Title page

Statistical Analysis Plan

Protocol title

Protocol for a Randomised, Double-Blinded, Placebo-Controlled Trial Investigating the Combined Effects of Statins and Exercise on Physiological Health Markers and Quality of Life in Patients With Dyslipidaemia

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Document status and purpose

This statistical analysis plan (SAP) supplements the main study protocol and prespecifies analyses for all primary, secondary, and exploratory outcomes. It is finalized prior to unblinding and follows contemporary guidance for SAP content in clinical trials (Gamble *et al.*, 2017).

Signature Page

We, the undersigned, approve and will adhere to the Statistical Analysis Plan detailed herein:

SAP authors

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Tórur Sjúrðarson[1]	PhD	Sponsor-investigator; SAP co-author		30.01.2026
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Section 2: Introduction

7. Background and Rationale (adapted from the published protocol)

Detailed background and rationale are presented in the published protocol (Sjúrðarson *et al.*, 2025). In brief, statins are first-line therapy for dyslipidaemia a but have been hypothesized to attenuate exercise-induced improvements in skeletal-muscle mitochondrial content and function as well as cardiorespiratory fitness (Mikus *et al.*, 2013). This trial is designed to quantify the exercise × statin interaction on mitochondrial function and related physiological and clinical markers in middle-aged adults with dyslipidaemia, using citrate synthase (CS) maximal activity as a validated biomarker of mitochondrial content/oxidative capacity and peak oxygen uptake (VO_{2peak}) as a complementary integrated marker of whole-body fitness. The central scientific question is whether concomitant high-dose atorvastatin attenuates adaptations normally observed with supervised high-intensity interval training.

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8. Objectives

Overall objective. To estimate the individual and combined effects of 12 weeks of atorvastatin and supervised exercise training on physiological, biochemical, and patient-reported outcomes in adults with dyslipidaemia.

Primary objective.

To evaluate the effect of 12 weeks of atorvastatin, exercise training, and their combination on skeletal-muscle CS maximal activity across all four intervention groups.
The main mechanistic contrast of interest is Exercise + Placebo vs Exercise + Atorvastatin, testing whether atorvastatin blunts training-induced mitochondrial adaptations.
Additional pre-specified pairwise comparisons among the four groups will be analyzed to fully characterize exercise, drug, and combined effects (see Section 12).

Key secondary objective.

To evaluate changes in VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$) across the four groups, with the same principal contrast (Exercise + Placebo vs Exercise + Atorvastatin), testing whether atorvastatin blunts training-induced adaptations in VO_{2peak}.

For details on outcome selection and rationale, see the published protocol.

Section 3: Study Methods

9. Trial design

This investigator-initiated, randomized, double-blinded (medication) and placebo-controlled trial evaluates the effects of high-dose atorvastatin and supervised high-intensity interval training (HIIT), alone or combined, over 12 weeks in adults with dyslipidaemia. Participants are allocated to one of four parallel arms:

1. Exercise + Placebo
2. Exercise + Atorvastatin
3. No Exercise + Atorvastatin
4. No Exercise + Placebo

Medication allocation is double-blinded (participants and investigators). Exercise allocation cannot be blinded to participants or trainers; however, outcome assessors and laboratory personnel will remain blinded to medication allocation, and data analysts will remain blinded to both medication and exercise allocation until database lock.

Interventions

- **Wash-out:** 4-week discontinuation of lipid-lowering therapy before baseline (week 0).
- **Medication:** Atorvastatin 40 mg (Week 1-2), then 80 mg daily; matching placebo in placebo arms.
- **Exercise:** Supervised high-intensity interval training (HIIT) three times per week, performed at or above 90 % of maximal aerobic power (MAP), with intensity monitored using power output (wattage), heart rate (HR), and ratings of perceived exertion (RPE).
- **Non-exercise arms:** Maintain habitual physical activity.

Study visits:

V0 = Screening, V1 = Baseline (all measurements completed before randomization), Week 6 = mid-intervention blood samples and questionnaires, V2 = Post-intervention (12 weeks).

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10. Randomization

Randomization uses a computer-generated list prepared by an independent statistician. Allocation is performed by a non-involved colleague after completion of baseline assessments. Participants are randomized in a 60:40 exercise:non-exercise ratio to achieve approximately:

Group	n
Exercise + Placebo	36
Exercise + Atorvastatin	36
No Exercise + Atorvastatin	24
No Exercise + Placebo	24

Randomization is stratified by:

1. Sex (male/female)
2. Prior active statin treatment (yes/no)

Block sizes are concealed from investigators. Randomization codes are securely stored and revealed only after database lock.

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11. Sample size calculations

Sample-size calculations were prespecified for the primary mechanistic contrast (Exercise + Placebo vs Exercise + Atorvastatin) for the primary endpoint (ΔCS) and the key secondary endpoint (ΔVO_{2peak}).

Power calculations (as prespecified in the published protocol) used prior training data (Sjúrðarson *et al.*, 2022*a*, 2022*b*): mean ΔCS ≈ 25 μmol·g^{-1}·min^{-1}, SD ≈ 18 μmol·g^{-1}·min^{-1}, and a target between-group difference of 17 μmol·g^{-1}·min^{-1}, consistent with attenuation magnitudes reported previously (Mikus *et al.*, 2013). For VO_{2peak}, we assumed Δ ≈ 3.6 ± 3.3 mL·kg^{-1}·min^{-1} and targeted a 3.0 mL·kg^{-1}·min^{-1} between-group difference.

Final enrolled sample size.

A total of N = 120 participants were randomized (36 per exercise arm; 24 per non-exercise arm). The primary mechanistic comparison—Exercise + Placebo vs Exercise + Atorvastatin—is effectively a two-group contrast, and power calculations were therefore based on the two exercise groups.

Using the effect-size assumptions prespecified in the published protocol, the achieved sample provides:

- **Citrate synthase (CS) activity:**
    - With full enrollment (n = 36 per group), power is approximately 97–98% to detect a 17 μmol·g^{-1}·min^{-1} difference (SD ≈ 18).
    - With 10% attrition (≈33 per group), power remains high at ≈94–95%.
- **VO_{2peak}:**
    - With full enrollment (n = 36 per group), power is approximately 96–97% to detect a 3.0 mL·kg^{-1}·min^{-1} difference (SD ≈ 3.3).
    - With 10% attrition (≈33 per group), power remains ≈93–95%.

Power calculations were performed in G*Power (version 3.1.9.7) using a two-sample, two-sided t-test with α = 0.05, assuming equal group sizes for the exercise arms. Power calculations are based on a two-sample t-test approximation for the primary exercise-arm contrast; the primary analysis will use a constrained mixed model, which is expected to provide similar or greater efficiency under the repeated-measures structure.

Interpretation note (pre-specified).

Because (i) a clinically meaningful CS difference is not firmly established and (ii) assay units/conditions vary across studies, true between-group differences smaller than 17 $\mu mol \cdot g^{-1} \cdot min^{-1}$ may still be clinically relevant.

For VO_{2peak}, relatively small differences may also be clinically meaningful. While meta-analytic evidence indicates that each 1-MET (≈3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) higher cardiorespiratory fitness is associated with substantially lower all-cause and cardiovascular mortality risk (Myers *et al.*, 2002; Kodama *et al.*, 2009), prospective cohorts with directly measured VO_{2peak}/VO_{2max} also demonstrate prognostic gradients per ~1 $mL \cdot kg^{-1} \cdot min^{-1}$, implying that differences on the order of ~2 $mL \cdot kg^{-1} \cdot min^{-1}$ are clinically meaningful (Keteyian *et al.*, 2008; Laukkanen *et al.*, 2016; Khan *et al.*, 2018; Tari *et al.*, 2024). Accordingly, a between-group difference of ~2.0 $mL \cdot kg^{-1} \cdot min^{-1}$ (≈0.6 MET) can be considered a clinically relevant difference in VO_{2peak}.

With 120 randomized participants, the study has approximately 80% power to detect between-group differences of ~12 $\mu mol \cdot g^{-1} \cdot min^{-1}$ in CS activity and ~2.1 $mL \cdot kg^{-1} \cdot min^{-1}$ in VO_{2peak}.

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12. Framework

Analyses will follow a superiority framework. For the primary endpoint (change in CS activity), all four groups will be compared with each other (six pre-specified pairwise contrasts). Multiplicity across the six tests will be controlled using the Holm–Šidák procedure, maintaining a familywise two-sided $\alpha = 0.05$. Superiority will be claimed only for contrasts meeting this adjusted criterion.

All secondary and exploratory outcomes, including VO_{2peak}, will be analyzed using the same general model framework, with emphasis on effect estimates and 95% confidence intervals; p-values will be reported without multiplicity adjustment and should not be used to infer definitive treatment effects.

12.1 Statistical Hypotheses

The primary mechanistic hypothesis is that supervised exercise training increases skeletal-muscle CS activity and that concomitant high-dose atorvastatin attenuates this response.

The key secondary hypothesis is that concomitant atorvastatin treatment attenuates training-induced improvements in cardiorespiratory fitness, assessed as the between-group difference in change in VO_{2peak} between Exercise + Placebo and Exercise + Atorvastatin.

For the primary endpoint (ΔCS), six pre-specified pairwise contrasts will be evaluated to characterize exercise, statin, and combined effects:

No.	Comparison	Scientific question
1	Exercise + Placebo > Exercise + Atorvastatin	Does atorvastatin blunt exercise-induced mitochondrial gains? *(Primary contrast)*
2	Exercise + Placebo > No Exercise + Atorvastatin	Benefit of exercise alone vs. drug alone
3	Exercise + Placebo > No Exercise + Placebo	Absolute effect of exercise training
4	Exercise + Atorvastatin > No Exercise + Atorvastatin	Can exercise mitigate potential statin-related attenuation?
5	Exercise + Atorvastatin > No Exercise + Placebo	Combined treatment vs. no intervention
6	No Exercise + Placebo > No Exercise + Atorvastatin	Do statins alone affect mitochondrial function?

Contrasts are listed in the hypothesized direction for interpretation; all tests will be two-sided.

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13. Statistical interim analyses and stopping guidance

No interim analyses for efficacy are planned. No early stopping guidelines were specified.

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14. Timing of final analysis

Data collection is considered complete after the last participant's last visit. Analyses will begin only after:

1. all data have been entered and cleaned,
2. all queries have been resolved, and
3. The randomization code has been formally unblinded following database lock.

No unblinded interim looks are permitted before database lock.

15. Timing of outcome assessments

Primary and secondary outcomes are measured at V1 (baseline) and V2 (12 weeks). Blood samples and questionnaire data are collected at V1, week 6, and V2.

Section 4: Statistical principles

16–18. Confidence Intervals, P-values, and Multiplicity

For all outcomes, we will report within-group estimated mean changes (V2–V1) and between-group differences in change (contrasts of V2–V1), each with 95% confidence intervals (CIs). Analyses will be two-sided and performed using $\alpha = 0.05$. Multiplicity will be controlled for the primary endpoint (six tests) using the Holm–Šidák procedure, maintaining a familywise two-sided $\alpha = 0.05$. For all other secondary and exploratory outcomes, confidence intervals and p-values will not be adjusted for multiple testing.

19–20. Adherence, Protocol Deviations, and Analysis Populations

Analysis Populations

Intention-to-Treat (ITT) – primary analysis set

All randomized participants will be included in the primary analyses and analyzed according to their allocated intervention group, irrespective of intervention initiation, adherence, or protocol deviations.

Per-Protocol (efficacy under adherence):
Participants without major protocol deviations who (i) complete V1 and V2 assessments and (ii) meet adherence criteria for their assigned intervention(s):

- Medication arms: ≥75% of planned doses at assigned dose (80 mg; 40 mg if medically indicated).
- Exercise arms: ≥75% session attendance and ≥75% of prescribed high-intensity interval time performed at ≥90% maximal aerobic power (MAP).

Adherence definitions and quantification

Medication adherence (%): (doses taken / doses planned) × 100; sources: medication logs + pill count.

Exercise adherence:

- **Session attendance (%):** (sessions attended / sessions prescribed) × 100 (3 sessions/week planned).
- **Intensity adherence (%):** (completed high-intensity interval time at ≥90% MAP / prescribed high-intensity interval time) × 100. MAP is defined as the lowest cycling power output eliciting VO_{2peak} during the incremental test. Primary source: power output; HR as backup. If session-level data are missing, within-participant imputation from temporally adjacent sessions in the same phase may be used.

Protocol Deviations

Major deviations include prohibited medications, <75% adherence to allocated medication/exercise criteria, withdrawal of consent, or non-attendance of V2 testing. All deviations will be listed and summarized by intervention group.

Section 5: Trial Population

21. Screening data

Screening and enrolment figures will be summarized in the CONSORT flow diagram. Individual-level screening data will not be reported.

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22. Eligibility criteria

Inclusion criteria:

- Age: 40–65 years.
- LDL-C >4.0 mmol/L, calculated via the Friedewald equation (LDLC=Total Cholesterol-(HDL-C+0.45×Triglycerides)).

- Written informed consent provided prior to any study procedures.

Exclusion criteria:

- Diagnosed with serious chronic disease including type 1 or 2 diabetes.
- Cancer.
- A history of atherosclerotic cardiovascular disease.
- A history of major depression or other severe psychiatric disorders.
- Severe renal dysfunction (creatinine clearance <30 mL/min).
- Severe hepatic impairment, defined as alanine-aminotransferase ≥3×the upper limit of normal.
- Active pregnancy or breastfeeding.
- Active cigarette or e-cigarette smoker.
- Regular (>2 hours per week) aerobic high-intensity exercise training

Rationale: These criteria ensure a metabolically homogeneous dyslipidaemic cohort without overt cardiovascular disease, while minimizing safety concerns for high-intensity exercise and statin exposure.

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23. Recruitment

CONSORT flow will report numbers assessed, randomized, allocated, treated, completed, and analyzed per arm.

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24. Withdrawal/Follow-up

Participants who discontinue the intervention will be encouraged to attend the post-intervention (V2) assessments whenever feasible to minimize missing data. Reasons for withdrawal or loss to follow-up will be summarized descriptively by randomization group. All randomized participants will be included in CONSORT flow diagrams and intention-to-treat analyses.

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25. Baseline Participant Characteristics

Baseline characteristics will be summarized descriptively for all randomized participants and stratified by randomization group:

1.Exercise + Atorvastatin; 2. Exercise + Placebo; 3. No Exercise + Atorvastatin; 4. No Exercise + Placebo. Unless otherwise specified, summaries will be based on the ITT population.

The distribution of each variable will be inspected visually using Q–Q plots and histograms. Variables with approximately normal distributions will be summarized as mean ± SD; non-normally distributed variables will be reported as median [25th–75th percentiles]. Categorical variables will be reported as counts and percentages.

Table 1 will summarize key demographic, anthropometric, cardiorespiratory, metabolic, biochemical, and patient-reported variables. The final variable list may include but is not limited to the following:

Variable	Total (n =)	Exercise + Atorvastatin	Exercise + Placebo	No Exercise + Atorvastatin	No Exercise + Placebo
Demographics					
Sex (M/F) (n (%))					
Age (years)					
Anthropometry					
Height cm					
Weight kg					
BMI $kg \cdot m^{-2}$					
Waist circumference (cm)					
Hip circumference (cm)					
Body fat (%)					
Lean mass (kg)					

Cardiorespiratory					
VO_{2peak} ($mL \cdot min^{-1}$)					
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)					
Resting heart rate (BPM)					
Systolic BP (mmHg)					
Diastolic BP (mmHg)					
Metabolic profile					
Fasting glucose (mmol/L)					
HbA_1c (mmol/mol)					
Fasting insulin (pmol/L)					
Fasting c-peptide (pmol/L)					
HOMA-IR					
Lipids (total, LDL, HDL, TG) mmol/L					
Apolipoproteins (A-I, A-II, B etc.)					
Muscle biochemistry					
Citrate synthase activity ($\mu mol \cdot g^{-1} \cdot min^{-1}$)					
3-HAD activity ($\mu mol \cdot g^{-1} \cdot min^{-1}$)					
PFK activity ($\mu mol \cdot g^{-1} \cdot min^{-1}$)					
Clinical and patient-reported					

SF-36 (total and subdomains)					
SAMS scores (0–10)					

Section 6: Analysis

26. Outcome definitions

Primary outcome

- *Citrate-synthase maximal activity* (µmol·g^{-1}·min^{-1}), measured in skeletal-muscle homogenates by fluorometry.
  The primary endpoint is the change from baseline (V1) to 12-week follow-up (V2).

Key secondary outcome

- *Maximal oxygen uptake (VO_{2peak})* (mL·kg^{-1}·min^{-1}), assessed during an incremental cycling test to exhaustion.
  The key secondary endpoint is the change from V1 to V2.

Additional secondary outcomes

Unless otherwise specified, outcomes refer to the within-participant change (V2 – V1).
They include (but are not limited to) variables in the following domains:

1. **Cardiorespiratory and hemodynamic:** VO_{2peak} (absolute), steady-state VO_2, resting HR, systolic and diastolic BP.
2. **Body composition and anthropometry:** body weight, fat %, lean mass (BIA), waist/hip circumference.
3. **Lipid and lipoprotein profile:** total, LDL, HDL, triglycerides, lipoprotein(a), apolipoproteins (A-I, B-100 etc.), CETP, LCAT, albumin, transthyretin.
4. **Glucose metabolism and insulin sensitivity:** fasting glucose, insulin, HbA_1c, HOMA-IR, Matsuda index, ISR, oral disposition index.

5. **Muscle biochemistry and mitochondrial function:** 3-HAD, PFK, CoQ10, intramuscular atorvastatin (CoQ10 and intramuscular atorvastatin will be quantified only where sufficient muscle tissue is available after primary analyses).
6. **Patient-reported outcomes:** SF-36 (total + subdomains), SAMS (severity & type).
7. **Exploratory outcomes:** anaerobic capacity (Wingate), systemic biomarkers (CoQ10, CRP, cytokines), white-blood-cell count, telomere length, PFAS, hemoglobin mass (CO-rebreathing), targeted / untargeted muscle proteomics, RPE (training/testing).

Note: Detailed laboratory and assay procedures (e.g., DIA-PASEF, UHPLC-MS) are specified in the main protocol. Outcome definitions may be refined based on data quality and scientific relevance before database lock.

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27. Analysis method

Analyses will primarily follow the intention-to-treat (ITT) principle (see Section 20), with complementary per-protocol (PP) analyses assessing efficacy under adherence conditions.

Primary Analysis

All continuous outcomes will be analyzed using constrained mixed models, with inherent baseline adjustment (all participants will be put in the same group at baseline). The model will include group (four arms), time (V1/V2; categorical), group × time interaction, sex (male/female), and prior active statin treatment (yes/no) as fixed effects and will be specified with an unstructured covariance pattern to account for repeated measurements on each participant and use Kenward–Roger degrees-of-freedom approximation. Model residuals and fitted values will be inspected, and right-skewed outcomes may be log-transformed.

Supplementary analysis

- **Per-protocol analysis:** conducted in the predefined PP population (see Section 20) to estimate efficacy under adherence conditions.

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28. Handling Missing Data

Missingness may occur due to withdrawal, assay failure, or QC exclusion.
Analyses will assume that outcome data are missing at random (MAR) conditional on observed data included in the analysis model. Missing data will be handled implicitly in the constrained mixed model using maximum likelihood estimation. The extent and reasons for missingness will be summarized by group.

Sensitivity analyses

Sensitivity analyses for the primary outcome (CS activity) and the pre-specified secondary outcome (VO_{2peak}) may be conducted if dropout exceeds 10% in any randomization group to assess robustness to missing-data assumptions. In such cases, simple plausibility-bound scenarios may be applied (e.g., baseline value carried forward). These analyses are intended as plausibility bounds rather than definitive MNAR analyses; confirmatory inference for ΔCS will remain based on the prespecified LMM under the MAR assumption; VO_{2peak} sensitivity results will be interpreted descriptively.

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29. Additional analyses (supportive/exploratory)

29.1 Pre-specified mechanistic endpoints (supportive)

Exploratory mechanistic outcomes (e.g., anaerobic capacity, systemic biomarkers including inflammatory markers and per- and polyfluoroalkyl substances) will generally be analyzed using the same model framework as in Section 27

29.2 High-dimensional discovery analyses (omics)

Untargeted proteomic and metabolomic data will be processed using current best-practice pipelines (e.g., DIA-NN, Spectronaut, and/or established R-based workflows). Statistical methods (e.g., moderated t-tests/linear models [LIMMA], empirical Bayes approaches, or mixed models where repeated measures are available) will be selected based on data dimensionality, variance structure, and diagnostics. Multiplicity in omics analyses will be addressed using false discovery rate (FDR) control (e.g., Benjamini–Hochberg), and findings will be reported as hypothesis-generating.

29.3 Genetic and effect-modification analyses (exploratory)

Pre-specified candidate polymorphisms will be evaluated as potential effect modifiers of statin and/or exercise responses. Models may include genotype (e.g., allele dosage) and its interaction with group × time terms; subgroup summaries (e.g., carriers vs non-carriers) may be presented where allele frequency permits. Results will be interpreted as exploratory with multiplicity control (e.g., FDR) applied where appropriate.

29.4 Sex-dependent analysis (exploratory)

Potential sex differences will be explored by extending the primary model to include a group × time × sex interaction. These analyses are intended to describe potential heterogeneity of response and will be interpreted as hypothesis-generating.

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30. Harms

Adverse events (AEs), including statin-associated muscle symptoms (SAMS), will be monitored prospectively from intervention initiation (first dose and/or first supervised training session) until the post-intervention visit (V2).

All reported events will be summarized descriptively by intervention group according to:

- **Frequency** (number and percentage of participants reporting ≥1 AE),
- **Severity** (mild, moderate, severe)
- **Assessed relationship to study intervention** (related, possibly related, unrelated).

Pre-specified questionnaires (e.g., a structured SAMS symptom inventory) will supplement spontaneous reports to ensure standardized data collection. Serious adverse events (SAEs) and withdrawals due to AEs will be listed individually and summarized by category.

Safety summaries will be based on the Safety population (participants with ≥1 exposure to the allocated intervention; consistent with the ITT definition). If sample size permits, exploratory subgroup summaries (e.g., by sex or adherence status) may be presented to describe patterns in AE reporting; no formal hypothesis testing is planned for safety endpoints.

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31. Statistical software

Primary and confirmatory analyses will be conducted in R (version ≥4.0). Python (version ≥3.10) may be used for supportive analyses, data processing, and independent verification where appropriate. Exact software and package versions used for the final locked analysis will be documented in the analysis log and/or supplementary materials.

References

Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, Williamson PR, Altman DG, Montgomery A, Lim P, Berlin J, Senn S, Day S, Barbachano Y & Loder E (2017). Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. *JAMA* **318,** 2337–2343.

Keteyian SJ, Brawner CA, Savage PD, Ehrman JK, Schairer J, Divine G, Aldred H, Ophaug K & Ades PA (2008). Peak aerobic capacity predicts prognosis in patients with coronary heart disease. *Am Heart J* **156,** 292–300.

Khan H, Kunutsor SK, Rauramaa R, Merchant FM & Laukkanen JA (2018). Long-Term Change in Cardiorespiratory Fitness in Relation to Atrial Fibrillation and Heart Failure (from the Kuopio Ischemic Heart Disease Risk Factor Study). *American Journal of Cardiology* **121,** 956–960.

Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, Yamada N & Sone H (2009). Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: A meta-analysis. *JAMA - Journal of the American Medical Association* **301,** 2024–2035. Available at: www.jamaarchivescme.com [Accessed June 22, 2021].

Laukkanen JA, Zaccardi F, Khan H, Kurl S, Jae SY & Rauramaa R (2016). Long-term Change in Cardiorespiratory Fitness and All-Cause Mortality: A Population-Based Follow-up Study. *Mayo Clin Proc* **91,** 1183–1188.

Mikus CR, Boyle LJ, Borengasser SJ, Oberlin DJ, Naples SP, Fletcher J, Meers GM, Ruebel M, Laughlin MH, Dellsperger KC, Fadel PJ & Thyfault JP (2013). Simvastatin impairs exercise training adaptations. *J Am Coll Cardiol* **62,** 709–714.

Myers J, Prakash M, Froelicher V, Do D, Partington S & Atwood JE (2002). Exercise Capacity and Mortality among Men Referred for Exercise Testing. *New England Journal of Medicine* **346,** 793–801.

Sjúrðarson T, Bejder J, Andersen AB, Bonne T, Kyhl K, Róin T, Patursson P, Gregersen NO, Skoradal M-B, Schliemann M, Lindegaard M, Weihe P, Mohr M & Nordsborg NB

(2022*a*). Effect of angiotensin-converting enzyme inhibition on cardiovascular adaptation to exercise training. *Physiol Rep* **10,** e15382.

Sjúrðarson T, Bejder J, Breenfeldt Andersen A, Bonne TC, Kyhl K, Thomassen M, Prats J, Oddmarsdóttir Gregersen N, Skoradal MB, Weihe P, Nordsborg NB & Mohr M (2022*b*). Robust arm and leg muscle adaptation to training despite ACE inhibition: a randomized placebo-controlled trial. *Eur J Appl Physiol*1–13.

Sjúrðarson T, Larsen S, Jensen SBK, Bejder J, Rasmussen J, Á Borg S, Kristiansen J, Meinhardsson JM, Olsen HW, Ellingsgaard H, Vigh-Larsen JF, Nordsborg NB & Mohr M (2025). Investigating the combined effects of statins and exercise on skeletal muscle mitochondrial content and function, cardiorespiratory fitness and quality of life in individuals with dyslipidaemia: protocol for a randomised placebo-controlled trial. *BMJ Open* **15,** e101425.

Tari AR, Brissach DE, Ingeström EML, Nauman J, Tyrell T, Foster C, Radtke K, Porcari JP, Lydersen S, Kaminsky LA, Myers J, Walker TL, Coombes JS, Stensvold D & Wisløff U (2024). Survival of the fittest? Peak oxygen uptake and all-cause mortality among older adults in Norway. ; DOI: 10.1016/j.pcad.2024.11.004.