at the end of the text)

## TABLES (In paper)

Baseline characteristics

## FIGURES (In paper)

Table of graphs depicting the within group values of primary and key secondary outcomes at measurement timepoints. Regression lines depicted with mean estimates and 95% confidence interval of the linear mixed effect regression.

## SUPPLEMENTAL ONLY (Tables)

1. Self-reported adherence to diet
2. Adverse rea
3. Adverse reactions & events following randomization

## SUPPLEMENTAL ONLY (Figures)

Flow of participants

Figure detailing the acute exercise bout

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## UNFORMATTED TABLES WITH INTENDED CONTENT

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 1 Baseline characteristics** | | | |
|  | Control | Exercise | Total |
| Age (years) |  |  |  |
| Sex (N (%) female) |  |  |  |
| SLE duration (years) |  |  |  |
| SLE activity markers |  |  |  |
| SLEDAI |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
| B2MG |  |  |  |
| LYMPHOCYTES |  |  |  |
| THROMBOCYTES |  |  |  |
|  |  |  |  |
| Antibodies |  |  |  |
| ANTI-sm |  |  |  |
| ANTI-DsDNA |  |  |  |
| NEITHER ANTI-DsDNA or ANTI-sm |  |  |  |
| Glucose-lowering medication, N (%) |  |  |  |
| None |  |  |  |
| Biguanide |  |  |  |
| Biguanide **+** SGLT2i **or** DPP4i |  |  |  |
| Biguanide + SGLT2i **+** DPP4i |  |  |  |
| Lipid-lowering medication, No (%) |  |  |  |
| None |  |  |  |
| Statin |  |  |  |
| Blood pressure lowering medication, No (%) |  |  |  |
| None |  |  |  |
| ARB **or** ACEi |  |  |  |
| ARB **or** ACEi + Thiazide **or** CCB |  |  |  |
| ARB **or** ACEi + Thiazide + CCB |  |  |  |
| Physical function |  |  |  |
| Absolute VO2 max (ml/min) |  |  |  |
| Relative VO2 max (ml/kg/min) |  |  |  |
| Watt max (W/kg) |  |  |  |
| 1 RM chest press (kg) |  |  |  |
| 1 RM leg extension (kg) |  |  |  |
| Body composition |  |  |  |
| Body weight (kg) |  |  |  |
| BMI (kg/m2) |  |  |  |
| Diet |  |  |  |
| Energy intake (kcal/day) |  |  |  |
| Physical activity level |  |  |  |
| Moderate and vigorous physical activity (hours/day) |  |  |  |
| Stepping (steps/day) |  |  |  |
| Sitting (hours/day) |  |  |  |
| Hyperglycemic clamp |  |  |  |
| Basal |  |  |  |
| Mean insulin secretion rate |  |  |  |
| Glucose Ra (mg \* kg−1 \* min−1) |  |  |  |
| Glucose Rd (mg \* kg−1 \* min−1) |  |  |  |
| Early phase hyperglycemia |  |  |  |
| Mean GIR (mg \* kg−1 \* min−1) |  |  |  |
| Mean insulin secretion rate |  |  |  |
| Peak insulin secretion rate |  |  |  |
|  |  |  |  |
| **Table 1 cont’d** |  |  |  |
| Steady state hyperglycemia |  |  |  |
| Late phase disposition index |  |  |  |
| Late phase insulin sensitivity index |  |  |  |
| Late phase insulin secretion rate |  |  |  |
| Mean GIR (mg \* kg−1 \* min−1) |  |  |  |
| Peak insulin secretion rate |  |  |  |
| Glucose Ra (mg \* kg−1 \* min−1) |  |  |  |
| Glucose Rd (mg \* kg−1 \* min−1) |  |  |  |
| Hyperglycemia and GLP-1 |  |  |  |
| Mean GIR (mg \* kg−1 \* min−1) |  |  |  |
| Mean insulin secretion rate |  |  |  |
| Peak insulin secretion rate |  |  |  |
| Hyperglycemia, GLP-1 and Arginine |  |  |  |
| Mean insulin secretion rate |  |  |  |
| Peak insulin secretion rate |  |  |  |
| Mixed meal tolerance test |  |  |  |
| 0-30 min |  |  |  |
| tAUC glucose |  |  |  |
| tAUC C-peptide |  |  |  |
| tAUC insulin |  |  |  |
| tAUC GLP-1total |  |  |  |
| tAUC GLP-1active |  |  |  |
| tAUC GIPtotal |  |  |  |
| tAUC paracetamol |  |  |  |
| 0-120 min |  |  |  |
| Oral disposition index |  |  |  |
| Oral insulin sensitivity index |  |  |  |
| tAUC glucose |  |  |  |
| tAUC C-peptide |  |  |  |
| tAUC insulin |  |  |  |
| tAUC GLP-1total |  |  |  |
| tAUC GLP-1active |  |  |  |
| tAUC GIPtotal |  |  |  |
| tAUC paracetamol |  |  |  |
| Data are presented as mean (SD) or median (IQR). CON, control group, DCON: Diet control group: MED: Moderate volume exercise, HED: High volume exercise, HbA1c: glycated hemoglobin A1c, LDL: low-density lipoprotein, BMI: body mass index (calculated as weight in kilograms divided by height in meters squared). SLGT2i: selective sodium glucose co-transporter 2 inhibitors*,* DPP4i*:* dipeptidyl peptidase 4 inhibitors, ARB: angiotensin II receptor blockers, ACEi: angiotensin converting enzyme inhibitors, CCB: calcium channel blockers. Ra: Rate of appearance, Rd: Rate of disappearance, GIR: Glucose infusion rate | | | |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 2 Within-group changes from baseline to 16-week follow-up in the primary and major secondary outcomes | | | | | | | | | | |
|  | CON | | DCON | | MED | | | HED | |
|  | Change | 95% CI | Change | 95% CI | Change | 95% CI | Change | | 95% CI |
|  |  |  |  |  |  |  |  | |  |
| Primary outcome |  |  |  |  |  |  |  | |  |
| Late-phase Disposition index |  |  |  |  |  |  |  | |  |
|  |  |  |  |  |  |  |  | |  |
| Major Secondary outcomes |  |  |  |  |  |  |  | |  |
| Late-phase insulin secretion rate |  |  |  |  |  |  |  | |  |
| Late-phase insulin sensitivity |  |  |  |  |  |  |  | |  |
| Oral disposition index |  |  |  |  |  |  |  | |  |
| Oral insulin sensitivity index |  |  |  |  |  |  |  | |  |
| Oral insulinogenic index |  |  |  |  |  |  |  | |  |
|  |  |  |  |  |  |  |  | |  |
| Data are least-squares means. CI: confidence intervals, CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise, | | | | | | | | | | |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 3 Pairwise comparisons of the change in the primary outcome and major secondary outcomes | | | | | | | | | | | | | | | | | | | |
|  | | | | | | | | | | | | | | | | | | | |
|  | HED vs. CON | |  | MED vs. CON | |  | DCON vs. CON | |  | HED vs. DCON | |  | MED vs. DCON | |  | HED vs. MED | | P |
|  | MD | 95% CI |  | MD | 95% CI |  | MD | 95% CI |  | MD | 95% CI |  | MD | 95% CI |  | MD | 95% CI |  |
| Primary outcome |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Late-phase Disposition index |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Major Secondary outcomes |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Insulin secretion rate |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Insulin sensitivity |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Oral disposition index |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Oral insulin sensitivity index |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Oral insulinogenic index |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| MD: Mean difference, CI: confidence intervals. CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise | | | | | | | | | | | | | | | | | | | |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 4 Within-group changes from baseline to 16-week follow-up in in other outcomes reflecting underlaying mechanisms of beta-cell function | | | | | | | | | | |
|  | CON | | DCON | | MED | | | HED | |
|  | Change | 95% CI | Change | 95% CI | Change | 95% CI | Change | | 95% CI |
| Basal |  |  |  |  |  |  |  | |  |
| Mean insulin secretion rate |  |  |  |  |  |  |  | |  |
| Glucose Ra (mg \* kg−1 \* min−1) |  |  |  |  |  |  |  | |  |
| Glucose Rd (mg \* kg−1 \* min−1) |  |  |  |  |  |  |  | |  |
| Early state hyperglycemia |  |  |  |  |  |  |  | |  |
| Mean GIR (mg \* kg−1 \* min−1) |  |  |  |  |  |  |  | |  |
| Mean insulin secretion rate |  |  |  |  |  |  |  | |  |
| Peak insulin secretion rate |  |  |  |  |  |  |  | |  |
| Steady state hyperglycemia |  |  |  |  |  |  |  | |  |
| Mean GIR (mg \* kg−1 \* min−1) |  |  |  |  |  |  |  | |  |
| Peak insulin secretion rate |  |  |  |  |  |  |  | |  |
| Glucose Ra (mg \* kg−1 \* min−1) |  |  |  |  |  |  |  | |  |
| Glucose Rd (mg \* kg−1 \* min−1) |  |  |  |  |  |  |  | |  |
| Hyperglycemia and GLP-1 |  |  |  |  |  |  |  | |  |
| Mean GIR (mg \* kg−1 \* min−1) |  |  |  |  |  |  |  | |  |
| Mean insulin secretion rate |  |  |  |  |  |  |  | |  |
| Peak insulin secretion rate |  |  |  |  |  |  |  | |  |
| Hyperglycemia, GLP-1 and Arginine |  |  |  |  |  |  |  | |  |
| Mean insulin secretion rate |  |  |  |  |  |  |  | |  |
| Peak insulin secretion rate |  |  |  |  |  |  |  | |  |
|  |  |  |  |  |  |  |  | |  |
| 0-30 min |  |  |  |  |  |  |  | |  |
| tAUC glucose |  |  |  |  |  |  |  | |  |
| tAUC C-peptide |  |  |  |  |  |  |  | |  |
| tAUC insulin |  |  |  |  |  |  |  | |  |
| tAUC GLP-1total |  |  |  |  |  |  |  | |  |
| tAUC GLP-1active |  |  |  |  |  |  |  | |  |
| tAUC GIPtotal |  |  |  |  |  |  |  | |  |
| tAUC paracetamol |  |  |  |  |  |  |  | |  |
| 0-120 min |  |  |  |  |  |  |  | |  |
| tAUC glucose |  |  |  |  |  |  |  | |  |
| tAUC C-peptide |  |  |  |  |  |  |  | |  |
| tAUC insulin |  |  |  |  |  |  |  | |  |
| tAUC GLP-1total |  |  |  |  |  |  |  | |  |
| tAUC GLP-1active |  |  |  |  |  |  |  | |  |
| tAUC GIPtotal |  |  |  |  |  |  |  | |  |
| tAUC paracetamol |  |  |  |  |  |  |  | |  |
|  |  |  |  |  |  |  |  | |  |
| Data are least-squares means. CI: confidence intervals, CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise, GIR: glucose infusion rate, Ra: Rate of appearance, Rd: Rate of disappearance: GLP-1: Glucagon-like-peptide 1, GIP: Gastric inhibitory polypeptide, tAUC: Total area under the curve | | | | | | | | | | |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 5 Pairwise comparisons of the change in other outcomes reflecting underlying mechanisms of beta-cell function | | | | | | | | | | | | | |
|  | HED vs. CON | | MED vs. CON | | DCON vs. CON | | | HED vs. DCON | | MED vs. DCON | | HED vs. MED | |
|  | MD | 95% CI | MD | 95% CI | | MD | 95% CI | MD | 95% CI | MD | 95% CI | MD | 95% CI |
|  | Hyperglycemic clamp | | | | | | | | | | | | |
| Basal |  | |  | |  | | |  | |  | |  | |
| Mean insulin secretion rate |  |  |  |  | |  |  |  |  |  |  |  |  |
| Glucose Ra (mg \* kg−1 \* min−1) |  |  |  |  | |  |  |  |  |  |  |  |  |
| Glucose Rd (mg \* kg−1 \* min−1) |  |  |  |  | |  |  |  |  |  |  |  |  |
| Early state hyperglycemia |  |  |  |  | |  |  |  |  |  |  |  |  |
| Mean GIR (mg \* kg−1 \* min−1) |  |  |  |  | |  |  |  |  |  |  |  |  |
| Mean insulin secretion rate |  |  |  |  | |  |  |  |  |  |  |  |  |
| Peak insulin secretion rate |  |  |  |  | |  |  |  |  |  |  |  |  |
| Steady state hyperglycemia |  |  |  |  | |  |  |  |  |  |  |  |  |
| Mean GIR (mg \* kg−1 \* min−1) |  |  |  |  | |  |  |  |  |  |  |  |  |
| Peak insulin secretion rate |  |  |  |  | |  |  |  |  |  |  |  |  |
| Glucose Ra (mg \* kg−1 \* min−1) |  |  |  |  | |  |  |  |  |  |  |  |  |
| Glucose Rd (mg \* kg−1 \* min−1) |  |  |  |  | |  |  |  |  |  |  |  |  |
| Hyperglycemia and GLP-1 |  |  |  |  | |  |  |  |  |  |  |  |  |
| Mean GIR (mg \* kg−1 \* min−1) |  |  |  |  | |  |  |  |  |  |  |  |  |
| Mean insulin secretion rate |  |  |  |  | |  |  |  |  |  |  |  |  |
| Peak insulin secretion rate |  |  |  |  | |  |  |  |  |  |  |  |  |
| Hyperglycemia, GLP-1 and Arginine |  |  |  |  | |  |  |  |  |  |  |  |  |
| Mean insulin secretion rate |  |  |  |  | |  |  |  |  |  |  |  |  |
| Peak insulin secretion rate |  |  |  |  | |  |  |  |  |  |  |  |  |
|  | Mixed meal tolerance test | | | | | | | | | | | | |
| 0-30 min |  |  |  |  | |  |  |  |  |  |  |  |  |
| tAUC glucose |  |  |  |  | |  |  |  |  |  |  |  |  |
| tAUC C-peptide |  |  |  |  | |  |  |  |  |  |  |  |  |
| tAUC insulin |  |  |  |  | |  |  |  |  |  |  |  |  |
| tAUC GLP-1total |  |  |  |  | |  |  |  |  |  |  |  |  |
| tAUC GLP-1active |  |  |  |  | |  |  |  |  |  |  |  |  |
| tAUC GIPtotal |  |  |  |  | |  |  |  |  |  |  |  |  |
| tAUC paracetamol |  |  |  |  | |  |  |  |  |  |  |  |  |
| 0-120 min |  |  |  |  | |  |  |  |  |  |  |  |  |
| tAUC glucose |  |  |  |  | |  |  |  |  |  |  |  |  |
| tAUC C-peptide |  |  |  |  | |  |  |  |  |  |  |  |  |
| tAUC insulin |  |  |  |  | |  |  |  |  |  |  |  |  |
| tAUC GLP-1total |  |  |  |  | |  |  |  |  |  |  |  |  |
| tAUC GLP-1active |  |  |  |  | |  |  |  |  |  |  |  |  |
| tAUC GIPtotal |  |  |  |  | |  |  |  |  |  |  |  |  |
| tAUC paracetamol |  |  |  |  | |  |  |  |  |  |  |  |  |
| MD: Mean difference, CI: confidence intervals. CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise, GIR: glucose infusion rate, Ra: Rate of appearance, Rd: Rate of disappearance: GLP-1: Glucagon-like-peptide 1, GIP: Gastric inhibitory polypeptide, tAUC: Total area under the curve | | | | | | | | | | | | | |

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| eTable 1 Adherence to diet | | | | | | | |  |  |
|  | Baseline (N=) | Week 4 (N=) | % adherence | Week 12 (N=) | % adherence | Week 16 (N=) | % adherence | % adherence after randomization | Mean reduction after randomization (% from baseline) |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| Total energy intake (Kcal/kg/day) |  |  |  |  |  |  |  |  |  |
| CON |  |  |  |  |  |  |  |  |  |
| DCON |  |  |  |  |  |  |  |  |  |
| MED |  |  |  |  |  |  |  |  |  |
| HED |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| Total carbohydrate (% of total energy intake) |  |  |  |  |  |  |  |  |  |
| CON |  |  |  |  |  |  |  |  |  |
| DCON |  |  |  |  |  |  |  |  |  |
| MED |  |  |  |  |  |  |  |  |  |
| HED |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| Fiber (% of total energy intake) |  |  |  |  |  |  |  |  |  |
| CON |  |  |  |  |  |  |  |  |  |
| DCON |  |  |  |  |  |  |  |  |  |
| MED |  |  |  |  |  |  |  |  |  |
| HED |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| Total fat (% of total energy intake) |  |  |  |  |  |  |  |  |  |
| CON |  |  |  |  |  |  |  |  |  |
| DCON |  |  |  |  |  |  |  |  |  |
| MED |  |  |  |  |  |  |  |  |  |
| HED |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| Saturated fat (% of total energy intake) |  |  |  |  |  |  |  |  |  |
| CON |  |  |  |  |  |  |  |  |  |
| DCON |  |  |  |  |  |  |  |  |  |
| MED |  |  |  |  |  |  |  |  |  |
| HED |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| Protein (% of total energy intake) |  |  |  |  |  |  |  |  |  |
| CON |  |  |  |  |  |  |  |  |  |
| DCON |  |  |  |  |  |  |  |  |  |
| MED |  |  |  |  |  |  |  |  |  |
| HED |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| Alcohol (% of total energy intake) |  |  |  |  |  |  |  |  |  |
| CON |  |  |  |  |  |  |  |  |  |
| DCON |  |  |  |  |  |  |  |  |  |
| MED |  |  |  |  |  |  |  |  |  |
| HED |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| Data are mean and standard deviation or median and interquartile range. CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise | | | | | | | | | |

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| eTabel 2 self-reported adherence to pharmacological treatmenta and management | | | | | | | | | | | | | | | | |
|  | Baseline |  |  |  | Week 4 |  |  |  | Week 12 |  |  |  | Week 16 |  |  |  |
|  | CON | DCON | MED | HED | CON | DCON | MED | HED | CON | DCON | MED | HED | CON | DCON | MED | HED |
| Proportion of participants attending consultation |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Self-reported adherence to Glucose-lowering medication |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Several times per week |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Once a week |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Several times per month |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Once a month |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Never |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Not relevant |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Does not take prescribed medication |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Missing values |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Self-reported adherence to blood pressure-lowering medication |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Several times per week |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Once a week |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Several times per month |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Once a month |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Never |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Not relevant |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Does not take prescribed medication |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Missing values |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Self-reported adherence to lipid-lowering medication |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Several times per week |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Once a week |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Several times per month |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Once a month |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Never |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Not relevant |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Does not take prescribed medication |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Missing values |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Glucose-lowering medication, N (%) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| None |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Biguanide |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Biguanide **+** SGLT2i **or** DPP4i |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Biguanide + SGLT2i **+** DPP4i |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lipid-lowering medication, No (%) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| None |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Statin |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood pressure lowering medication, No (%) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| None |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ARB **or** ACEi |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ARB **or** ACEi + Thiazide **or** CCB |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ARB **or** ACEi + Thiazide + CCB |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Data presented as N (%)  There were five adherence categories in relation to how often the participants would forget to take their medicine: 1) several times per week 2) once a week 3) several times per month 4) once a month 5) never.  Adherence (%) in these categories is calculated as follows: Total N - (does not take the prescribed medicine + numbers of participants with no medication + missing values) since adherence is calculated based on the participants that are prescribed medication and taking the medication. Not the total number of participants (N).  aHow often does the participant forget the medication | | | | | | | | | | | | | | | | |

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| eTable 3 Free-living physical activity | | | | |
|  | Baseline (N=) | Week 4 (N=) | Week 12 (N=) | Week 16 (N=) |
|  |  |  |  |  |
| Valid days (N) |  |  |  |  |
| CON |  |  |  |  |
| DCON |  |  |  |  |
| MED |  |  |  |  |
| HED |  |  |  |  |
|  |  |  |  |  |
| Wear time (hours/day) |  |  |  |  |
| CON |  |  |  |  |
| DCON |  |  |  |  |
| MED |  |  |  |  |
| HED |  |  |  |  |
|  |  |  |  |  |
| Total physical activity (counts per minute) |  |  |  |  |
| CON |  |  |  |  |
| DCON |  |  |  |  |
| MED |  |  |  |  |
| HED |  |  |  |  |
|  |  |  |  |  |
| MVPA (min/day) |  |  |  |  |
| CON |  |  |  |  |
| DCON |  |  |  |  |
| MED |  |  |  |  |
| HED |  |  |  |  |
|  |  |  |  |  |
| Sitting time (min/day) |  |  |  |  |
| CON |  |  |  |  |
| DCON |  |  |  |  |
| MED |  |  |  |  |
| HED |  |  |  |  |
|  |  |  |  |  |
| Stepping (steps/day) |  |  |  |  |
| CON |  |  |  |  |
| DCON |  |  |  |  |
| MED |  |  |  |  |
| HED |  |  |  |  |
|  |  |  |  |  |
| Data are mean and standard deviation or median and interquartile range. CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise, MVPA: Moderate and vigorous physical activity | | | | |

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| eTable 4 Intensity and duration in aerobic training | | | | | | | |
| Intensity (internal and external load) in aerobic training | | | | | | | |
| Familiarization week 1-2 | Average %HRmax, N (%) | | Number of minutes 60-79% HRmax, (N=) | Number of minutes 80-100% HRmax, (N=) | Minutes spent in 80-100% HRmax, N (%) | Average watt, (N=) |  |
| MED |  | |  |  |  |  |  |
| HED |  | |  |  |  |  |  |
| Week 3-10 | Average %HRmax, N (%) | | Number of minutes 60-79% HRmax, (N=) | Number of minutes 80-100% HRmax, (N=) | Minutes spent in 80-100% HRmax, N (%) | Average watt, (N=) | Increase in average watt from week 1-2 to 3-10 N (%) |
| MED |  | |  |  |  |  |  |
| HED |  | |  |  |  |  |  |
| Week 11-16 | Average %HRmax, N (%) | | Number of minutes 60-79% HRmax, (N=) | Number of minutes 80-100% HRmax, (N=) | Minutes spent in 80-100% HRmax, N (%) | Average watt, (N=) | Increase in average watt from week 3-10 to week 11-16 N (%) |
| MED |  | |  |  |  |  |  |
| HED |  | |  |  |  |  |  |
| Week 3-16 | Number of minutes 60-79% HRmax, (N=) | | Number of minutes 80-100% HRmax, (N=) | Number of minutes within target %HRmax, N (%) | Minutes spent in 80-100% HRmax, N (%) | Average watt, (N=) | Increase in average watt from week 3 to week 16, N (%) |
| MED |  | |  |  |  |  |  |
| HED |  | |  |  |  |  |  |
| Duration of aerobic training | | | | | | | |
| Familiarization week 1-2 | Number of minutes prescribed pr. week, (N=) | Number of minutes performed pr week, (N=) | | Number of minutes completed from prescribed, N (%) | Number of minutes performed within target %HRmax, N (%) | Number of minutes pr. sessions, (N=) | Number of sessions pr. week, (N=) |
| MED |  |  | |  |  |  |  |
| HED |  |  | |  |  |  |  |
| Week 3-10 | Number of minutes prescribed pr. week, (N=) | Number of minutes performed pr week, (N=) | | Number of minutes completed from prescribed, N (%) | Number of minutes performed within target %HRmax, N (%) | Number of minutes pr. sessions (N=) | Number of sessions pr. week, (N=) |
| MED |  |  | |  |  |  |  |
| HED |  |  | |  |  |  |  |
| Week 11-16 | Number of minutes prescribed pr. week, (N=) | Number of minutes performed pr week, (N=) | | Number of minutes completed from prescribed, N (%) | Number of minutes performed within target %HRmax, N (%) | Number of minutes pr. sessions (N=) | Number of sessions pr. week, (N=) |
| MED |  |  | |  |  |  |  |
| HED |  |  | |  |  |  |  |
| Week 3-16 | Number of minutes prescribed pr. week, (N=) | Number of minutes performed pr week, (N=) | | Number of minutes completed from prescribed, N (%) | Number of minutes performed within target %HRmax, N (%) | Number of minutes pr. sessions (N=) | Number of sessions pr. week, (N=) |
| MED |  |  | |  |  |  |  |
| HED |  |  | |  |  |  |  |
| Data are mean and standard deviation or median and interquartile range. HRmax: Maximum heart rate, MED: Moderate volume exercise, HED: High volume exercise | | | | | | | |

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| eTable 5 Resistance training in the large muscle groups | | | | |
| Familiarization week 1-2 | Number of sets prescribed pr. week, (N=) | Number of sets performed pr. week, (N=) | Number of sets completed from prescribed, N (%) | Number of sets performed within target RIR, N (%) |
| MED |  |  |  |  |
| Leg press |  |  |  |  |
| Leg extension |  |  |  |  |
| Leg curl |  |  |  |  |
| Chest press |  |  |  |  |
| Back row |  |  |  |  |
| Total |  |  |  |  |
| HED |  |  |  |  |
| Leg press |  |  |  |  |
| Leg extension |  |  |  |  |
| Leg curl |  |  |  |  |
| Chest press |  |  |  |  |
| Back row |  |  |  |  |
| Total |  |  |  |  |
| Week 3-10 | Number of sets prescribed pr. week, (N=) | Number of sets performed pr. week, (N=) | Number of sets completed from prescribed, N (%) | Number of sets performed within target RIR, N (%) |
| MED |  |  |  |  |
| Leg press |  |  |  |  |
| Leg extension |  |  |  |  |
| Leg curl |  |  |  |  |
| Chest press |  |  |  |  |
| Back row |  |  |  |  |
| Total |  |  |  |  |
| HED |  |  |  |  |
| Leg press |  |  |  |  |
| Leg extension |  |  |  |  |
| Leg curl |  |  |  |  |
| Chest press |  |  |  |  |
| Back row |  |  |  |  |
| Total |  |  |  |  |
| Week 11-16 | Number of sets prescribed pr. week, (N=) | Number of sets performed pr. week, (N=) | Number of sets completed from prescribed, N (%) | Number of sets performed within target RIR, N (%) |
| MED |  |  |  |  |
| Leg press |  |  |  |  |
| Leg extension |  |  |  |  |
| Leg curl |  |  |  |  |
| Chest press |  |  |  |  |
| Back row |  |  |  |  |
| Total |  |  |  |  |
| HED |  |  |  |  |
| Leg press |  |  |  |  |
| Leg extension |  |  |  |  |
| Leg curl |  |  |  |  |
| Chest press |  |  |  |  |
| Back row |  |  |  |  |
| Total |  |  |  |  |
| Week 3-16 | Number of sets prescribed pr. week, (N=) | Number of sets performed pr. week, (N=) | Number of sets completed from prescribed, N (%) | Number of sets performed within target RIR, N (%) |
| MED |  |  |  |  |
| Leg press |  |  |  |  |
| Leg extension |  |  |  |  |
| Leg curl |  |  |  |  |
| Chest press |  |  |  |  |
| Back row |  |  |  |  |
| Total |  |  |  |  |
| HED |  |  |  |  |
| Leg press |  |  |  |  |
| Leg extension |  |  |  |  |
| Leg curl |  |  |  |  |
| Chest press |  |  |  |  |
| Back row |  |  |  |  |
| Total |  |  |  |  |
| Data are mean and standard deviation or median and interquartile range. RIR: repetitions in reserve, MED: Moderate volume exercise, HED: High volume exercise | | | | |

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| --- | --- | --- | --- | --- | --- | --- |
| eTable 6 Volume load (tonnage) in resistance training in the large muscle groups | | | | | | |
| Familiarization week 1-2 | Number of repetitions pr week, (N=) | Number of repetitions pr. set, (N=) | Average kilogram lifted pr. set, (N=) | Number of sets performed pr week, (N=) | Tonnage pr week, (N=) |  |
| MED |  |  |  |  |  |  |
| Leg press |  |  |  |  |  |  |
| Leg extension |  |  |  |  |  |  |
| Leg curl |  |  |  |  |  |  |
| Chest press |  |  |  |  |  |  |
| Back row |  |  |  |  |  |  |
| Total |  |  |  |  |  |  |
| HED |  |  |  |  |  |  |
| Leg press |  |  |  |  |  |  |
| Leg extension |  |  |  |  |  |  |
| Leg curl |  |  |  |  |  |  |
| Chest press |  |  |  |  |  |  |
| Back row |  |  |  |  |  |  |
| Total |  |  |  |  |  |  |
| Week 3-10 | Number of repetitions pr week, (N=) | Number of repetitions pr. set, (N=) | Average kilogram lifted pr. set, (N=) | Number of sets performed, (N=) | Tonnage pr week, (N=) | Tonnage increase from week 1-2 to week 3-10, N (%) |
| MED |  |  |  |  |  |  |
| Leg press |  |  |  |  |  |  |
| Leg extension |  |  |  |  |  |  |
| Leg curl |  |  |  |  |  |  |
| Chest press |  |  |  |  |  |  |
| Back row |  |  |  |  |  |  |
| Total |  |  |  |  |  |  |
| HED |  |  |  |  |  |  |
| Leg press |  |  |  |  |  |  |
| Leg extension |  |  |  |  |  |  |
| Leg curl |  |  |  |  |  |  |
| Chest press |  |  |  |  |  |  |
| Back row |  |  |  |  |  |  |
| Total |  |  |  |  |  |  |
| Week 11-16 | Number of repetitions pr week, (N=) | Number of repetitions pr. set, (N=) | Average kilogram lifted pr. set, (N=) | Number of sets performed, (N=) | Tonnage pr week, (N=) | Tonnage increase from week 3-10 to week 11-16, N (%) |
| MED |  |  |  |  |  |  |
| Leg press |  |  |  |  |  |  |
| Leg extension |  |  |  |  |  |  |
| Leg curl |  |  |  |  |  |  |
| Chest press |  |  |  |  |  |  |
| Back row |  |  |  |  |  |  |
| Total |  |  |  |  |  |  |
| HED |  |  |  |  |  |  |
| Leg press |  |  |  |  |  |  |
| Leg extension |  |  |  |  |  |  |
| Leg curl |  |  |  |  |  |  |
| Chest press |  |  |  |  |  |  |
| Back row |  |  |  |  |  |  |
| Total |  |  |  |  |  |  |
| Week 3-16 | Number of repetitions pr week, (N=) | Number of repetitions pr. set, (N=) | Average kilogram lifted pr. set, (N=) | Number of sets performed, (N=) | Tonnage, (N=) | Tonnage increase from week 3 to week 16, N (%) |
| MED |  |  |  |  |  |  |
| Leg press |  |  |  |  |  |  |
| Leg extension |  |  |  |  |  |  |
| Leg curl |  |  |  |  |  |  |
| Chest press |  |  |  |  |  |  |
| Back row |  |  |  |  |  |  |
| Total |  |  |  |  |  |  |
| HED |  |  |  |  |  |  |
| Leg press |  |  |  |  |  |  |
| Leg extension |  |  |  |  |  |  |
| Leg curl |  |  |  |  |  |  |
| Chest press |  |  |  |  |  |  |
| Back row |  |  |  |  |  |  |
| Total |  |  |  |  |  |  |
| Data are mean and standard deviation or median and interquartile range. Tonnage: weight (kg) x repetitions x sets, MED: Moderate volume exercise, HED: High volume exercise | | | | | | |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| eTable 7 Exercise modification and causes in aerobic training | | | | | | | |
| Familiarization week 1-2 | Fatigue, (N=) | Musculoskeletal discomfort, (N=) | Motivational, (N=) | Other reasons, (N=) | Missed exercises, (N=) | Number of participants with ≥1 modification (%) | Number of sessions with ≥1 modification (%) |
| MED |  |  |  |  |  |  |  |
| HED |  |  |  |  |  |  |  |
| Week 3-10 | Fatigue, (N=) | Musculoskeletal discomfort, (N=) | Motivational, (N=) | Other reasons, (N=) | Missed exercises, (N=) | Number of participants with ≥1 modification (%) | Number of sessions with ≥1 modification (%) |
| MED |  |  |  |  |  |  |  |
| HED |  |  |  |  |  |  |  |
| Week 11-16 | Fatigue, (N=) | Musculoskeletal discomfort, (N=) | Motivational, (N=) | Other reasons, (N=) | Missed exercises, (N=) | Number of participants with ≥1 modification (%) | Number of sessions with ≥1 modification (%) |
| MED |  |  |  |  |  |  |  |
| HED |  |  |  |  |  |  |  |
| Week 3-16 | Fatigue, (N=) | Musculoskeletal discomfort, (N=) | Motivational, (N=) | Other reasons, (N=) | Missed exercises, (N=) | Number of participants with ≥1 modification (%) | Number of sessions with ≥1 modification (%) |
| MED |  |  |  |  |  |  |  |
| HED |  |  |  |  |  |  |  |
| Data are mean and standard deviation or median and interquartile range. MED: Moderate volume exercise, HED: High volume exercise | | | | | | | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| eTable 8 Exercise modification and causes in resistance training | | | | | | | | |
| Familiarization week 1-2 | Fatigue, (N=) | Musculoskeletal discomfort, (N=) | Motivational, (N=) | Other reasons, (N=) | Missed exercises, (N=) | Number of participants with ≥1 modification (%) | Number of sessions with ≥1 modification (%) | |
| MED |  |  |  |  |  |  |  | |
| Leg press |  |  |  |  |  |  |  | |
| Leg extension |  |  |  |  |  |  |  | |
| Leg curl |  |  |  |  |  |  |  | |
| Chest press |  |  |  |  |  |  |  | |
| Back row |  |  |  |  |  |  |  | |
| Total |  |  |  |  |  |  |  | |
| HED |  |  |  |  |  |  |  | |
| Leg press |  |  |  |  |  |  |  | |
| Leg extension |  |  |  |  |  |  |  | |
| Leg curl |  |  |  |  |  |  |  | |
| Chest press |  |  |  |  |  |  |  | |
| Back row |  |  |  |  |  |  |  | |
| Total |  |  |  |  |  |  |  | |
| Week 3-10 | Fatigue, (N=) | Musculoskeletal discomfort, (N=) | Motivational, (N=) | Other reasons, (N=) | Missed exercises, (N=) | Number of participants with ≥1 modification (%) | Number of sessions with ≥1 modification (%) | |
| MED |  |  |  |  |  |  |  | |
| Leg press |  |  |  |  |  |  |  | |
| Leg extension |  |  |  |  |  |  |  | |
| Leg curl |  |  |  |  |  |  |  | |
| Chest press |  |  |  |  |  |  |  | |
| Back row |  |  |  |  |  |  |  | |
| Total |  |  |  |  |  |  |  | |
| HED |  |  |  |  |  |  |  | |
| Leg press |  |  |  |  |  |  |  | |
| Leg extension |  |  |  |  |  |  |  | |
| Leg curl |  |  |  |  |  |  |  | |
| Chest press |  |  |  |  |  |  |  | |
| Back row |  |  |  |  |  |  |  | |
| Total |  |  |  |  |  |  |  | |
| Week 11-16 | Fatigue, (N=) | Musculoskeletal discomfort, (N=) | Motivational, (N=) | Other reasons, (N=) | Missed exercises, (N=) | Number of participants with ≥1 modification (%) | Number of sessions with ≥1 modification (%) | |
| MED |  |  |  |  |  |  |  | |
| Leg press |  |  |  |  |  |  |  | |
| Leg extension |  |  |  |  |  |  |  | |
| Leg curl |  |  |  |  |  |  |  | |
| Chest press |  |  |  |  |  |  |  | |
| Back row |  |  |  |  |  |  |  | |
| Total |  |  |  |  |  |  |  | |
| HED |  |  |  |  |  |  |  | |
| Leg press |  |  |  |  |  |  |  | |
| Leg extension |  |  |  |  |  |  |  | |
| Leg curl |  |  |  |  |  |  |  | |
| Chest press |  |  |  |  |  |  |  | |
| Back row |  |  |  |  |  |  |  | |
| Total |  |  |  |  |  |  |  | |
| Week 3-16 | Fatigue, (N=) | Musculoskeletal discomfort, (N=) | Motivational, (N=) | Other reasons, (N=) | Missed exercises, (N=) | Number of participants with ≥1 modification (%) | Number of sessions with ≥1 modification (%) | |
| MED |  |  |  |  |  |  |  | |
| Leg press |  |  |  |  |  |  |  | |
| Leg extension |  |  |  |  |  |  |  | |
| Leg curl |  |  |  |  |  |  |  | |
| Chest press |  |  |  |  |  |  |  | |
| Back row |  |  |  |  |  |  |  | |
| Total |  |  |  |  |  |  |  | |
| HED |  |  |  |  |  |  |  | |
| Leg press |  |  |  |  |  |  |  | |
| Leg extension |  |  |  |  |  |  |  | |
| Leg curl |  |  |  |  |  |  |  | |
| Chest press |  |  |  |  |  |  |  | |
| Back row |  |  |  |  |  |  |  | |
| Total |  |  |  |  |  |  |  | |
| Data are mean and standard deviation or median and interquartile range. MED: Moderate volume exercise, HED: High volume exercise | | | | | | | |

|  |  |  |  |
| --- | --- | --- | --- |
| eTabel 9 Adherence for aerobic and resistance training | | | |
| Familiarization week 1-2 | Aerobic training, N (%) | Resistance training, N (%) | Total training, N (%) |
| MED |  |  |  |
| HED |  |  |  |
| Week 3-10 | Aerobic training, N (%) | Resistance training, N (%) | Total training, N (%) |
| MED |  |  |  |
| HED |  |  |  |
| Week 11-16 | Aerobic training, N (%) | Resistance training, N (%) | Total training, N (%) |
| MED |  |  |  |
| HED |  |  |  |
| Week 3-16 | Aerobic training, N (%) | Resistance training, N (%) | Total training, N (%) |
| MED |  |  |  |
| HED |  |  | Total training, N (%) |
| Total | Aerobic training, N (%) | Resistance training, N (%) |  |
| MED |  |  |  |
| HED |  |  |  |
| Data are mean and standard deviation or median and interquartile range. RIR: repetitions in reserve, MED: Moderate volume exercise, HED: High volume exercise. Adherence: For prescribed aerobic training ≥ 70% of minutes should be within the target heart rate zones.  For prescribed resistance training, ≥ 70% of the sets should be performed at or below the maximum RIR. | | | |

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| eTable 10 Coefficient of variation and precision during the hyperglycemic clamp | | | | | | | | | | | |
|  | | | | | | | | | | | |
|  | | | | | | | | | | | |
|  | CON |  |  | DCON |  |  | MED |  |  | HED |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
|  | 0 weeks (SD or IQR) | 16 weeks (SD or IQR) |  | 0 weeks (SD or IQR) | 16 weeks (SD or IQR) |  | 0 weeks (SD or IQR) | 16 weeks (SD or IQR) |  | 0 weeks (SD or IQR) | 16 weeks (SD or IQR) |
|  |  |  |  |  |  |  |  |  |  |  |  |
| Coefficient of variance (%) |  |  |  |  |  |  |  |  |  |  |  |
| Basal |  |  |  |  |  |  |  |  |  |  |  |
| Early phase hyperglycemia |  |  |  |  |  |  |  |  |  |  |  |
| Steady phase hyperglycemia |  |  |  |  |  |  |  |  |  |  |  |
| Hyperglycemia + GLP-1 |  |  |  |  |  |  |  |  |  |  |  |
| Hyperglycemia + GLP-1 + Arginine |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| Off-target |  |  |  |  |  |  |  |  |  |  |  |
| Steady phase hyperglycemia |  |  |  |  |  |  |  |  |  |  |  |
| Hyperglycemia + GLP-1 |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| Data are means and standard deviations/median or interquartile ranges at baseline or follow-up or estimated within-group difference in change from baseline to follow-up with 95% confidence intervals. CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise, GIR: glucose infusion rate, Ra: Rate of appearance, Rd: Rate of disappearance: GLP-1: Glucagon-like-peptide 1 | | | | | | | | | | | |

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| eTable 11 Sensitivity analyses - Pairwise comparisons of the change in the primary outcome and indices of beta-cell function and insulin sensitivity | | | | | | | | | | | | | | | | | |
|  | | | | | | | | | | | | | | | | | |
|  | HED vs. CON | P-value |  | MED vs. CON | P-value |  | DCON vs. CON | P-value |  | HED vs. DCON | P-value |  | MED vs. DCON | P-value |  | HED vs. MED | P-value |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Per protocol# |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Primary outcome |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Late-phase Disposition index (hyperglycemic clamp) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Major Secondary outcomes |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Late-phase insulin sensitivity (hyperglycemic clamp) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Late-phase insulin secretion rate (hyperglycemic clamp) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Oral disposition index (MMTT) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Oral insulin sensitivity (MMTT) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Oral insulinogenic index (MMTT) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Imputation |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Primary outcome |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Late-phase Disposition index (hyperglycemic clamp) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Secondary outcomes |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Late-phase insulin sensitivity (hyperglycemic clamp) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Late-phase insulin secretion rate (hyperglycemic clamp) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Oral disposition index (MMTT) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Oral insulin sensitivity (MMTT) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Oral insulinogenic index (MMTT) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Data are estimated mean difference in changes between groups with 95% confidence intervals. CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise, MMTT: Mixed meal tolerance test  # Adjusted for sex, age, diabetes duration, baseline maximal oxygen consumption | | | | | | | | | | | | | | | | | |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| eTable 12 Baseline values and within group changes (0-16 weeks) for other outcomes from the mixed meal tolerance test derived outcomes | | | | | | | | | | | |
|  | | | | | | | | | | | |
|  | CON | |  | DCON | |  | MED | |  | HED | |
|  |  |  |  |  |  |  |  |  |  |  |  |
|  | 0 weeks (SD or IQR) | Change (95% CI) |  | 0 weeks (SD or IQR) | Change (95% CI) |  | 0 weeks (SD or IQR) | Change (95% CI) |  | 0 weeks (SD or IQR) | Change (95% CI) |
|  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| 0-15 min |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| Incremental AUC |  |  |  |  |  |  |  |  |  |  |  |
| iAUC glucose |  |  |  |  |  |  |  |  |  |  |  |
| iAUC C-peptide |  |  |  |  |  |  |  |  |  |  |  |
| iAUC insulin |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GLP-1total |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GLP-1active |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GIPtotal |  |  |  |  |  |  |  |  |  |  |  |
| iAUC paracetamol |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| Total AUC |  |  |  |  |  |  |  |  |  |  |  |
| tAUC glucose |  |  |  |  |  |  |  |  |  |  |  |
| tAUC C-peptide |  |  |  |  |  |  |  |  |  |  |  |
| tAUC insulin |  |  |  |  |  |  |  |  |  |  |  |
| tAUC GLP-1total |  |  |  |  |  |  |  |  |  |  |  |
| tAUC GLP-1active |  |  |  |  |  |  |  |  |  |  |  |
| tAUC GIPtotal |  |  |  |  |  |  |  |  |  |  |  |
| tAUC paracetamol |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| 0-30 min |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| Incremental AUC |  |  |  |  |  |  |  |  |  |  |  |
| iAUC glucose |  |  |  |  |  |  |  |  |  |  |  |
| iAUC C-peptide |  |  |  |  |  |  |  |  |  |  |  |
| iAUC insulin |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GLP-1total |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GLP-1active |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GIPtotal |  |  |  |  |  |  |  |  |  |  |  |
| iAUC paracetamol |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| Total AUC |  |  |  |  |  |  |  |  |  |  |  |
| tAUC glucose |  |  |  |  |  |  |  |  |  |  |  |
| tAUC C-peptide |  |  |  |  |  |  |  |  |  |  |  |
| tAUC insulin |  |  |  |  |  |  |  |  |  |  |  |
| tAUC GLP-1total |  |  |  |  |  |  |  |  |  |  |  |
| tAUC GLP-1active |  |  |  |  |  |  |  |  |  |  |  |
| tAUC GIPtotal |  |  |  |  |  |  |  |  |  |  |  |
| tAUC paracetamol |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| 0-60 min |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| Incremental AUC |  |  |  |  |  |  |  |  |  |  |  |
| iAUC glucose |  |  |  |  |  |  |  |  |  |  |  |
| iAUC C-peptide |  |  |  |  |  |  |  |  |  |  |  |
| iAUC insulin |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GLP-1total |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GLP-1active |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GIPtotal |  |  |  |  |  |  |  |  |  |  |  |
| iAUC paracetamol |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| Total AUC |  |  |  |  |  |  |  |  |  |  |  |
| tAUC glucose |  |  |  |  |  |  |  |  |  |  |  |
| tAUC C-peptide |  |  |  |  |  |  |  |  |  |  |  |
| tAUC insulin |  |  |  |  |  |  |  |  |  |  |  |
| tAUC GLP-1total |  |  |  |  |  |  |  |  |  |  |  |
| tAUC GLP-1active |  |  |  |  |  |  |  |  |  |  |  |
| tAUC GIPtotal |  |  |  |  |  |  |  |  |  |  |  |
| tAUC paracetamol |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| 0-180 min |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| Incremental AUC |  |  |  |  |  |  |  |  |  |  |  |
| iAUC glucose |  |  |  |  |  |  |  |  |  |  |  |
| iAUC C-peptide |  |  |  |  |  |  |  |  |  |  |  |
| iAUC insulin |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GLP-1total |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GLP-1active |  |  |  |  |  |  |  |  |  |  |  |
| iAUC paracetamol |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| Total AUC |  |  |  |  |  |  |  |  |  |  |  |
| tAUC glucose |  |  |  |  |  |  |  |  |  |  |  |
| tAUC C-peptide |  |  |  |  |  |  |  |  |  |  |  |
| tAUC insulin |  |  |  |  |  |  |  |  |  |  |  |
| tAUC GLP-1total |  |  |  |  |  |  |  |  |  |  |  |
| tAUC GLP-1active |  |  |  |  |  |  |  |  |  |  |  |
| tAUC paracetamol |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| Data are means and standard deviations/median or interquartile ranges at baseline or follow-up or estimated within-group difference in change from baseline to follow-up with 95% confidence intervals. CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise, GLP-1: Glucagon-like-peptide 1, GIP: Gastric inhibitory polypeptide, tAUC: total area under the curve, iAUC: incremental area under the curve. | | | | | | | | | | | |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| eTable 13 Other Pairwise comparisons of secondary outcomes derived from the mixed meal tolerance test | | | | | | | | | | | | | | | | | |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | HED vs. CON | P-value |  | MED vs. CON | P-value |  | DCON vs. CON | P-value |  | HED vs. DCON | P-value |  | MED vs. DCON | P-value |  | HED vs. MED | P-value |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Total AUC |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 0-15 min |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| tAUC C-peptide |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| tAUC insulin |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| tAUC GLP-1total |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| tAUC GLP-1active |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| tAUC GIPtotal |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| tAUC paracetamol |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 0-60 min |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| tAUC glucose |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| tAUC C-peptide |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| tAUC insulin |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| tAUC GLP-1total |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| tAUC GLP-1active |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| tAUC GIPtotal |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| tAUC paracetamol |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 0-180 min |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| tAUC glucose |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| tAUC C-peptide |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| tAUC insulin |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| tAUC GLP-1total |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| tAUC GLP-1active |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| tAUC GIPtotal |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| tAUC paracetamol |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Incremental AUC |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 0-15 min |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC glucose |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC C-peptide |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC insulin |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GLP-1total |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GLP-1active |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GIPtotal |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC paracetamol |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 0-30 min |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC glucose |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC C-peptide |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC insulin |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GLP-1total |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GLP-1active |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GIPtotal |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC paracetamol |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 0-60 min |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC glucose |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC C-peptide |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC insulin |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GLP-1total |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GLP-1active |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GIPtotal |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC paracetamol |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 0-180 min |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC glucose |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC C-peptide |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC insulin |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GLP-1total |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC GLP-1active |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| iAUC paracetamol |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Data are estimated mean difference in changes between groups with 95% confidence intervals. CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise, GLP-1: Glucagon-like-peptide 1, GIP: Gastric inhibitory polypeptide, tAUC: total area under the curve, iAUC: incremental area under the curve | | | | | | | | | | | | | | | | | |

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| eTable 14 Within-group changes (0-16 weeks) cardiometabolic, body composition and fitness | | | | | | | | |
|  | CON | | DCON | | MED | | HED | |
|  | Change | 95% CI | Change | 95% CI | Change | 95% CI | Change | 95% CI |
|  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
| Glycemic control |  |  |  |  |  |  |  |  |
| HbA1c (mmol/mol) |  |  |  |  |  |  |  |  |
| HbA1c (%) |  |  |  |  |  |  |  |  |
| Fasting glucose (mmol/l) |  |  |  |  |  |  |  |  |
| Fasting insulin (pmol/l) |  |  |  |  |  |  |  |  |
| Fasting C-peptide (pmol/l) |  |  |  |  |  |  |  |  |
| Glucose-lowering medication, No (%) |  |  |  |  |  |  |  |  |
| Reductiona |  |  |  |  |  |  |  |  |
| Discontinuationb |  |  |  |  |  |  |  |  |
| Intensificationc |  |  |  |  |  |  |  |  |
| Lipid-lowering medication, No (%) |  |  |  |  |  |  |  |  |
| Reductiona |  |  |  |  |  |  |  |  |
| Discontinuationb |  |  |  |  |  |  |  |  |
| Intensificationc |  |  |  |  |  |  |  |  |
| Blood pressure lowering medication, No (%) |  |  |  |  |  |  |  |  |
| Reductiona |  |  |  |  |  |  |  |  |
| Discontinuationb |  |  |  |  |  |  |  |  |
| Intensificationc |  |  |  |  |  |  |  |  |
| Lipids |  |  |  |  |  |  |  |  |
| LDL cholesterol (mmol/l) |  |  |  |  |  |  |  |  |
| Fasting triglycerides (mmol/l) |  |  |  |  |  |  |  |  |
| Blood pressure |  |  |  |  |  |  |  |  |
| Systolic (mmHg) |  |  |  |  |  |  |  |  |
| Diastolic (mmHg) |  |  |  |  |  |  |  |  |
| Fitness |  |  |  |  |  |  |  |  |
| Absolute VO2 max (ml/min) |  |  |  |  |  |  |  |  |
| Relative VO2 max (ml/kg/min) |  |  |  |  |  |  |  |  |
| Watt max (W/kg) |  |  |  |  |  |  |  |  |
| 1 RM chest press (kg) |  |  |  |  |  |  |  |  |
| 1 RM leg extension (kg) |  |  |  |  |  |  |  |  |
| Body composition |  |  |  |  |  |  |  |  |
| Body weight (kg) |  |  |  |  |  |  |  |  |
| BMI (kg/m2) |  |  |  |  |  |  |  |  |
| Data are least-squares means. CI: confidence intervals, CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise  aReduction defined as at least one step down on the pre-defined algorithm.  bDiscontinuation defined as, discontinuation of all drugs when therapeutic target was met.  cIntensification defined as at least one step up on the pre-defined algorithm. | | | | | | | | |

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| eTable 15 Pairwise comparisons of the change in cardiometabolic, body composition and fitness | | | | | | | | | | | | | | | | | |
|  | | | | | | | | | | | | | | | | | |
|  | HED vs. CON | P-value |  | MED vs. CON | P-value |  | DCON vs. CON | P-value |  | HED vs. DCON | P-value |  | MED vs. DCON | P-value |  | HED vs. MED | P-value |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Glycemic control |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| HbA1c (mmol/mol) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| HbA1c (%) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Fasting glucose (mmol/l) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Fasting insulin (pmol/l) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Fasting C-peptide (pmol/l) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Glucose-lowering medication, No (%) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Reduction |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Discontinuation |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Intensification |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lipid-lowering medication, No (%) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Reduction |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Discontinuation |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Intensification |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood pressure lowering medication, No (%) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Reduction |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Discontinuation |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Intensification |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lipids |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Total cholesterol (mmol/l) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| LDL cholesterol (mmol/l) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Fasting triglycerides (mmol/l)a |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood pressure |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Systolic (mmHg) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Diastolic (mmHg) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Fitness |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Absolute VO2 max (ml/min) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Relative VO2 max (ml/kg/min) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Watt max (W/kg) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 1 RM chest press (kg) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 1 RM leg extension (kg) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Body composition |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Body weight (kg) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| BMI (kg/m2) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Data are estimated mean difference in changes between groups with 95% confidence intervals. CON: control group, DCON: Dietary control group, MED: Moderate volume exercise, HED: High volume exercise, HbA1c: Glycated hemoglobin 1Ac, GLP-1: Glucagon-like-peptide 1, GIP: Gastric inhibitory polypeptide | | | | | | | | | | | | | | | | | |

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| --- | --- | --- | --- | --- | --- |
| eTable 16 Adverse events after randomization | | | | | |
| Event | All n (%) | CON n (%) | DCON n (%) | MED n (%) | HED n (%) |
|  |  |  |  |  |  |
| Serious AE |  |  |  |  |  |
|  |  |  |  |  |  |
| All AE |  |  |  |  |  |
|  |  |  |  |  |  |
| Gastrointestinal |  |  |  |  |  |
| Nausea |  |  |  |  |  |
| Vomiting |  |  |  |  |  |
| Diarrhea |  |  |  |  |  |
| Constipation |  |  |  |  |  |
| Dyspepsia |  |  |  |  |  |
| Flatulens |  |  |  |  |  |
| Abdominal distension |  |  |  |  |  |
| Abdominal pain |  |  |  |  |  |
| Other |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
| Infections |  |  |  |  |  |
|  |  |  |  |  |  |
| Musculoskeletal pain and discomfort |  |  |  |  |  |
| Back pain |  |  |  |  |  |
| Lower extremities |  |  |  |  |  |
| Upper extremities |  |  |  |  |  |
| other |  |  |  |  |  |
|  |  |  |  |  |  |
| Musculoskeletal injury, defined as pain or discomfort  resulting in inability to exercise for ≥7days |  |  |  |  |  |
| Back pain |  |  |  |  |  |
| Lower extremities |  |  |  |  |  |
| Upper extremities |  |  |  |  |  |
| other |  |  |  |  |  |
|  |  |  |  |  |  |
| Complications associated with clinical or experimental procedures |  |  |  |  |  |
|  |  |  |  |  |  |
| Metabolism and nutrition disorders |  |  |  |  |  |
| Decreased appetite |  |  |  |  |  |
| Increased appetite |  |  |  |  |  |
| Hunger |  |  |  |  |  |
| Other |  |  |  |  |  |
| Nervous system disorders |  |  |  |  |  |
| Headache |  |  |  |  |  |
| Dizziness |  |  |  |  |  |
| Other |  |  |  |  |  |
|  |  |  |  |  |  |
| Events related to dysglycemia |  |  |  |  |  |
| Events related to blood pressure management |  |  |  |  |  |
|  |  |  |  |  |  |
| Other |  |  |  |  |  |
|  |  |  |  |  |  |
| Values are number and percentage (%) of participants with adverse event for each group. All events are self‐reported to reported to the study nurse, dietitian or trainers and occurred after randomization. | | | | | |