# 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**

SAP author(s): Malte Lund Adamsen

Sponsor: Bente Klarlund Pedersen, MD, PhD, Professor, Centre for Physical Activity Research, Dept. 7641, Rigshospitalet, Denmark

Investigators: Malte Lund Adamsen, MD, Centre for Physical Activity Research, Dept. 7641, Rigshospitalet, Denmark.

Statistical advisor: Julie Lyng Forman, MSc, PhD; Professor of Biostatistics at university of copenhagen

Table of Contents

[BACKGROUND AND RATIONAL 3](#_Toc87442267)

[OBJECTIVES 4](#_Toc87442268)

[HYPOTHESIS 5](#_Toc87442269)

[TRIAL DESIGN, DATA COLLECTION AND OUTCOMES ASSESSMENT 6](#_Toc87442270)

[OUTCOMES 6](#_Toc87442271)

[STUDY POPULATION, ANALYSIS SET AND STATISTICAL PRINCIPLES 9](#_Toc87442272)

[STATISTICAL METHODS 11](#_Toc87442273)

[DEVIATIONS FROM THE ORIGINAL PROTOCOL 12](#_Toc87442274)

[IMPLEMENTATION OF THE SAP 14](#_Toc87442275)

[EXPECTED WRITING COMMITTEE 14](#_Toc87442276)

[EXPECTED OUTLINE OF THE REPORT 15](#_Toc87442277)

[OVERVIEW OF CONTENT (Unformatted tables with specific variables are placed at the end of the text) 15](#_Toc87442278)

[TABLES (In paper) 15](#_Toc87442279)

[FIGURES (In paper) 15](#_Toc87442280)

[ONLINE ONLY (Tables) 16](#_Toc87442281)

[ONLINE ONLY (Figures) 17](#_Toc87442282)

[REFERENCES 19](#_Toc87442283)

[UNFORMATTED TABLES WITH INTENDED CONTENT 21](#_Toc87442284)

## BACKGROUND AND RATIONAL

## OBJECTIVES

### Primary aim:

### Secondary aims:

### Primary objective:

### Major secondary objective:

### Other objectives:

## HYPOTHESES

### Primary hypothesis

### Secondary Hypotheses

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

## 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 database1.

## OUTCOMES

### Primary outcomes (timeframe 0 to 12 weeks)

Domain: Aerobic Capacity

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. (Unit is ml/min/kg)

* Volumes of gases measured by indirect calorimetry.

Domain: Fatigue

Measurement: Krupp’s Fatigue severity scale2, as the average of all 9 domains (0-7).

* This scale has been verified for use in Danish SLE patients3.

### Key Secondary Outcome (Timeframe 0 to 12 weeks)

Domain:

Measurement:

Domain:

Measurement:

### Other secondary outcomes (timeframe 0 to 12 weeks).

Domain:

Measurement:

Domain:

Measurement:

## STUDY POPULATION, ANALYSIS SET AND STATISTICAL PRINCIPLES

## STATISTICAL METHODS

## 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, Anna A. Lützen, Kanwal Zahid Siddiqi, 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

## REFERENCES

## 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 | | | |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 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, | | | | | | | | | | |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 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 | | | | | | | | | | | | | | | | | | | |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 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 | | | | | | | | | | |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 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 | | | | | | | | | | | | | |

ONLINE ONLY

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 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 | | | | | | | | | |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 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 | | | | | | | | | | | | | | | | |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 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 | | | | |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 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 | | | | | | | |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 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 | | | | |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 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. | | | |

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 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 | | | | | | | | | | | |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 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 | | | | | | | | | | | | | | | | | |

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 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 | | | | | | | | | | | | | | | | | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 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. | | | | | | | | |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 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 | | | | | | | | | | | | | | | | | |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 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. | | | | | |