Exercise and quality of life during androgen deprivation therapy – a randomized trial

Short title: Patient school 1

Lauri Rantaniemi[1], Jarno Riikonen[2], Hanna Ojala[3], Ilkka Pietilä[3], Teuvo L.J. Tammela[1,2], Teemu J. Murtola[1,2]

1. Tampere University, Faculty of Medicine and Health Technology, Tampere, Finland

2. Tampere University Hospital, Department of Urology, Tampere, Finland

3. Tampere University, Faculty of Social Sciences, Tampere, Finland

1 BACKGROUND

Prostate cancer is the most common non-cutanoeus cancer and among the top three causes of cancer deaths among men in Finland and other Western countries. Burden of health care costs due to the condition rise up to 180 million euros/year in Finland (1).

Androgens are vital for prostate cancer progression, and androgen deprivation therapy is cornerstone in management of advanced or recurrent prostate cancer that is beyond curative treatment. In androgen deprivation therapy (ADT) serum testosterone is lowered either medically or surgically to a level lower than 1,72 µmol/l (50 ng/dl). (2) These prevents activation of androgen receptors in prostate cancer cells, leading to involution of the prostate tumor and metastases, decreased proliferation and increased apoptosis of prostate cancer cells (3,4).

Common side effects of ADT include fatigue, weight gain, muscle loss, decreased libido and erectile dysfunction, amounting to decreased quality of life (5). Low serum testosterone has also been linked with increased risk for type II diabetes and metabolic syndrome (6). Also associations with elevated risk for memory impairment and cardiovascular disease have been proposed (7,8).

Systematic review published in 2012 found strong evidence for improved overall quality of life among ADT-treated prostate cancer patients participating in supervised resistance training. Moderate evidence was found also for improved physical and social well-being. The authors recommended exercise for all prostate cancer patients on ADT and called for further studies comparing supervised and unsupervised exercise (9). A recent randomized trial found equal fatigue reduction and vitality increase both with supervised and unsupervised exercise (10).

2 STUDY GOALS

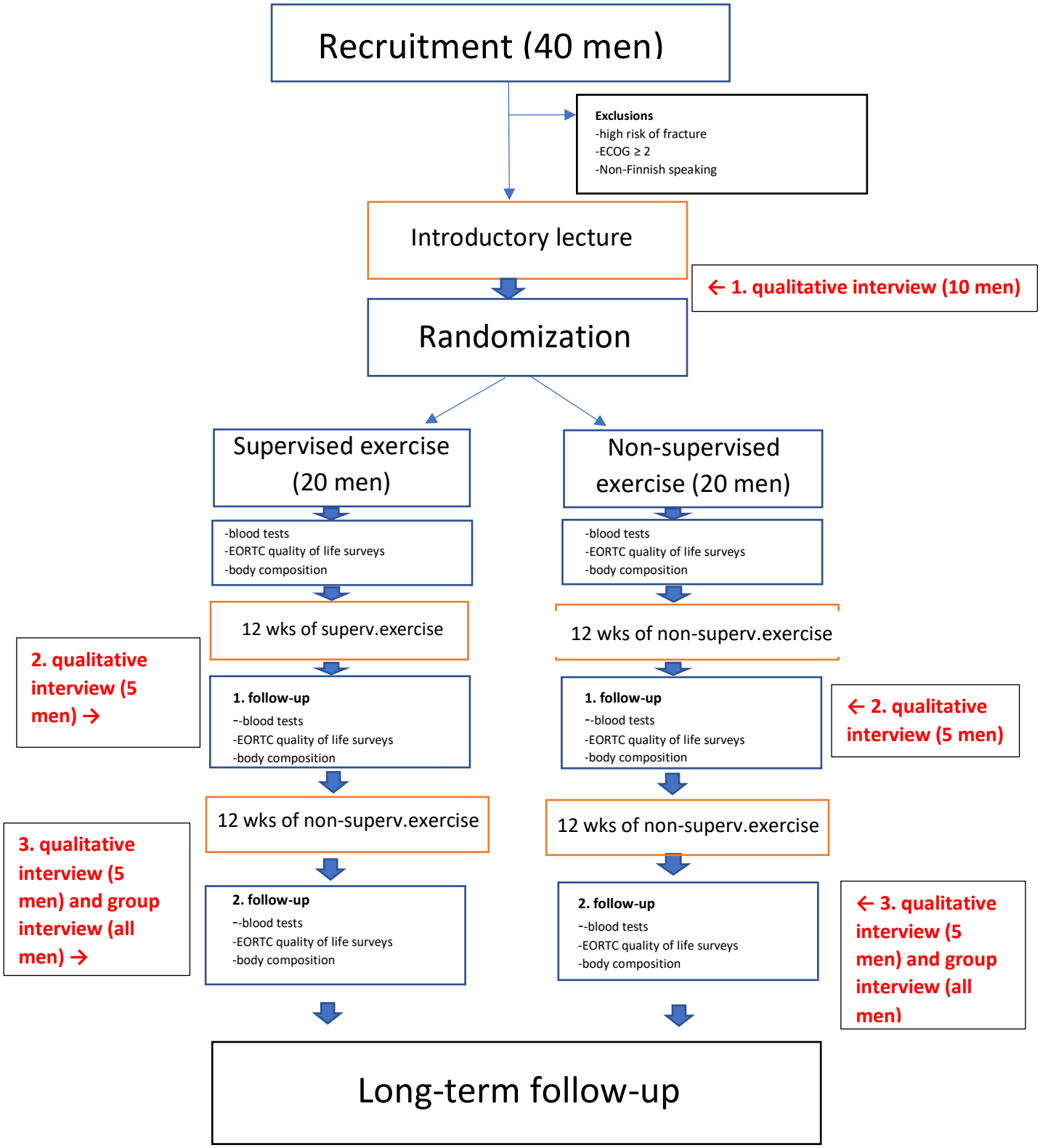
The study compares effects of supervised and unsupervised exercise on plasma lipid parameters (total cholesterol, LDL, HDL and triglycerides) and glucose levels (fasting plasma glucose, glycated hemoglobin), overall quality of life and on average daily exercise activity in men with prostate cancer and under ADT. As secondary outcome we will study effect on continued exercise activity after the intervention, changes in body composition, blood pressure and risk of fractures, castration resistance as well as death due to prostate cancer and due to any cause.

Study hypothesis is that supervised exercise will improve quality of life, lipid and glucose parameters and increase daily exercise activity more that non-supervised exercise. We also expect higher continued exercise activity, greater changes in body composition and blood pressure and lowered risk of fractures and death in the supervised exercise group.

3 STUDY SETTING

This is a randomized, controlled clinical trial. The study aims to recruit 40 men on ADT for prostate cancer. This will be a pilot study to estimate effect sizes in Finnish population to inform further larger trial. For this reason the sample size will be smaller compared to previous studies on the topic (10,11) and no power calculation is performed yet.

Figure: Study flow chart



4 INCLUSION- AND EXCLUSION CRITERIA

Inclusion criteria:

- ADT for prostate cancer, regardless of treatment duration
- Willingness to participate in the study; signing of informed consent

Exclusion criteria:

- Unability for physical exertion; ECOG 2 or higher
- High risk for bone fractures as evaluated by the attending clinician
- Non-Finnish speaking; unability to comprehend Finnish

5 INTERVENTION

All participants attend introductory lecture, where a urologist informs them about adverse effects of ADT and positive effects of exercise during ADT, exercise instructor gives advice for training both at home and in the gym and nutritional therapeutist tells about nutrition to overcome adverse effects of ADT and support training.

After the introductory lecture tha participants are randomized 1:1 to either the supervised or non-supervised exercise group (Figure). Men in the supervised group participate in progressive group exercise sessions twice a week for total of 12 weeks at the Varala sports academy in Tampere, Finland. Each exercise session includes both aerobic and resistance training targeting all major muscle groups (Additional document I, exercise program). The non-supervised group will exercise independently for 12 weeks according to the instructions given at the introductory lecture. The first control visit will be after this first period of 12 weeks of exercise.

After the first follow-up visit both group will continue non-supervised exercise for 12 weeks, after which the second control visit will be arranged. Special focus on the second control visit is to see how many in each group has been able to carry on active exercising, i.e. has the intervention promoted long-term change in exercise activity.

Both study group will be given Polar wrist activity monitors to be used 24 h/day for the entire course of the study.

All participants are asked to fill validated quality of life surveys EORTC QLQC-30 (overall quality of life) and EORTC QLQC-PR25 (prostate cancer-specific quality of life) at baseline and again at 1st and 2nd control visits. Plasma lipid and glucose parameters, blood pressure and body composition wll be measured at each of these visits.

At each visit a separate blood sample is taken and stored for future measurement of biomarkers associated with prostate cancer progression, glucose and lipid metabolism and effects of exercise.

6 QUALITATIVE EVALUATION OF SUBJECTIVE CAPABILITIES AND QUALITY OF LIFE

On each visit a qualitative evaluation will be performed based on individual- and group interviews to evaluate how men find ADT and exercise affecting their quality of life and how they perceive the intervention as a means to increase their physical activity. On the interviews information will be collected on:

1. How men on ADT perceive their quality of life and what is their subjective definition of quality of life?
   - What kind of side-effects they have had from ADT, how they cope with them in everyday life and how cancer, ADT and ADT side-effects have affected their quality of life?
   - What role exercise has had in their lives before prostate cancer and after it, and how the amount of exercise is tied to their perceived quality of life?

2. What kind of opportunities and obstacles of exercise the participants find in their lives?
   - How men in the supervised exercise group think the intervention will affect their exercise activity in the future? Can supervised exercise help to overcome obstacles for exercising?
   - How men in the non-supervised exercise group cope with obstacles for exercise?

Baseline interveiw, before the study randomization: A group of 10 men are interviewed before randozation to the exercise groups. The goal is to find how participants expect the intervention to affect their activity and quality of life before they know in which group they will participate.

Second interview at the first control visit: Men in the supervised exercise group are interviewed about the role of their group and supervision on their exercise activity and perceived quality of life. Non-supervised group is interviewed how they have managed to follow the given exercise program and how ot has affected their quality of life. All men are asked how they think they exercise habits would have differed had they been randomized to the other intervention group. Additionally their views about how they will be able to carry on exercising will be asked.

Third interview at the second control visit: The questions will evaluate how men have carried on with the exercise; have they been able to increase it or has it rather decreased; have the men found that the exercise intervention has affected their quality of life.

7 STUDY OUTCOMES AND STATISTICAL ANALYSIS

Primary outcomes:

- Daily total activity, measured during the entrie course of study with wrist activity monitor in metabolic equivalents of task (MET) units
- Fasting plasma cholesterol, LDL, HDL and triglycerides, measured at baseline and again at the 1st and 2nd control visits
- Fasting plasma glucose and glycated haemoglobin (HbA1C), measured at baseline and again at the 1st and 2nd control visits
- Overall quality of life and prostate cancer-specific quality of life, measured with validated Finnish versions of EORTC QLQC-30 v.3.0 ja EORTC QLQ-PR25 at baseline and at each control visit

Seconday outcomes:

- Change in daily activity after the end of supervised group exercise intervention; difference compared to the non-supervised group. Measured with wrist activity monitor in MET units
- Body mass composition, bioimpedance-based measurement of lean body mass, fat mass and skeletal mass as percentage of total body mass measured with TANITA MC-780 device

- Blood pressure level, measured at baseline and each control visit
- Subjective effect of exercise on quality of life and perceived adverse effects of ADT, as based on qualitative interviews

Long-term follow-up

The participants are followed via patient files and national health care registries. Outcomes to be followed are:

- Time from baseline to castration resistance (progression of prostate cancer despite ADT as evidenced by constantly rising PSA or radiological disease progression)
- Bone fractures
- Diagnosis of memory impairment
- Diagnosis of diabetes mellitus
- Diagnosis of cardiovascular disease
- Prostate cancer death
- Death due to any causei

Statistical analysis

All comparisons are done between the supervised and non-supervised exercise arms. Medians of daily activity (in MET units) and quantitative quality of life (as points from the EORTC surveys) at baseline and at each control visit are compared with either Mann-Whitney U-test or Student's t-test depending on normality of the data distribution. Difference in medians of plasma lipid parameters and glucose parameters are analyzed similarly.

Of the secondary outcomes median time to castration resistance and death are compared between the trail arms using Kaplan-Meier analysis and log-rank test. Analysis for risks of castration resistance, death, prostate cancer death, cardiovascular disease, bone fracture and memory impairment will be analysed using Cox regression with months from the study randomization as the time metric. The regression model will be adjusted for the study arm, age at baseline, time between prostate cancer diagnosis and randomization, ADT method and the time on ADT before participating in the trial.

8 ETHICAL CONSIDERATIONS

8.1 BENEFITS AND RISK OF HARM FOR THE PARTICIPANTS

Evidence for quality of life improvement due to exercise is strong, and therefore the participants likely benefit from the study participation in both study arms. Participating in an exercise program increases risk of musculoskeletal injuries and possibly cardiovascular events. Such risks are minimized by selecting participants with adequate physical condition and tailoring the research program according to individual performance level.

8.2 FUNDING

Astellas Pharma funds the group exercise sessions during the study, but does not otherwise participate in the design or conduct of the study, data analysis, writing of results nor in the decision to publish the results. Clinical trial will be funded with grants from commercially independent sources, such as Pirkanmaa Hospital District.

8.3 CONFLICTS OF INTEREST

LR: None

JR: Congress participation at the expense of Astellas and Ferring. Consulting fees from: Astellas, Ferring, Pfizer, Bayer, Lidds, Myovant.

HO: None

IP: None.

TLJT: Consulting fees from: Astellas Pharma, Orion Pharma and Bayer AG.

TJM: Lecture fees from: Astellas Pharma, Jansen and MSD. Consutling fees from: Astellas Pharma and Janssen.

9 REFERENCES

1. Mäklin S, Rissanen P. Syöpien aiheuttamat kustannukset. Syöpäjärjestöjen julkaisuja nro 67, 2006. Luettavissa osoitteessa: http://www.cancer.fi/@Bin/1697304/Syöpien+aiheuttamat+kustannukset.pdf
2. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, Fossati N, Gross T, Henry AM, Joniau S, Lam TB, Mason MD, Matveev VB, Moldovan PC, van den Bergh RC, Van den Broeck T, van der Poel HG, van der Kwast TH, Rouviere O, Schoots IG, Wiegel T, Cornford P: EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol 2017, 71(4):618-629.
3. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. CA Cancer J Clin. 1972 Jul-Aug;22(4):232-40.
4. Culig, Z. & Santer, F.R. Androgen receptor signaling in prostate cancer. Cancer Metastasis Rev (2014) 33: 413. doi:10.1007/s10555-013-9474-0
5. Rowan G Casey, Niall M Corcoran, and S Larry Goldenberg. Quality of life issues in men undergoing androgen deprivation therapy: a review. Asian J Androl. 2012 Mar; 14(2): 226–231.
6. Zitzmann M. Testosterone deficiency, insulin resistance and the metabolic syndrome. Nature reviews Endocrinology. 2009;5:673–681.
7. Gandaglia G, Sun M, Popa I, Schiffmann J, Abdollah F, Trinh QD, Saad F, Graefen M, Briganti A, Montorsi F, Karakiewicz PI. The impact of androgen-deprivation therapy (ADT) on the risk of cardiovascular (CV) events in patients with non-metastatic prostate cancer: a population-based study. BJU Int. 2014 Dec;114(6b):E82-9. doi: 10.1111/bju.12732

8. Nead KT, Gaskin G, Chester C, Swisher-McClure S, Leeper NJ, Shah NH. Association Between Androgen Deprivation Therapy and Risk of Dementia. JAMA Oncol. 2017 Jan 1;3(1):49-55. doi: 10.1001/jamaoncol.2016.3662.

9. Keogh JW, MacLeod RD. Body composition, physical fitness, functional performance, quality of life, and fatigue benefits of exercise for prostate cancer patients: a systematic review. J Pain Symptom Manage. 2012 Jan;43(1):96-110. doi: 10.1016/j.jpainsymman.2011.03.006.

10. Taaffe DR, Newton RU, Spry N, Joseph D, Chambers SK, Gardiner RA, Wall BA, Cormie P8, Bolam KA, Galvão DA. Effects of Different Exercise Modalities on Fatigue in Prostate Cancer Patients Undergoing Androgen Deprivation Therapy: A Year-long Randomised Controlled Trial. Eur Urol. 2017 Feb 26. doi: 10.1016/j.eururo.2017.02.019

11. Peter Østergren, Anne-Mette Ragle, Henrik Jakobsen, Tobias Wirenfeldt Klausen, Anders Vinther, Jens Sønksen. Group-based exercise in daily clinical practice to improve physical fitness in men with prostate cancer undergoing androgen deprivation therapy: study protocol. BMJ Open. 2016;6:e011460. doi:10.1136/bmjopen-2016-011460

10 ADDITIONAL DOCUMENTS

Additional document I:

Exercise program

	Nimi:								
		Viikko 1		**Viikko 2**		**Viikko 3**		**Viikko 4**	
	Säädöt	**d.**	**d.**	**d.**	**d.**	**d.**	**d.**	**d.**	**d.**
1 Alasoutu 	Istuin: Rintatuki:	Sarjat: 15-15 Kg:	Sarjat: 15-15 Kg:	Sarjat: 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 12-12-12 Kg:
2 Reisiojennus 	Istuin: Kahva: Nilkkatyyny:	Sarjat: 15-15 Kg:	Sarjat: 15-15 Kg:	Sarjat: 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 12-12-12 Kg:
3 Rintaprässi 	Istuin: Kahva:	Sarjat: 15-15 Kg:	Sarjat: 15-15 Kg:	Sarjat: 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 12-12-12 Kg:

4 Vatsarutistus  		Sarjat: 15-15 Kg:	Sarjat: 15-15 Kg:	Sarjat: 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 12-12-12 Kg:
		d.	**d.**	**d.**	**d.**	**d.**	**d.**	**d.**	**d.**
5 Reisikoukistus  	Istuin: Kahva: Nilkkatyyny:	Sarjat: 15-15 Kg:	Sarjat: 15-15 Kg:	Sarjat: 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 12-12-12 Kg:

6 Selkäojennus 	Nakke-pude: Kahva:	Sarjat: 15-15 Kg:	Sarjat: 15-15 Kg:	Sarjat: 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 12-12-12 Kg:
7 Jalkaprässi 	Istuin:	Sarjat: 15-15 Kg:	Sarjat: 15-15 Kg:	Sarjat: 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 12-12-12 Kg:
Kuntopyörä	Istuin:	Aika/km	Aika/km	Aika/km	Aika/km	Aika/km	Aika/km	Aika/km	Aika/km
Crosstrainer	Aika: Matka:								
Porrasnousu	Aika: Korkeus:								
Juoksumatto	Aika: Matka:								
Soutulaite	Aika: Matka:								

Lankku	Aika:								

	Nimi:								
		Viikko 5		**Viikko 6**		**Viikko 7**		**Viikko 8**	
		d.	**d.**	**d.**	**d.**	**d.**	**d.**	**d.**	**d.**
1 Alasoutu 	Istuin: Rintatuki:	Sarjat: 12-12-12 Kg:	Sarjat: 12-12-12 Kg:	Sarjat: 12-12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:
2 Reisiojennus 	Istuin: Kahva: Nilkkatyyny:	Sarjat: 12-12-12 Kg:	Sarjat: 12-12-12 Kg:	Sarjat: 12-12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:
3 Rintaprässi 	Istuin: Kahva:	Sarjat: 12-12-12 Kg:	Sarjat: 12-12-12 Kg:	Sarjat: 12-12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:

4 Vatsarutistus  		Sarjat: 12-12-12 Kg:	Sarjat: 12-12-12 Kg:	Sarjat: 12-12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:
		d.	**d.**	**d.**	**d.**	**d.**	**d.**	**d.**	**d.**
5 Reisikoukistus  	Istuin: Kahva: Nilkkatyyny:	Sarjat: 12-12-12 Kg:	Sarjat: 12-12-12 Kg:	Sarjat: 12-12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:

6 Selkäojennus 	Kahva: Nakke-pude:	Sarjat: 12-12-12 Kg:	Sarjat: 12-12-12 Kg:	Sarjat: 12-12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:
7 Jalkaprässi 	Istuin:	Sarjat: 12-12-12 Kg:	Sarjat: 12-12-12 Kg:	Sarjat: 12-12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 12-12-12 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:
Kuntopyörä	Istuin:	Aika/km	Aika/km	Aika/km	Aika/km	Aika/km	Aika/km	Aika/km	Aika/km
Crosstrainer	Aika: Matka:								
Porrasnousu	Aika: Korkeus:								
Juoksumatto	Aika: Matka:								
Soutulaite	Aika: Matka:								
Lankku	Aika:								

	Nimi:								
		Viikko 9		**Viikko 10**		**Viikko 11**		**Viikko 12**	
		d.	**d.**	**d.**	**d.**	**d.**	**d. (st)**	**d. (fw)**	**d. (fw)**
1 Alasoutu 	Istuin: Rintatuki:	Sarjat: 10-10-10 Kg:	Sarjat: 10-10-10 Kg:	Sarjat: 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:
2 Reisiojennus 	Istuin: Kahva: Nilkkatyyny:	Sarjat: 10-10-10 Kg:	Sarjat: 10-10-10 Kg:	Sarjat: 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:
3 Rintaprässi 	Istuin: Kahva:	Sarjat: 10-10-10 Kg:	Sarjat: 10-10-10 Kg:	Sarjat: 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:

4 Vatsarutistus  		Sarjat: 10-10-10 Kg:	Sarjat: 10-10-10 Kg:	Sarjat: 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:
		d.	**d.**	**d.**	**d.**	**d.**	**d. (st)**	**d. (fw)**	**d. (fw)**
5 Reisikoukistus  	Istuin: Kahva: Nilkkatyyny:	Sarjat: 10-10-10 Kg:	Sarjat: 10-10-10 Kg:	Sarjat: 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:

6 Selkäojennus 	Kahva: Nakke-pude:	Sarjat: 10-10-10 Kg:	Sarjat: 10-10-10 Kg:	Sarjat: 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:
7 Jalkaprässi 	Istuin:	Sarjat: 10-10-10 Kg:	Sarjat: 10-10-10 Kg:	Sarjat: 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:	Sarjat 10-10-10 Kg:
Kuntopyörä	Istuin:	Aika/km	Aika/km	Aika/km	Aika/km	Aika/km	Aika/km	Aika/km	Aika/km
Crosstrainer	Aika: Matka:								
Porrasnousu	Aika: Korkeus:								
Juoksumatto	Aika: Matka:								
Soutulaite	Aika: Matka:								
Lankku	Aika:								