# HYPERtension reduction through WALKing stairs versus brisk walking in individuals with increased cardiometabolic risk - The HYPERWALK randomized controlled trial

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**CREDiT Statement:**
PA, CJS, EK, RS, AUM, SW, HW, MH, AN, IS, RC, ES, GF, JN, DE, KS and EAZ contributed to **conceptualization, methodology, and investigation**.
PA, CJS, EK, RS, AUM, SW, HW, MH, AN, RSa, ES, EF, ML, GF, CK, JN, HH, DE and EAZ were involved in **writing, review, and editing**.
PA and EAZ contributed to **original draft writing**.
DE, HH and EAZ contributed to **software**.
PA, CJS, RS, SW, HW, MH, EK, CK, RC, GF, and JN handled **supervision and project administration**
PA, CJS, RS, AUM, EK, DE, SW, MH, AN, ES, GF were responsible for **funding acquisition**.
EF managed **project administration,**
ML handled **project communication**.

# Contents

# Administrative information

**Writers of the Protocol, signature and date:**

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Emmanuel Zavalis

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David Ebrahimi

**Signature of senior statistician responsible, signature and date:**

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**Protocol v.1**

**Intended for registration on ClinicalTrials.gov**

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- **NSV Project Funding 2025**: CJS

The study funders had no role or authority regarding the study.

**Ethics approval number: 2014-05912-01**
This protocol and the analytical methods have been devised in accordance to the SPIRIT(*1*) and the SAP checklist(*2*).

[13092025] Protocol amendment prior to start of enrollment: stratification by site and age instead of by sex and age to adjust for potential differences in population and to provide better support for substudies.

# Introduction

Physical inactivity is a significant contributor to a wide range of chronic health conditions, including type 2 diabetes, cardiovascular diseases, cancer, and cognitive dysfunction, ultimately leading to a reduced lifespan (*3*–*6*). Hypertension, a leading risk factor for cardiovascular morbidity and mortality, is particularly influenced by sedentary behavior, even in a recent randomized trial (*7*, *8*). Despite the well-established benefits of physical activity, including its comparable effects to antihypertensive medications (*9*) sedentary lifestyles remain widespread, affecting approximately 37% of individuals in Western countries (*10*–*13*).

Even modest increases in physical activity can positively impact health outcomes. For example, incorporating short bursts of activity during sedentary periods has been shown to provide health benefits (*14*–*17*), with high-intensity exercises providing the greatest benefits (*18*, *19*). Stair walking, a simple and accessible form of high-intensity exercise, offers a cost-effective and time-efficient strategy for increasing physical activity levels. However, prior randomized controlled trials (RCTs) on stair walking have been limited by small sample sizes (*20*, *21*) and the need for supervised training programs which may be impractical for widespread implementation (*22*).

Physical activity interventions remain underutilized in hypertension management, despite consensus regarding their inclusion in clinical guidelines (*23*). Furthermore, the World Health Organization's 2024 recommendation of 2.5 hours of moderate-intensity physical activity per week, provide general guidance but lacks specific, actionable strategies proven by randomized trials (*24*). This limits their practical implementation by both clinicians and patients.

To address these gaps, the HYPERWALK trial investigates the impact of doubling physical activity levels through remote monitoring, personalized feedback, and goal-oriented motivation on systolic blood pressure (SBP), with and without the inclusion of stair walking. The trial will compare two active interventions with each other and with a control group that receives no reminders, feedback, or tailored goals.

# Trial design

The trial is designed as a randomized, controlled, investigator- and analyst-blinded multicenter trial with three parallel groups and a primary endpoint of SBP at six months. It will test for superiority of combined stair walking and brisk walking to solely brisk walking, and the superiority of both active arms to a passive control group. Randomization will be conducted with equal allocation in/among the groups.

The three randomization arms are:

A. Combined stair walking and brisk walking
B. Brisk walking only
C. Control

Arms A and B are the active, experimental arms.

## Randomization procedure

Random numbers generated by a computer will be used to randomize participants, stratified by ~~sex~~ site grouped according to anticipated population similarities into four groups as follows:

- Liljeholmen + Boo
- SÖS + Ersta
- Huddinge separate
- Södertälje separate

[13092025]

and age (cutoff 65 years) through a randomization list with random permuted blocks created and uploaded by the external trial statistician. Allocation will be done by a researcher in the trial team that will not meet the participants. If a participant discontinues their involvement, their trial-specific code will not be reused, and they will not be allowed to re-enter the trial. Allocation will be performed by informing the patient after the completion of baseline data collection, with randomization conducted directly using the eCRF. Participants will be notified remotely.

## Blinding

Blinding participants is not possible due to the nature of the intervention. To decrease the risk of bias, allocation will be revealed after baseline data collection by personnel not involved in outcome assessments. To preserve blinding of assessors, participants will be instructed to not disclose their group during follow-up. Additionally, study personnel will report whether blinding was upheld after data collection is completed during the follow-up.

## Study setting

The trial will recruit participants from six study sites in Stockholm, Sweden, including three hospitals—Karolinska University Hospital in Huddinge, Södersjukhuset, and Södertälje Hospital—and three primary care or outpatient cardiology clinics: Liljeholmen Primary Care Center, Boo Primary Care Center, and Ersta Cardiology Outpatient Clinic. Participants will be primarily referred from primary care, with some referrals from specialized care. Additional partner sites from Region Örebro, Västra Götalands Region, and Region Sörmland may join the trial to facilitate multi-regional and timely participant inclusion. In addition, we may recruit through online self-signup via social media advertisement.

## Primary hypothesis

Doubling physical activity through goal-directed physical activity regimens is expected to reduce SBP at a 6-month follow-up compared to routine care. This study will specifically have two primary hypotheses to assess the efficacy of this intervention with two different activity

regimens i) incorporating stair-walking or ii) only brisk walking. The hypotheses to be tested are:

- Any goal-directed instruction (i.e. both active arms) is superior to no instruction, where participants carry the activity tracker without feedback (passive control). Hence the analysis will be arms A & B vs arm C
- Combined stair-walking and brisk walking is superior to brisk walking alone. Hence the analysis will be arm A vs arm B

## Secondary hypotheses

Physical activity acts as a polypill, influencing multiple pathways in individuals with increased cardiometabolic risk (*25*). Therefore, the same group comparisons as in the primary hypothesis will be made for diastolic blood pressure, glucose metabolism (homeostatic model assessment - HOMA index and glycated hemoglobin A1c - HbA1c), and lipid levels (low-density lipoprotein - LDL cholesterol and triglycerides). Additionally, physical activity levels during the intervention period will be assessed to determine which intervention is most effective at increasing physical activity.

## Subgroup hypotheses

A subgroup analysis incorporating age (35-65 vs. >65), sex, body mass index (BMI) (27-30 vs. >30), and baseline physical activity levels (0-75 vs. ≥75 active minutes) into the statistical model will be performed to assess potential interactions as exploratory analyses.

## Substudies

Within the HYPERWALK trial, we aim to perform a variety of **hypothesis-generating** substudies to explore the broader effects of the interventions based on multiple measurements including on:

- *Cardiometabolic* parameters, including additional lipid and glucose metabolism analyses, including oral glucose tolerance testing or mixed meal tolerance testing.
- *Arrhythmias*, e.g. ventricular extra systoles, and atrial fibrillation burden as well as electrocardiogram (ECG) phenotype.
- Parameters of importance to the strata ≥65 of age such as orthostatism, falls, and frailty.
- *Functional capacity, fitness, and muscular strength* in further detail.
- *Self-assessed health-related outcomes and adherence deep dive*: Assess the effect of a diverse range of predictors of adherence to better tailor future interventions.
- *Health economic analysis*
- *Long-term follow-up of clinical outcomes from national registries*
- Mechanistic and translational pathways through assessment of adipose tissue and muscle tissue biology and possibly echocardiogram parameters.

# Study population

## Eligibility criteria

The HYPERWALK study aims to assess the effect of different exercise strategies for increasing physical activity in sedentary individuals with hypertension and increased BMI.

BMI has shown a strong correlation to cardiovascular risk (*26*), which is more pronounced at or above the threshold of 30 kg/m$^2$ (*27*); therefore, we aim to primarily include obese participants. However, an upper limit of 40 kg/m$^2$ will be set to decrease the risk of exercise-related injuries. To ensure comparability with the evidence on glucagone-like peptide-1 receptor (GLP-1R) agonists like semaglutide (*28*, *29*) overweight people (BMI ≥27) will also be included.

Assessing sedentary lifestyle is challenging, as objective measuring of physical activity (through digital activity trackers) is costly and time-consuming and may influence prospective participants' behavior. Self-reported physical activity levels, meanwhile, tend to be inflated (*30*). To address this, an inclusive approach will be employed through widely used and validated questionnaires: the Stanford Brief Activity Survey (*31*) and the Swedish indicator questions, similar to the Exercise Vital Sign of Kaiser Permanente (*32*), which is validated and recommended in the Swedish clinical setting (*33*). Participants classified as sedentary by either questionnaire will be eligible to improve sensitivity in detecting participants with low levels of physical activity. As previously outlined in the Introduction, sedentariness is associated with increased metabolic and cardiovascular risk.

### Inclusion criteria

**Men and women, 35 years of age** or older with increased cardiometabolic risk defined by all the following three criteria:

1. **Clinically confirmed diagnosis of hypertension** (any diagnosis of hypertension in the Electronic Health Record - EHR), with or without medical treatment.
2. **Overweight or obese.** BMI ranging between 27 - 40
3. **An inactive lifestyle** is defined by either of two approaches:
    - **a.** Light intensity or inactive lifestyle according to the **Stanford Brief Activity Survey (SBAS)**
    - **b.** Light intensity or inactive lifestyle according to the **physical activity section of the Swedish National Board of Health and Welfare Lifestyle questionnaire.**

### Exclusion Criteria

- **Any medical condition that is an absolute contraindication to physical activity per FYSS (Physical Activity in the Prevention and Treatment of Disease) 2021 p. 182**(*34*) **or Pacemaker/implantable-cardioverter defibrillator (ICD):**
    - Severe symptomatic aortic stenosis.
    - Acute pulmonary embolism, myocarditis, pericarditis, or systemic infection (including fever, muscle pain, lymphadenopathy).
    - Suspected or known aortic dissection.
    - Severe hypertension (grade 3 – SBP > 180 mmHg or diastolic blood pressure - DBP > 110 mmHg) (regardless of symptoms, as a precaution).
    - Unstable coronary artery disease (unstable angina/sub-optimally treated stable angina/recent acute myocardial infarction <8 weeks).
    - Symptomatic uncontrolled arrhythmia.
    - Symptomatic uncontrolled heart failure.
    - Pacemaker or ICD.
    - Pregnancy.
- Other exclusion criteria

- Smartphone with **operating system incompatible with Fitrockr** (iOS < 16/Android OS <10)
- Inability to understand Swedish or English.
- Any other condition that may interfere with the participant's ability to comply with the study protocol, e.g. severe mental illness or cognitive disorder.
- **Inability to walk stairs**.

# Recruitment

For a clinically representative population, we aim to recruit continuously from routine annual hypertension visits at academic primary care centers. This approach minimizes the potential confounding of medication changes through/during the intervention period. Screening visits will be scheduled >1 month after the primary care visit. Online sign-ups will also be allowed. Consent will be collected digitally through electronic consent, allowing for remote pre-screening.

## Retention

Personnel will attempt to verify withdrawal or motivate continuation in all patients that are lost to follow-up. The reason for withdrawal will be tabulated. Efforts will be made to verify and ascertain reasons for loss to follow-up. Time point for withdrawal or loss to follow-up will be tabulated as well. The number, along with the reasons of losses to follow-up (dropouts and withdrawals) over the course of the trial will be summarized by the treatment arm.

To promote retention, participants will receive a text chat message via FitRockr, approximately once per month, allowing the opportunity to discuss their study experience and any issues, including feedback regarding study participation. Additionally, staff will contact participants to ensure that participants charge their accelerometer.

### Enrolment information

We will provide the following recruitment metrics: number of days recruiting, number of patients screened, and the number of patients recruited (per day and total). Furthermore, screened but non-recruited individuals will be documented, including the reason for non-recruitment.

### CONSORT diagram

A CONSORT flow diagram (Appendix A) will summarize the participant information as seen by the attached diagram. Reasons for ineligibility, non-randomization and exclusion will be provided.

### Baseline characteristics

Participants will be described based on age, gender, time since hypertension diagnosis, standardized daily hypertension treatment dose (as defined in (*35*)), BMI, diabetes, and BMI both overall and separately for each treatment arm.

Categorical data will be summarized as numbers and percentages. Continuous data will be summarized as mean and standard deviation (SD) if data are normally distributed or media and interquartile range (IQR) for skewed data. Minimum and maximum values will also be presented for continuous data. Tests for differences between the groups and possible statistical significance will not be undertaken for baseline characteristics, rather the clinical importance of any imbalance will be noted.

# Sample size

As the main outcome analysis is an analysis of covariance (ANCOVA), for the primary outcome of SBP, sample size calculations were based on ANCOVAs of simulated data. For the simulations, we assume a standard deviation of $13^2$ mmHg for all groups and timepoints.

Empiric autocorrelations values from a previous individual patient data (IPD) meta-analysis (*36*), which range from 0.137 and 0.5134, were used. Using this information, statistical power was assessed through simulations with varying difference between the intervention arms and different sample sizes (1000 simulations). With an autocorrelation of 0.137 (most conservative) and 50 participants per arm the trial is powered to detect a difference between each arm of 2 mmHg (>80% simulated power) for the two primary tests. We consider a 4-mmHg difference clinically meaningful for comparison of the active arms to the control group and 2 mmHg meaningful for the comparison between the active arms.

# Intervention

Insufficient time and knowledge among general practitioners are among the many barriers to counseling patients on physical activity (*37*). The interventions in this trial are designed to simplify and personalize current recommendations.

In brief, eligible participants' baseline physical activity levels will be assessed remotely for a week, during which they will be instructed to maintain their usual activity level. Subsequently, participants will be randomized to double their activity levels with or without the incorporation of stair-walking. The calculated target time (CTT) is expressed in moderate intensity activity minutes, with one minute of stair-walking corresponding to two minutes of moderate intensity activity. The CTT will be distributed as follows for the two active arms:

**Stair-Walking Group**

- 25% of CTT will come from stair walking.
    - 37.5 minutes of stair walking corresponds to 1750 steps (or 250 steps per day) or 46.6 steps per minute. The daily step goal is calculated as:
        - $Daily\ steps = \frac{\frac{1}{4} * CTT * 46.\overline{6}}{7}$ or $Daily\ steps = CTT * 1.\overline{6}$
- 50% (or 2/4) of the calculated target time will come from brisk walking.

For highly sedentary participants (<75 moderate intensity activity minutes per week) the minimum protocol will be applied 250 daily stair steps (37.5 min a week) and 75 minutes of brisk walking.

**Walking Group**

The goal is to double the baseline moderate-intensity activity level exclusively through brisk walking. For highly sedentary participants (<75 moderate intensity activity minutes per week) the minimum protocol will be applied, corresponding to 150 minutes of brisk walking.

The ***Passive control*** group will be recommended to adhere to the guideline-recommended level of physical activity.

All groups will receive the Swedish Heart Lung Foundation´s short text on lifestyle habits. An incremental titration of activity levels will be performed with increases of 25% increments towards intended levels per week. Both active groups will receive instructions on how to maintain their prescribed physical activity levels, and wearable activity monitors will track their progress. Individual feedback will be provided regularly, to monitor adherence and progress throughout the 6-month intervention period. Passive controls will not receive the same encouragement.

## Monitoring and promoting adherence

Activity levels will be monitored using a wearable activity tracker (Garmin© Vivosmart 4) in all groups throughout the study. Participants will receive individual feedback through the mobile app (Fitrockr©), designed to track progress and maintain motivation throughout the study period. The design of the adherence monitoring and feedback is based on prior literature and will therefore use push notifications, positive reinforcement, and follow-up through phone calls monthly (*38–40*).

During the titration phase, participants will receive more frequent feedback than later in the study. After the titration phase they will receive feedback twice every week. For the stair-walking group, feedback will include number of stair steps walked (and the percentage of recommended dose), moderate intensity physical activity minutes (and the percentage of recommended dose), and daily steps. The brisk walking group will receive feedback with moderate intensity physical activity minutes (and the percentage of recommended dose), and

daily steps. All groups will receive standardized reminders to wear and charge their digital activity tracker and synchronize their data.

Details regarding the setup of the digital activity tracker (Garmin© Vivosmart 4) and of the mobile app (Fitrockr©) for data collection and individualized guidance will be provided before the study start and outlined in the final Appendix.

Adherence will be presented in the primary publication as moderate intensity activity minutes for the three study arms.

## Criteria for discontinuation and concomitant care

Participants have the right to cease their involvement in the trial at any point at their own discretion. Investigators can terminate a subject's participation due to unacceptable harm. The reason for discontinued participation will be tabulated for all participants that exit the trial. Participants are allowed any concomitant care as needed.

## Insurances

All participants in the trial are covered by the Swedish Patient Insurance (Patientskadeförsäkring). Additionally, a 'särskilt personskadeskydd' insurance is obtained by the responsible researcher via Legal, Financial and Administrative Services Agency (Kammarkollegiet). Moreover, the responsible researcher holds a professional insurance via Folksam and the Swedish Medical Association (Sveriges Läkarförbund). These insurance policies ensure comprehensive coverage for trial subjects throughout the study duration.

# Measurements

## Data management and auditing

All data will be registered and stored using an electronic Case Report Form (eCRF) based on the web application BASS, which is compliant to local information safety requirements (bank-level security, with pseudonymization). Monitoring will adhere to Good Clinical Practice (GCP) guidelines. Data will be managed by a statistician independent of this study (defined in the role assignments section)**.** The database will be maintained until further notice (at least 20 years after inclusion of the last patient) and be reported in accordance with the Personal Data Act (PUL, 1998:204). The authority responsible for the database is Karolinska Institutet, and the cleaned data will be made available to all principal investigators of the study.

## Auditing

For the first 2 months of enrollment at each center, weekly monitoring will be conducted by the trialists. This includes reviewing inputs to the eCRF, eligible patients, randomized participants' initial assessments, and the documentation and instructions for the trial

## Data collection methods

After collection of all data points at follow-up visits, the assessor will be questioned whether blinding was upheld. All measured variables will be performed 1-2 weeks prior to randomization and at the 26-week (6 months) follow-up. Remote monitoring is outlined in the chart below.

| | Time | Virtual | Screening visit (-1-2w) | Follow-up (26 w) |
|---|---|---|---|---|
| (Selection criteria & past medical history) | 30 min | X | | |
| **Anthropometrics**<br>BMI, waist circum. | 5 min | | X | X |
| **Physical examination and physiological assessment**<br>Blood pressure<br>Orthostatic test (>65)<br>12 lead ECG | 30 min | | X | X |
| **Blood samples** | 20 min | | X | X |
| **Breakfast** | 15 min | | X | X |
| **Fitness assessment**<br>10s. one-legged stance (>65)<br>Sit to stand test<br>Hand grip<br>6MWT | 10 min | | X | X |
| **Remote monitoring**<br>Monitor install and instruct<br>24h BP cuff and instruct<br>72h 3-lead aECG (Cortrium C3+) | 30 min | | X | X |
| (Questionnaires) | 30-40 min | X | | |
| (Clinical and risk factor anamnesis) | 15 min | X | | |
| **Total estimated time** | | | **~2h** | **~2h** |

**Selection criteria, and past medical history: - 30 min**

Demographics will be collected during pre-screening. This includes contact information, personal identification number, highest level of education and category of monthly income. Eligibility criteria pertaining to the selection criteria will be collected (as outlined in the Exclusion criteria).

Past medical history will be collected using information from the electronic healthcare record regarding cardiovascular, pulmonary, musculoskeletal, metabolic, psychiatric, and oncological disease. The purpose is both to collect baseline information but also to calculate cardiovascular risk scores such as NORRISK, Framingham and others for substudies.

**Biological samples: - 10 min**

Certified personnel will collect blood from each participant while they are in a fasting state. The blood will be analyzed at certified laboratories with no knowledge of allocation, for cholesterol (total/high lipoprotein - HDL/calculated LDL), triglycerides, glucose, HbA1c, and insulin, as well as blood phosphatidylethanol (B-Peth) for certain sites. Blood samples will be frozen and stored in Karolinska Institutet Biobank, in compliance with local laws.

**Questionnaires:**

Participants above 65 years of age will complete the Tilburg frailty indicator and KASAM-13 questionnaire (sense of coherence). All participants will complete the Generalized Anxiety Disorder 7 (GAD7) questionnaire for anxiety screening and the EQ-5D-5L questionnaire for health-related quality of life (HRQOL). They will also be allowed to select among the collected data which one they are most interested in addressing with this intervention.

**Anthropometrics**

Participants' weight, and body composition will be measured using a bioimpedance scale provided by the trialists (Omron BF511), and their height will be measured to a precision of 0.1 cm. Waist circumference will be measured with the participant standing, using a metal tape (midaxillary line).

placed horizontally along the mid-axillary line just below the umbilicus. All measurements will be input into the eCRF. BMI will be calculated directly within the eCRF.

**Physical examination and physiological assessment**

Office blood pressure will be measured using a trialist-provided monitor (Omron 9210T) with measurements five times, separated by one minute, on the dominant arm and transmitting the data with timestamps electronically to the eCRF. The average of the last three measurements, computed automatically in the eCRF, will be used for analysis of outcomes.

An orthostatic blood pressure measurement will be performed following this using standard protocols at 1, 3, 5 and 10 minutes after rising from seated position.

A 12-lead ECG will be performed according to standard protocols in specific sites.

Patients with grade 2 hypertension (≥160-179/100-109 mmHg) will be referred to primary care to ensure immediate initiation or uptitration of medical treatment, adhering to the 2023 European Society of Hypertension Guidelines. Additionally, participants with a prior diagnosis of hypertension who are already under medical treatment but still present with grade 2 hypertension, will be referred to the primary care to consider an adjustment or increase in their treatment regimen.

**Fitness assessments:**

- *6-minute walk test* (meters walked in 6 minutes): used to estimate aerobic capacity. Participants will walk back and forth on a flat hard surface as fast as possible for 6 minutes. The distance walked is measured(*41*).

- *Hand Grip Strength:* assessed to measure muscle strength. The Jamar hydraulic dynamometer will be used, and the participants will measure their grip strength in both hands (*42*).
- *10-second one-legged stance test:* to assess balance in participants over the age of 65, participants will stand with elbows extended, place the dorsal part of the non-support foot on the back of the opposite leg, and fix their gaze on an eye-level point at a 2 m-distance. Ability to complete 10-s balance test (yes or no) on right and left foot will be tabulated(*43*).
- *VO2 Max: Measured using the Ekblom Bak protocol* (*44*)*, step*-up box (*45*) and sit to stand test (*46*) will be performed only in specific sites.

**Clinical and risk factor anamnesis**

Tobacco, alcohol, and dietary anamnesis will be collected using the Swedish National Board of Welfare's screening questions for lifestyle factors (found in the appendix). Participants will be asked about their medication history and their adherence to medication listed in their EHR at the time of the appointment, and input into the eCRF. This allows future assessments of adjustments in blood pressure medications during the trial in a standardized way as in Min et al. (*35*). Falls in the elderly strata as well as harms as outlined in the harms section will be collected as well.

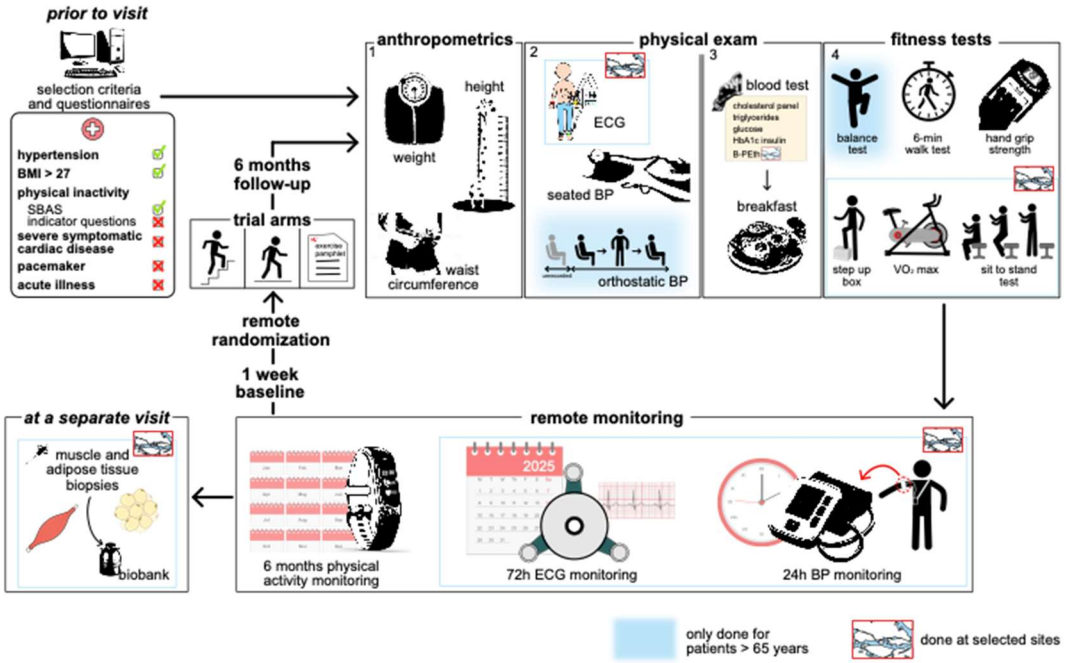
**Remote monitoring:**

*Digital activity tracker (Vivosmart 4 by Garmin)*

Physical activity levels for all participants will be monitored with a digital activity tracker. The band should be worn loosely enough that it can move back and forth on the wrist of a participant; however, during activity it may benefit from a snugger fit.

The accelerometer will continuously record each participant's pulse rate through pulse oximetry, movement through accelerometer and barometric-derived altitude measurements. Moreover, an array of different data points including sleep, daily steps among many others. To be registered in the Fitrockr app, an activity must be ongoing for more than ten minutes, however in the research database all movement is recorded and saved.

Continuous Holter ECG Continuous 2-lead registration for 5-7 days through an adhesive patch electrode on the chest to collect information about the heart rhythm in specific sites (Cortrium C3+).



**Registry data collected up to 10 years after study completion:**

- **Health economic parameters** – Healthcare consumption and health-related productivity loss associated with investigated interventions will be assessed by extracting resource use from the relevant registries, including data from the Swedish Social Insurance Agency.
- **Incidence of type 2 diabetes mellitus, chronic kidney disease, non-alcoholic fatty liver disease, myocardial infarction, heart failure, as well as cardiovascular disease, and medication history and vital status** – this will be extracted by linking with national quality-of-care registries including the Swedish National Patient Registry, Regional Primary Care Registries, National Prescribed Drug registry and the Swedish Population Registry.

## Harms

Harm here is defined as an untoward event irrespective of causal relationship. Only harms that lead to hospitalization or study withdrawal will be tabulated. These may include severe injury to the musculoskeletal system, cardiovascular events, and falls among the elderly.

# Dissemination policy

### Publication Policy

The Publications group will review all publications following the guidelines given below and report its recommendations to the Steering Committee.

### A. Data analysis and release of results

Analysis of clinical outcomes will be performed by a blinded statistician. The Steering Committee will provide recommendations on the timing and meetings for presenting endpoint data.

### B. Review process

Each paper or abstract, as described below, must be submitted to the appropriate Publications group for review of its suitability and scientific merit prior to submission. The group may recommend changes to the authors and will submit its recommendations to the Steering Committee for approval.

### C. Primary outcome papers

Primary outcome papers will present primary and secondary outcome data as described in this protocol.

### D. Other study papers, abstracts, and presentations

All studies other than those designated as “Primary Outcome” fall within this category, including the publication of the present protocol. All papers and abstracts must be approved by the Publications group before they are submitted. If a topic is suggested by a member or external individual, they can be considered the lead authors of the study. Disputes regarding authorship will be settled by the Study Chair in consultation with the Chair of the Publication group.

### XIII. Close-out Procedures

Regardless of the timing and circumstances of the end of the study, close-out will proceed in two stages 1) interim period for analysis and documentation of study results 2) Debriefing of participants and dissemination of study results.

### A. Interim

Efforts will be made to reduce the time between the completion of data collection and release of study results. We expect it to take about 3 to 4 months to compile the final results paper for an appropriate journal.

### B. Reporting of study results

The study results will be shared with participating physicians, referring physicians, patients, and the general medical community. Results will be openly reported on the site of trial registration. No later than 3 years after trial completion, a completely de-identified dataset will be delivered to an appropriate data archive for sharing (Individual Participant Data a.k.a. IPD).

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# Statistical analysis plan for the HYPERWALK randomized controlled trial.

*Following SAP guidelines in Gamble et al. JAMA 2017 Guidelines:* Information from sections 1-3 from is found in the protocol

## Statistical Principles

### Confidence intervals (CI) and p-values

The applicable tests will be 2-sided and will for the primary outcomes be performed using a 0.05 significance level. For secondary hypotheses alpha of 0.005 will be considered significant, while 0.05 will be considered suggestive following previous recommendations (*48*). The same testing approach as in the primary analysis will be used for the secondary outcomes.

### Adherence and Protocol Deviations

### Adherence Criteria

Adherence is defined as participating in more than 80% of the follow-up time monitored remotely using the digital activity tracker (Garmin Vivosmart 4). The prescribed level will be based on a 1-week baseline measurement, converted into moderate-intensity physical activity minutes. The target for the active groups (calculated target time, CTT) will be double the baseline moderate-intensity activity minutes, as described in the intervention section of the HYPERWALK protocol.

Adherence will be presented as the number and percentage of participants meeting the adherence criteria measured by the digital activity tracker. Descriptive statistics will be presented by randomization group presenting % and 95% CIs.

### Definition of Analysis populations

The intention-to-treat population will include all randomized patients, according to the treatment they were randomized to receive. Per-protocol will be assessed for those considered adherent as defined previously as a sensitivity analysis.

# Analysis methods

**Outcome definitions:**

*Primary outcome*

6 months change in systolic blood pressure from baseline (mmHg).

*Secondary outcomes*

6 months change in diastolic blood pressure from baseline (mmHg)
6 months change in fasting LDL directly measured (mmol/L)
6 months change in fasting Triglycerides directly measured (mmol/L)
6 months change in fasting HbA1c from baseline (mmol/mol)
6 months change in HOMA-index (HOMA-IR) from baseline (with glycaemia in mmol/L and insulin in mU/L)

**Statistical methods**

The average change in SBP at 6 months follow-up will be presented, and the results will be analyzed using ANCOVA: a linear regression model including the treatment variable and adjusting for baseline SBP and the factors used in the randomization: sex and age (categorised as <65 or ≥65). One model will be fitted including the two active arms only (arm A vs arm B) and one including a treatment variable coded as (arm A & arm B) vs arm C. Evidence for an intervention effect will be assessed using the p-value of the (binary) treatment variable No other pre-planned covariates will be included in the models; baseline characteristics which show a clinically meaningful imbalance, will be included at the discretion of the trial statistician. The same approach as for the primary analyses will be used for the secondary outcomes.

**Sensitivity analysis**

A sensitivity analysis of the primary outcome will be performed as on treatment for those defined as adherent, following the definition of adherence in the section describing the intervention.

**Subgroup analyses**

A subgroup analysis will assess interaction of the intervention with either age, sex, BMI, or baseline physical activity levels for the two fitted models.

**Missing data**

Missing data will only be imputed for the longitudinal digital activity tracker data as missing at random and use the last observation carried forward approach.

**Statistical Software**

R and Python with scripts will be provided in results publication

# Appendix A. CONSORT diagram

Trial template for the CONSORT diagram showing the flow of participants through each stage of this randomized trial.