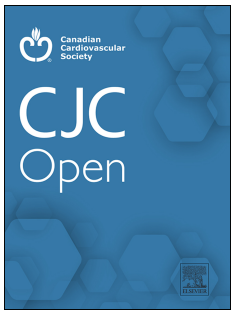

The VENERE study: EffectiVenEss of a rehabilitation treatment with Nordic walking in obEse or oveRweight diabetic patiEnts with cardiovascular disease

Anna Torri, MD, Eleonora Volpato, PsyD, PhD, Giampiero Merati, MD, Martina Milani, MD, Anastasia Toccafondi, Damiano Formenti, PhD, Francesca La Rosa, PhD, Simone Agostini, PhD, Cristina Agliardi, PhD, Letizia Oreni, MSc, Alice Sacco, MD, Marta Rescaldani, MD, Stefano Lucreziotti, MD, Ada Giglio, MD, Giulia Ferrante, MD, Maristella Barbato, MD, Claudio Montalto, MD, Stefano Buratti, MD, Nuccia Morici, MD, PhD

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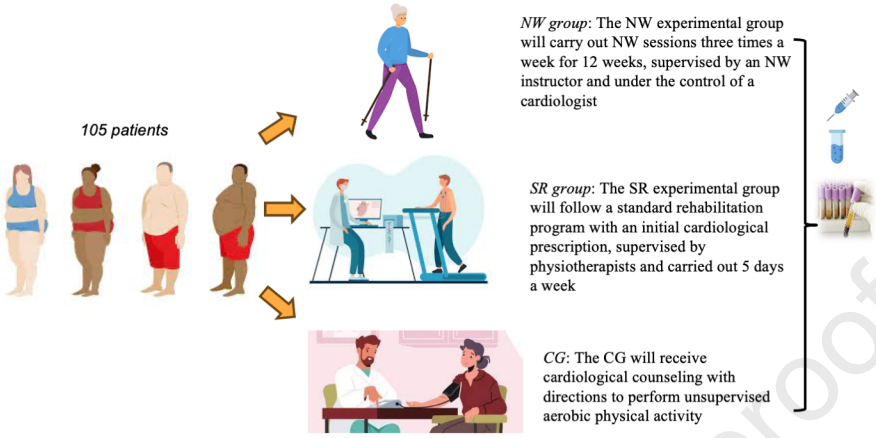
The VENERE study: EffectiVenEss of a rehabilitation treatment with Nordic walking in obEse or oveRweight diabetic patiEnts with cardiovascular disease



NW: Nordic Walking; SR: Standard Rehabilitation; CG: control group

The VENERE study: EffectiVenEss of a rehabilitation treatment with Nordic walking in obEse or oveRweight diabetic patiEnts with cardiovascular disease

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Highlights

- The article introduces the trial design of the VENERE study.
- A pathway of care for type 2 diabetes, cardiovascular disease, and overweight/obesity is described.
- Biomarker assessment introduces phenotyping of diabetics with cardiovascular events.
- Results will guide regional stakeholders for specific reimbursement strategies.

Abstract

Background: Nordic walking (NW) has several potential benefits for individuals with cardiovascular disease (CV), type 2 diabetes, and obesity/overweight. It improves cardiovascular health, including exercise capacity and blood pressure control. It enhances glycemic control and insulin sensitivity in diabetes. It aids in weight management and body composition improvement. NW offers additional advantages such as improved muscular strength, joint mobility, physical activity levels, and psychological well-being.

Methods: This open-label study with three arms will aim to evaluate the efficacy, safety, and adherence to exercise prescription in obese/overweight diabetic patients with CV complications. The primary objective will be to assess the CV performance of participants after a 6- and 12-month follow-up period, following a 3-month NW intervention, compared with standard rehabilitation (SR) and cardiological counseling (control group, CG) training lasting 3 months.

Results: The results of the study will provide valuable insights into the comparative effectiveness of a NW intervention versus SR and CG training in improving cardiovascular performance in obese/overweight diabetic patients with CV complications. Additionally, safety and adherence data will help inform the feasibility and sustainability of the exercise prescription over an extended period.

Conclusions: These findings may have implications for the development of tailored exercise programs for this specific patient population, with the aim of optimizing cardiovascular health outcomes.

This protocol **was registered** on ClinicalTrials.gov with reference ID: NCT05987410 on 10 August 2023.

Key words: Nordic walking (NW); cardiovascular disease; type 2 diabetes; overweight; obesity; Six Minute Walking Test (6MWT); adherence; rehabilitation; biomarkers

INTRODUCTION

In industrialized countries, obesity has become an epidemic affecting millions of individuals. In Italy, 35.3% of adults are overweight and 9.8% are obese.[1] Obesity contributes to various health issues such as heart disease, stroke, metabolic syndrome, atrial fibrillation, heart failure, insulin resistance, hypertension, and atherosclerosis. Chronic inflammation is a common factor linking these conditions.[2]

Obesity significantly impacts overall health, particularly cardiovascular (CV) disease. Obesity and diabetes are major risk factors for CV disease and are closely related to the development and complications of atherosclerosis.[3,4]The American Heart Association recognizes obesity as a modifiable risk factor for CV disease, independent of other factors such as hypertension, dyslipidemia, and type 2 diabetes mellitus. Diabetes is a common comorbidity associated with obesity.[4] In obese patients, inflammation leads to insulin resistance, which can result in carbohydrate intolerance and type 2 diabetes.[5]

Chronic inflammation increases the risk of CV diseases, and recent research suggests that altered expression of microRNAs in adipose tissue contributes to inflammation and the development of CV diseases.[6,7] Physical exercise has been shown to activate the sympathetic nervous system and the hypothalamic-pituitary axis, leading to the release of cortisol and catecholamines.[8] These hormones act as immunomodulators, inhibiting pro-inflammatory cytokine production and promoting the production of anti-inflammatory cytokines.

For overweight/obese and diabetic patients with a history of CV events, an integrated multidisciplinary treatment approach is the most effective strategy for secondary CV

prevention. This approach includes weight loss, physical exercise, pharmacological strategies, psychological intervention, treatment of sleep apnea, and bariatric surgery.[9,10]

Patients with recent CV events are usually referred for cardiologist-supervised exercise prescription, which in most cases is performed in hospital rehabilitation departments. In obese patients with CV events, exercise programs are often initiated during inpatient rehabilitation but tend to be discontinued once the program ends.[11] The most used procedures consist of exercises on a cycle ergometer with a sub-maximal load. In the obese patient, however, these workloads are unable to produce acceptable weight loss. Generally, with less than 150 minutes a week of moderate-intensity aerobic physical exercise weight loss is minimal, becoming significant only with 250–400 minutes a week of aerobic activity.

Rehabilitation programs are then often abandoned once the patient has completed inpatient rehabilitation. Some estimates indicate that the 6-month dropout rate from exercise programs following in-hospital rehabilitation is 50%. In addition, from a psychological point of view, patients with a recent CV event report a worsening of their quality of life (QoL) and symptoms of psychological distress including anxiety and depression.[12-14] Physical exercise has been shown to improve QoL and well-being.[15] Potential mechanisms for the relationship between physical activity and QoL/well-being include activity-induced changes in brain neurotransmitters and endogenous opioids, known to be associated with depression, anxiety, and other constructs of mood. Other beneficial effects of physical exercise to mental health may be due to increases in the levels of IGF-1, PI3K, BDNF, and ERK, and reduction of GSK3β. In addition, exercise increases the activity of the PGC-1α/FNDC5/Irisin pathway, promoting neuron survival and maintaining good mental health.[16] Psychological constructs and personality traits can also influence well-being.[17,18] Elavsky et al.[19] reported that increased self-efficacy and positive affect from a physical activity intervention were significantly associated with greater well-being and life satisfaction. Research has also shown that personality traits

(for example, neuroticism, extraversion, and agreeableness) can predict well-being/life satisfaction. However, further investigations are needed to verify whether these are genuine causal mechanisms.[19,20]

Structured activity programs should be implemented early after a CV event and continued at home. Walking is a safe and accessible activity, but alone it may not provide sufficient caloric restriction for metabolic improvements in obese and diabetic patients. Including aerobic activities that engage a greater percentage of muscle mass, such as Nordic walking (NW), can be beneficial in improving metabolic setup and body composition, and reducing CV risk in these patients.[21,22] NW is a biomechanically correct walking technique that originated in Finland in the 1930s as an off-season training method for cross-country skiers. In NW, the use of special sticks is combined with "conventional" walking: this involves a greater caloric expenditure, with an energy consumption higher by 20%–30% compared with walking without sticks. The technique also tones the upper part of the body, in particular triceps, shoulders, and back, with the involvement of about 90% of the body's muscles, while maintaining a reduced load on ligaments and joints.[23] Accordingly, it could be considered an optimal technical resource to promote an effective program with prolonged patient engagement.

In summary, obesity has widespread effects on health, particularly CV disease. Multidisciplinary approaches, including pharmacological treatments and structured exercise programs, are essential for managing obesity and its associated complications in overweight/obese and diabetic patients with CV events.

Study aims and objectives

The goal of the study is to evaluate the efficacy (in terms of CV performance) and safety of exercise prescription and adherence to it, after 6- and 12-month follow-up of a 3-month NW intervention in obese/overweight diabetic patients with CV complications, compared with

receiving standard rehabilitation (SR) for 3 months or cardiological counseling only (control group, CG) for 3 months.[24-26]

The primary aim will be to verify the improvement of *CV performance parameters* in the Six Minute Walking Test (6MWT) at baseline, at 3 months (end of the rehabilitation intervention), and at 6 months (change at 3 months and 6 months from baseline: primary at 3-month and co-primary at 6-month). Contemporary metabolic evaluation using the K5 wearable device (Cosmed, Italy) will be adopted.

The following will be *secondary exploratory objectives* of the study:

- To evaluate the cardiovascular performance parameters in terms of O_2 consumption, O_2 cost of locomotion, respiratory exchange ratio, ventilation, energy expenditure, work efficiency, and substrate utilization;
- To verify improvements in *body composition* from baseline, at 3 months and 6 months;
- To evaluate variations in the *inflammatory state*, by measuring levels of cytokines and inflammatory proteins (IL-1β, TNF-α, IL-6, IL-33, sST2, TGFβ, IL-18, IL-37, ADAM-17, NTpro-BNP, calprotectin), anti-inflammatory marker (IL-10), and neurotransmitters (catecholamines, beta-endorphins, serotonin) in the serum of the enrolled subjects;
- To measure miR-126-3p, miR-221-3p and miR-223-3p expression in the serum of enrolled subjects;
- To genotype subjects for SNPs of P2X7R, NLRP3, TNFα, IL-6, VDR, and BDNF genes;
- To investigate the *efficacy* and *safety* (number of adverse events) of NW in obese diabetics with CV comorbidity;
- To investigate the short- and medium-term (3- and 6-month) *adherence* of patients to exercise programs based on NW;

- To investigate *major adverse cardiac and CV events*, defined as mortality from all causes, heart attack, stroke, and rehospitalization for CV causes (MACCE), at 6 months and at 1 year from the start of treatment;
- To investigate the effect of NW on the patient's *QoL*, on *perception of body image*, and the level of *usual daily physical activity* (baseline, 3 months, and 6 months);
- To evaluate the effect of NW practice on *anxiety* and *depression* (baseline, at 3 months, and at 6 months).

Trial design

This is an open-label, single-center, randomized controlled interventional pilot study with three parallel arms. The study is planned to run from June 2023 to November 2024.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

This study was approved by the Ethics Committee of IRCCS Fondazione Don Carlo Gnocchi, Milan, Italy, reference ID: 27/2023/CE_FdG/FC/SA, on 21 June 2023. It was also registered on ClinicalTrials.gov, reference ID: NCT05987410, on 10 August 2023. Written informed consent will be obtained from all participants, in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice.

The protocol has been reported following the SPIRIT checklist (*Supplemental Table S1*).[27]

Participants

Study setting and recruitment

Patients will be identified from acute medical units, outpatient departments, and cardiovascular wards. A network of the following centers has been established, that will refer possible participants to us:

- Cardiology 1-Hemodynamics- Intensive Coronary Care Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan
- Cardiology Division, Milan Polyclinic, Milan
- Cardiology Division, Fatebenefratelli-Sacco Hospital, Milan
- Cardiology Division, San Carlo Hospital, Milan
- Cardiology Division, San Paolo Hospital, Milan

After having been identified by the local medical team as being eligible, participants will be approached by the research team of the Cardio-Respiratory Rehabilitation Unit of the IRCCS Santa Maria Nascente, Don Carlo Gnocchi Foundation in Milan (Italy).

Inclusion and exclusion criteria

Eligible for inclusion will be adult patients who are overweight [body mass index (BMI) ≥27 kg/m^2] or obese (BMI ≥30 kg/m^2) with diabetes mellitus and with a CV event (any of the composite of acute coronary syndrome and coronary revascularization) in at least three months before the recruitment.

Patients will be excluded if they experience one of the following:

- unable to walk independently and continuously;
- acute joint or spine pathologies that make movement impossible;
- dementia as indicated by their medical record and/or a score on the Montreal Cognitive Assessment (MoCA) of ≤15.5;[28]
- chemotherapy within 6 months before surgery;
- advanced renal failure;
- acute CV event <3 before recruitment, with ejection fraction (EF) <40%, arrhythmias, valvular disease, intracerebral/subdural hemorrhage, uncontrolled arterial hypertension;

- home oxygen therapy and non-invasive ventilation [excluding continuous positive airway pressure (CPAP)].

All these exclusion criteria were required by the Ethics Committee that evaluated the protocol, in order to improve the safety of the study, considering the outdoor activity.

Interventions

The first phase will be devoted to the screening by centers of possible participants. This will be followed in October 2023 by the randomization procedure.

If eligible for inclusion in the study, prospective participants will be informed of the objectives and characteristics of the study, as well as the procedures for informed consent and processing of personal data. The opportunity will be provided for potential participants to ask for any information they may need.

Once the informed consent to participate and consent to process personal data have been signed, the participant will be assigned to one of the following arms:

NW group: The NW experimental group will carry out NW sessions three times a week for 12 weeks, supervised by an NW instructor and under the control of a cardiologist. The initial duration of each NW session will be 85 minutes: 10 minutes of warm-up activity, 60 minutes of NW, and 15 minutes of cool-down activity. The intensity of the course will be increased gradually each week, starting at 70% to 85% of heart rate (HR) reserve.

SR group: The SR experimental group will follow a standard rehabilitation program with an initial cardiological prescription, supervised by physiotherapists and carried out 5 days a week. Sessions will last 40 minutes, including 5 minutes of warm-up activity, 30 minutes of aerobic physical activity on a conveyor belt or cycle ergometer, and 5 minutes of cool-down activity. The intensity of the aerobic activity will gradually increase each week, starting at 70% to 85% of HR reserve.

For both the NW and SR arm the approach will be group-based.

CG: The CG will receive cardiological counseling with directions to perform unsupervised aerobic physical activity.

Participants in all the groups will receive directions advising them to follow a balanced diet plan that proposes a moderate (300–400 kcal) daily caloric restriction below their usual caloric expenditure, estimated based on initial body composition measurements.

The interventions of the three arms are all group based.

It is not foreseen that any other type of pharmacological treatment will be required in addition to the standard cardiological therapy typically set in the post-event period. Participants assigned to the CG will receive standard cardiology counseling with physical activity encouraged. The groups will also be followed and supervised from the perspective of dietary therapy, using a similar approach across groups of initial assessment of dietary tendencies followed by diet-therapeutic prescription.

Outcomes

The *primary outcome* will be represented by cardiovascular performance defined by the 6MWT (difference between baseline evaluation and 3-month follow-up) and metabolic evaluation using K5 device at the beginning and at the end of the rehabilitation treatment, and after 3 months of observation.

Secondary outcomes will be:

- body composition;
- variation of biochemical and metabolic parameters;
- level of usual physical activity;
- adherence to treatment with NW;
- levels of anxiety and depression;
- QoL;

- body image;
- MACCE evaluated at 6 months and 1 year after the start of treatment;
- circulatory levels of inflammation-related microRNAs;
- levels of inflammatory, anti-inflammatory, and neurotransmitter cytokines and proteins;
- genotyping of subjects for selected SNPs of P2X7R, NLRP3, TNFα, IL-6, VDR P2X7R, and BDNF genes, related to the inflammatory state and response to rehabilitation treatment.

Safety outcome will be any kind of injury of the weight-bearing joints, especially the knees and ankles, during physical activity.

Participant timeline

Each potential participant will undergo, during the entry visit, an initial screening with a psychologist, physiotherapist, cardiologist, and dietician, to ascertain the possibility of inclusion in the study based on the proposed inclusion and exclusion criteria. Included participants will be evaluated at baseline (T0), after 3 months (T1, end of intervention), after 6 months from T0 (T2), and after 1 year from T0 (T3).

Sample size

The sample size was calculated considering the primary outcome of the study, i.e., the change in distance on the 6MWT, and assuming that the treatment reported in the available literature[40] is similar to the type of treatment and duration of the current study. For the calculation, a sample size was calculated to detect a minimal between-group difference of 70 m, assessed as clinically relevant for patients with cardiorespiratory disorders, and 80% power, 5% significance, and 10% dropout rate were considered.[41] In addition, an independent-sample mean comparison model was used. Significance level was adjusted for multiple comparisons with the Bonferroni correction. The comparison between the groups with NW with the aforementioned "moderate-intensity continuous training" (training of moderate and continuous intensity) led to an estimate of 35 patients per group, for a total of 105 patients.

METHODS: ASSIGNMENT OF INTERVENTIONS

Randomization

Sequence generation, allocation concealment, and implementation

Randomization will be carried out centrally by the Research and Development Unit (RDU), using a random number generator in the Research Electronic Data Capture Platform (REDCap, http://redcap.dongnocchi.it/).

Blinding will be not applied.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection

Table I shows the principal evaluations at each timepoint in the study.

Evaluated at each time point will be:

1. Anthropometric and demographic parameters: basic anthropometry: height, weight, BMI, body circumferences to assess for adiposity (waist, hip, and limbs), and skinfold thickness.
2. Nutritional parameters
    i. Four-day diet questionnaire;[29]
    ii. Body composition using mono-compartmental and vectorial bioelectrical impedance analysis (BIA 101 BIVA®PRO, Akern, Italy).
3. Cardiovascular parameters
    i. 6MWT: This is a sub-maximal exercise test used to assess aerobic capacity and endurance. The distance covered over a time of 6 minutes is used as the outcome by which to compare changes in performance capacity. This in combination with the breath-by-breath O_2 consumption (K5, Cosmed, Italy) evaluation allows a more in-depth cardiometabolic evaluation.
    ii. Hand grip, as an estimator of anaerobic alactacid power.
    iii. Echocardiocolor Doppler, the standard imaging modality for the assessment of heart valve disease severity and heart physiology, specifically diastolic function cardiac diameters and volumes, indexed mass, and left ventricular ejection fraction (LVEF).
4. QoL parameters: The Short Form Health Survey 36 (SF-36)[30] is a generic, multidimensional instrument consisting of 36 questions subdivided into eight scales: physical functioning (10 items); limitations due to physical health (4 items), limitations due to emotional problems (3 items); energy and fatigue (4 items); emotional well-being (5 items); social activities (2 items); pain (2 items); and general health perception (5 items). The final item (1 item) evaluates change in health status from the previous year. All the items are rated on a Likert scale, but with a score that is variable and weighted for each item. In this study, the SF-12 will be adopted.[31]
5. Daily physical activity: The International Physical Activity Questionnaire (IPAQ)[32] is a 27-item self-reported measure of physical activity for use with adult patients aged 15 to 69 years.

The IPAQ can be used in clinical settings and population research comparing physical activity levels across international populations. The IPAQ comprises a set of four questionnaires. Long (five independently requested activity domains) and short (four generic items) versions are available for use with telephone or self-administration methods. In this study the short form (IPAQ-SF) will be used.

6. Psychological parameters
    i. The Generalized Anxiety Disorder Scale (GAD-7): A self-rated questionnaire consisting of seven questions assessing anxiety state (cut-off score is ≥8).[33]
    ii. The Patient Health Questionnaire-9 (PHQ-9): A short, self-administered tool developed specifically for use in primary care. It can be used for screening, diagnosing, monitoring, and measuring the severity of depression.[34]
    iii. The Body Shape Questionnaire-34 (BSQ-34): A self-reported questionnaire developed to measure concern about body shape and body appearance in the normal and clinical population.[35]
    iv. A semi-structured interview will be conducted with each participant to compare expectations, interoception, and level of satisfaction with the course, as well as adherence to it (reported number of sessions attended, which will then be compared with the actual data).
    v. The Patient Activation Measure (PAM 13i): A 10- or 13-item questionnaire adopted to explore the ability to play an active role in managing the therapeutic process.[36]
7. Parameters of balance and motor coordination
    i. Balance tests will be conducted with the accelerometer on the center of mass or force platform.

ii. Timed Up and Go (TUG) will be used as a coordination test. This measures the length of time taken to stand up, walk a distance of 10 feet, turn, walk back, and sit down again.[37]

8. Clinical specimens will be used for the following analyses:

i. Measurement of basic hematological and metabolic biochemistry: blood count, kidney, electrolytic panel, lipid profile, glycated Hb, transaminase, hsCRP.

ii. Measurement of serum cytokines and inflammatory proteins (IL-1β, TNF-α, IL-6, IL-33, sST2, TGFβ, IL-18, IL-37, ADAM-17, pro-BNP, calprotectin), anti-inflammatory proteins (IL-10), and neurotransmitters (catecholamines, beta-endorphins, serotonin) at T0, T1, and T2 by enzyme-linked immunosorbent assays (ELISA) and enzyme-linked lectin assay (ELLA).

iii. Serum expression of miR-126-3p, miR-221-3p, miR-223-3p at T0, T1, and T2 by digital droplet PCR (ddPCR).

iv. Genotyping of enrolled subjects (at T0) for the SNPs of P2X7R, NLRP3, TNFα, IL-6, VDR, and BDNF genes that will be evaluated by allelic discrimination real-time PCR.

9. Evaluations during the intervention phase

i. HR monitoring.

ii. Fatigue as perceived immediately at the end of the activity (perceptive load). The Borg rating of perceived exertion (RPE) scale[38] will be used. This is a tool for estimating effort and exertion, breathlessness, and fatigue during physical work. The Borg CR10 scale is a category-ratio scale anchored at the number 10, which represents extreme intensities.

iii. The Total Quality Recovery Scale (TQR) questionnaire[39] will be used to assess the recovery state between training sessions. It will be used once a week, in the morning after one of the training sessions.

Data management

The data will be collected electronically via an interface that conforms with the data privacy laws in Italy (D.L. 101/2018) and Europe (GDPR No. 679/2016). The data will be pseudoanonymized and they may be disclosed on the occasion of scientific conferences or through scientific or statistical publications only in anonymous and/or aggregated form, in ways that will not allow the identity of the interested party to be traced. Details required for randomization will be communicated to the RDU and an individualized allocation provided over the telephone. The RDU will not be otherwise involved in the running of the study. The results will be analyzed on an intention-to-treat basis.

Statistical methods

In the first instance, a descriptive statistic of the collected variables will be proposed, i.e., the main cardiovascular parameters, body composition, and inflammatory/immune status. The descriptive statistics will involve frequencies (relative and in percentage), mean and standard deviation, or median and interquartile range for categorical, normally distributed numeric, and non-normally distributed numeric variables, respectively.

Comparisons between physiological parameters at the various time points of the study will be evaluated by analysis of variance for repeated measures (ANOVA), Friedman's test, or McNemar's test for normally distributed numeric, non-normally distributed numeric, or categorical variables, respectively. In individual groups, the possible relationships between variables will be tested by linear or multiple binary logistic regression, dependent on numerical or dichotomous outcomes, respectively. Finally, differences between the three groups in the single time points will be evaluated using ANOVA tests, Kruskal-Wallis and Chi-squared tests (or Fisher's tests when necessary) for numerical variables with normal distribution, numerical variables with non-normal distribution, or categorical data, respectively. For multiple comparisons, the p-value will be adjusted with Bonferroni correction. The normality of the

distributions will be evaluated using the Shapiro-Wilk test. For all tests applied, a p-value <0.05 will be considered statistically significant.

RESULTS

Expected results

The experimental NW group is expected to maintain the achieved weight loss or further reduce weight and to have a CV and inflammatory profile improved compared to that of the SR group and, especially, the CG group. Furthermore, it is expected that the outdoor physical activity will create the conditions for a continuation of the activity long-term (which will be evaluated at the follow-up) and increase the usual daily physical activity, thus significantly improving QoL. Also, from a psychological point of view, we expect the intervention groups to demonstrate reduced levels of anxiety and depression and a better perception of their body image.

DISCUSSION

The demonstration of a relationship between NW, decreased/maintained weight loss, and improvement of the cardiometabolic risk profile of diabetic patients will indicate whether this technique could be useful in current clinical practice. Improving cardiometabolic risk profile can reduce secondary incidence of major cardiovascular events and hospitalizations for heart failure, reducing national health system expenditure. Improvements in QoL and reduced anxiety and depression may reduce the cost of psychotropic drugs and specialized treatments. Early de-medicalization of physical exercise may contribute significantly to reducing healthcare costs because of the associated reduction in rehabilitation treatment in hospital. This process will be assessed in terms of its economic viability and organizational sustainability. Characteristic factors that may make the model generalizable to other contexts will also be identified.

Strengths and limitations

A key limitation could be poor adherence to the NW or SR protocol, with participants potentially abandoning the study. It has been demonstrated in the literature that patient compliance to treatment based on physical exercise prescription is significantly better if the patient is coached to continue participating. Adequate contact between the program leaders and the enrolled patients will be necessary to minimize the dropout rate. It has also been demonstrated that group work is more motivating when groups members have homogeneous pathologies, especially in the case of obesity, where participating as part of a group helps to overcome fears of exposure in people with poor body image.

Clinical implications

A key benefit of NW compared with SR using a treadmill or cycle ergometer is that it substantially de-medicalizes the rehabilitation process. NW takes place in outdoor environments, which may be more favorable to the psychological, as well as physical, recovery of patients with recent CV events. We also expect that the typical involvement of the upper limbs and therefore the para-vertebral muscles and shoulder girdle in NW may confer additional advantages compared with SR, in which only the lower limbs are activated, due to the greater simultaneous involvement of different muscle groups. Furthermore, the high demand for rhythmic coordination in NW, compared to simple walking or pedaling, may also improve balance and stability, which is useful in usual daily activities. Once the safety and non-inferiority of NW compared with SR for CV and respiratory outcomes is established, NW may also have a significant impact on patients' QoL. It is an activity that can be integrated easily into day-to-day life and encourage common activity interests in patients with homogeneous pathologies. Participation in the study will not lead to any modification of usual assistance and pharmacological treatment of the participants.

Future research

The goal of future research will be to use this multidimensional evaluation profile to gain a greater understanding of how various cardiac rehabilitation methods can be applied to stratified sections of the reference population, and any social and environmental advantages of the various methods.

Dissemination

The dissemination program will be conceived to support the dialogue between science and main societal actors, taking in consideration their participation in the research and innovation process according to the main principles envisioned by Responsible Research Innovation (RRI). This network will be the first step of a larger *governance* program, aimed at creating new forms of inclusion with engagement of researchers, policy makers, representatives from civil society organizations, education and industry, in order to develop new pathway of care and to assess their value for the health system.

The results of this trial will be presented according to the CONSORT reporting statement (Figure 1).[42]

CONCLUSIONS

Cardiac rehabilitation is undergoing a new era with several landmark paradigm shifts from a concept of "movement" to a broad and effective structured secondary prevention program aimed at minimizing the patient's residual risk after a CV event. To achieve this aim, sustainable approaches promoting patient engagement are needed. This study will be the first step toward phenotyping, at a deeper level, a complex and high-risk subset of patients and introducing the concept of structured and prescribed physical activity as a necessary tool for well-being.

Figure legend

Figure 1: Study procedure.

Patient Consent: The authors confirm that a patient consent form has been obtained for each patient recruited in this trial.

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Declaration of interest

None to declare.

Author contributions

AnnT is the principal investigator of this study and refined the protocol. EV, FLR, SA, CA, GM and NM contributed to the study design. AnnT, EV, FLR, SA, CA, GM and NM wrote the manuscript. GF, CM, MM, SL, AG and SB will recruit the patients. AnnT, AnaT AEV, NM, SA, CA and FLR will conduct the trial. NM, AnnT and AnaT will supervise the trial. LO, the medical statistician for the study, will contribute to the statistical design and analysis of data. EV has contributed to the project design and dataset implementation. All authors have revised the protocol critically for important intellectual content and approved the final manuscript.

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References

1. Sbraccia, P., Busetto, L., Santini, F., Mancuso, M., Nicoziani, P., Nicolucci, A., 2021. Misperceptions and barriers to obesity management: Italian data from the ACTION-IO study. Eat Weight Disord 26, 817–828. https://doi.org/10.1007/s40519-020-00907-6
2. Henning, R.J., 2021. Obesity and obesity-induced inflammatory disease contribute to atherosclerosis: a review of the pathophysiology and treatment of obesity. Am J Cardiovasc Dis 11, 504–529.
3. La Sala, L., Pontiroli, A.E., 2020. Prevention of Diabetes and Cardiovascular Disease in Obesity. IJMS 21, 8178. https://doi.org/10.3390/ijms21218178
4. Powell-Wiley, T.M., Poirier, P., Burke, L.E., et al., 2021. Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation 143. https://doi.org/10.1161/CIR.0000000000000973
5. Wondmkun, Y.T., 2020. Obesity, Insulin Resistance, and Type 2 Diabetes: Associations and Therapeutic Implications. Diabetes Metab Syndr Obes 13, 3611–3616. https://doi.org/10.2147/DMSO.S275898
6. Berg, A.H., Scherer, P.E., 2005. Adipose Tissue, Inflammation, and Cardiovascular Disease. Circ Res 96, 939–949. https://doi.org/10.1161/01.RES.0000163635.62927.34
7. Gholami, M., Larijani, B., Zahedi, Z., et al., 2019. Inflammation related miRNAs as an important player between obesity and cancers. J Diabetes Metab Disord 18, 675–692. https://doi.org/10.1007/s40200-019-00459-2

8. Smith, S.M., Vale, W.W., 2006. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues Clin Neurosci 8, 383–395. https://doi.org/10.31887/DCNS.2006.8.4/ssmith
9. Després, J.-P., Carpentier, A.C., Tchernof, A., Neeland, I.J., Poirier, P., 2021. Management of obesity in cardiovascular practice. J Am Coll Cardiol 78, 513–531. https://doi.org/10.1016/j.jacc.2021.05.035
10. Wharton, S., Lau, D.C.W., Vallis, M., et al., 2020. Obesity in adults: a clinical practice guideline. Can Med Assoc J 192, E875–E891. https://doi.org/10.1503/cmaj.191707
11. Sunamura, M., Ter Hoeve, N., Van Den Berg-Emons, R.J.G., Boersma, E., Geleijnse, M.L., Van Domburg, R.T., 2020. Patients who do not complete cardiac rehabilitation have an increased risk of cardiovascular events during long-term follow-up. Neth Heart J 28, 460–466. https://doi.org/10.1007/s12471-020-01413-1
12. Marzolini, S., Mertens, D.J., Oh, P.I., Plyley, M.J., 2010. Self-reported compliance to home-based resistance training in cardiac patients. Eur J Cardiovasc Prev Rehab 17, 35–49. https://doi.org/10.1097/HJR.0b013e32832da020
13. Pimple, P., Lima, B.B., Hammadah, M., et al., 2019. Psychological Distress and Subsequent Cardiovascular Events in Individuals With Coronary Artery Disease. JAHA 8, e011866. https://doi.org/10.1161/JAHA.118.011866
14. Welsh, J., Banks, E., Joshy, G., Butterworth, P., Strazdins, L., Korda, R.J., 2021. Does psychological distress directly increase risk of incident cardiovascular disease? Evidence from a prospective cohort study using a longer-term measure of distress. BMJ Open 11, e039628. https://doi.org/10.1136/bmjopen-2020-039628
15. Mahmood, S.S., Levy, D., Vasan, R.S., Wang, T.J., 2014. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. The Lancet 383, 999–1008. https://doi.org/10.1016/S0140-6736(13)61752-3

16. Taylor, J.L., Popovic, D., Lavie, C.J., 2022. Exercise Modalities and Intensity to Improve Functional Capacity and Psychological/Mental Health in Cardiac Rehabilitation: A Role for Nordic Walking? Can J Cardiol 38, 1135–1137. https://doi.org/10.1016/j.cjca.2022.03.020
17. Kubzansky, L.D., Huffman, J.C., Boehm, J.K., et al., 2018. Positive Psychological Well-Being and Cardiovascular Disease. J Am Coll Cardiol 72, 1382–1396. https://doi.org/10.1016/j.jacc.2018.07.042
18. Sahoo, S., Padhy, S.K., Padhee, B., Singla, N., Sarkar, S., 2018. Role of personality in cardiovascular diseases: An issue that needs to be focused too! Indian Heart Journal 70, S471–S477. https://doi.org/10.1016/j.ihj.2018.11.003
19. Elavsky, S., 2009. Physical activity, menopause, and quality of life: the role of affect and self-worth across time. Menopause 16, 265–271. https://doi.org/10.1097/gme.0b013e31818c0284
20. Conroy, D.E., Maher, J.P., Elavsky, S., Hyde, A.L., Doerksen, S.E., 2013. Sedentary behavior as a daily process regulated by habits and intentions. Health Psychol 32, 1149–1157. https://doi.org/10.1037/a0031629
21. Sadowska-Krępa, E., Gdańska, A., Rozpara, M., Pilch, W., Přidalová, M., Bańkowski, S., 2020. Effect of 12-Week Interventions Involving Nordic Walking Exercise and a Modified Diet on the Anthropometric Parameters and Blood Lipid Profiles in Overweight and Obese Ex-Coal Miners. Obes Facts 13, 201–212. https://doi.org/10.1159/000506403
22. Witkowska, A., Grabara, M., Kopeć, D., Nowak, Z., 2021. The Effects of Nordic Walking Compared to Conventional Walking on Aerobic Capacity and Lipid Profile in Women Over 55 Years of Age. J Phys Act Health 18, 669–676. https://doi.org/10.1123/jpah.2020-0182

23. Baek, S., Ha, Y., 2021. Estimation of energy expenditure of Nordic walking: a crossover trial. BMC Sports Sci Med Rehabil 13, 14. https://doi.org/10.1186/s13102-021-00240-0

24. Perez-Suarez, I., Martin Rincon, M., Gonzalez-Henriques, J.J., Fezzardi, C., Perez-Regalado, S., Galvan-Alvarez, V., Juan-Habib, J.W., Morales-Alamo, D., Calbet, J.A.L, 2018. Accuracy and Precision of the COSMED K5 Portable Analyser. Front Physiol 21; 9:1764. doi: 10.3389/fphys.2018.01764

25. Guidetti, L., Meucci, M., Bolletta, F., Emerenziani, G.P., Gallotta, M.C., Baldari, C., 2018. Validity, reliability and minimum detectable change of COSMED K5 portable gas exchange system in breath-by-breath mode. PLoS One 31;13:e0209925. doi: 10.1371/journal.pone.0209925

26. Crouter, S.E., LaMunion, S.R., Hibbing, P.R., Kaplan, A.S., Basset, DR. J., 2019. Accuracy of the Cosmed K5 portable calorimeter. PloS One 16, 14. doi: 10.1371/journal.pone.0226290

27. Chan, A.W., Tetzlaff, J.M., Altman, D.G., et al., 2013. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Inter Med 158(3), 200-207.

28. Nasreddine, Z.S., Phillips, N.A., Bédirian, V., et al., 2005. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. J Am Geriatr Soc 53, 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

29. Piccoli, A., Nigrelli, S., Caberlotto, A., Bottazzo, S., Rossi, B., Pillon, L., et al., 1995. Bivariate normal values of the bioelectrical impedance vector in adult and elderly populations. Am J Clin Nutr 61(2), 269–270. doi: 10.1093/ajcn/61.2.269.

30. Ware, J.E., Kosinski, M., Dewey, J.E., 2000. How to Score Version Two of the SF-36 Health Survey. RI Quality Metric Incorporated, Lincoln.

31. Turner-Bowker, D., Hogue, S.J., 2014. Short Form 12 Health Survey (SF-12), in: Michalos, A.C. (Ed.), Encyclopedia of Quality of Life and Well-Being Research. Springer Netherlands, Dordrecht, pp. 5954–5957. https://doi.org/10.1007/978-94-007-0753-5_2698

32. Craig, C.L., Marshall, A.L., Sjöström, M., et al., 2003. International Physical Activity Questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 35, 1381–1395. https://doi.org/10.1249/01.MSS.0000078924.61453.FB

33. Spitzer, R.L., Kroenke, K., Williams, J.B.W., Löwe, B., 2006. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 166, 1092–1097. https://doi.org/10.1001/archinte.166.10.1092

34. Kroenke, K., Spitzer, R.L., 2002. The PHQ-9: A New Depression Diagnostic and Severity Measure. Psychiatr Ann 32, 509–515. https://doi.org/10.3928/0048-5713-20020901-06

35. Cooper, P.J., Taylor, M.J., Cooper, Z., Fairburn, C.G., 2013. Body Shape Questionnaire. https://doi.org/10.1037/t06040-000

36. Graffigna, G., Barello, S., Bonanomi, A., Lozza, E., Hibbard, J., 2015. Measuring patient activation in Italy: Translation, adaptation and validation of the Italian version of the patient activation measure 13 (PAM13-I). BMC Med Inform Decis Mak 15, 109. https://doi.org/10.1186/s12911-015-0232-9

37. Kear, B.M., Guck, T.P., McGaha, A.L., 2017. Timed Up and Go (TUG) Test: Normative reference values for ages 20 to 59 years and relationships with physical and mental health risk factors. J Prim Care Community Health 8, 9–13. https://doi.org/10.1177/2150131916659282

38. Williams, N., 2017. The Borg Rating of Perceived Exertion (RPE) scale. Occup Med 67, 404–405. https://doi.org/10.1093/occmed/kqx063

39. Kenttä G, Hassmén, P., 1998. Overtraining and recovery. A conceptual model. Sports Med 26(1), 1–16. doi: 10.2165/00007256-199826010-00001.

40. Terada, T., Cotie, L.M., Tulloch, H., et al., 2022. Sustained Effects of Different Exercise Modalities on Physical and Mental Health in Patients With Coronary Artery Disease: A Randomized Clinical Trial. Can J Cardiol 38, 1235–1243. https://doi.org/10.1016/j.cjca.2022.03.017

41. Wise, R.A., Brown, C.D., 2005; Minimal clinically important differences in the six-minute walk test and the incremental shuttle walking test. COPD 2:125-129. Doi: 10.1081/copd-200050527.

42. The CONSORT Group, Schulz, K.F., Altman, D.G., Moher, D., 2010. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Med 8, 18. https://doi.org/10.1186/1741-7015-8-18

Table I: Structure of parameter detection and measurement according to the time frame of the study

Variable	T0 (baseline)	T1: end of the intervention phase at 3 months	T2: 6 months' post-intervention	T3: follow-up at 12 months' post-intervention
Anthropometric and demographic parameters				
Basic anthropometry	X	X	X	X
Nutritional parameters				
Four-day diet questionnaire	X	X	X	X
Body composition by mono-compartmental and vectorial bioimpedancemetry	X	X	X	X
Cardiovascular parameters				
Six Minute Walking Test (6MWT) with O_2 consumption	X	X	X	
Hand grip	X	X	X	
Echocardiocolor Doppler: cardiac diameters and volumes, indexed mass, LVEF, myocardial strain	X			
Quality of life parameters				
SF-36 questionnaire	X	X	X	X
Daily physical activity				
International Physical Activity Questionnaire (IPAQ)	X	X	X	X
Psychological parameters				
Generalized Anxiety Disorder Scale (GAD-7)	X	X	X	X
Patient Health Questionnaire-9 (PHQ-9)	X	X	X	X
Body Shape Questionnaire-34 (BSQ-34)	X	X	X	X
Patient Activation Measure: (PAM 13i)	X	X	X	X
Semi-structured interview to compare expectations, interoception, and level of satisfaction with the course, as well as adherence to it	X	X	X	X
Parameters of balance and motor coordination				
Balance tests with accelerometer on center of mass or force platform	X	X	X	
Timed Up and Go (TUG)	X	X	X	
Biohumoral parameters				

Basic hematological and metabolic biochemistry	X	X	X	
Cytokines and inflammatory proteins; anti-inflammatory markers; neurotransmitters	X	X	X	
miRNAs: miR-223-3p, miR-221	X	X	X	
Genotyping of for the SNPs of the P2X7R, NLRP3, TNFα, IL-6, VDR genes, and the BDNF gene	X	X	X	
Evaluations during the intervention phase	X			
Heart rate monitor	X			
Borg Scale	X			
Total Quality Recovery Scale (TQR) questionnaire once a week, in the morning after one of the training sessions	X			
Cardiological re-evaluation to highlight any changes in MACCE				X