## Appendix A: List of participants

**Recruitment and follow-up:** Diabetes Unit, Sant'Andrea Hospital, Rome, Italy: Giuseppe Pugliese, Stefano Balducci, Martina Vitale, Tiziana Cirrito, Lucilla Bollanti, Francesco G. Conti.

**Supervised exercise training:** Metabolic Fitness Association, Monterotondo, Rome, Italy: Stefano Balducci, Gianluca Balducci, Enza Spinelli.

**DXA and vertebral morphometry evaluation:** Radiology Unit, Sant'Andrea University Hospital, Rome, Italy Giuseppe Argento, Luca Pugliese, Andrea Laghi.

**QUS and pQCT evaluation:** Metagym Fitness Centre, Florence, Italy: Cosimo R. Russo; Diabetes Unit, Sant'Andrea Hospital, Rome, Italy: Jonida Haxhi, Valeria D'Errico.

**Physical Fitness evaluation:** Department of Human Movement and Sport Sciences, ''Foro Italico'' University, Rome, Italy: Massimo Sacchetti, Giorgio Orlando, Olimpia Andreani; Diabetes Unit, Sant'Andrea Hospital, Rome, Italy: Gianvito Rapisarda, Eugenio Santacroce.

**Questionnaire evaluation:** Centre for Applied Biological & Exercise Sciences, Faculty of Health & Life Sciences, Coventry University, Coventry, UK: Silvano Zanuso.

**Laboratory testing:** Laboratory of Clinical Chemistry, Sant'Andrea Hospital, Rome, Italy: Patrizia Cardelli, Gerardo Salerno, Stefano Cavallo.

**Statistical Analysis:** Centre for Outcomes Research and Clinical Epidemiology (CORE), Pescara, Italy: Antonio Nicolucci, Giuseppe Lucisano.

**Steering Committee:** Giuseppe Pugliese, Stefano Balducci, Francesco G. Conti, Massimo Sacchetti, Cosimo R, Russo, Giuseppe Argento, Silvano Zanuso, Patrizia Cardelli, Antonio Nicolucci.



Balducci S, *et al. BMJ Open* 2019; 9:e027429. doi: 10.1136/bmjopen-2018-027429

## Appendix B: Questionnaires

**B1: History of Falls questionnaire**

**B2: Physical Activity Scale for the Elderly (PASE) questionnaire**

**B3: Self-report questionnaire for musculoskeletal (MS) symptoms**



Balducci S, *et al. BMJ Open* 2019; 9:e027429. doi: 10.1136/bmjopen-2018-027429

## B1: History of Falls questionnaire

| | |
|---|---|
| **A. Activities prior to falling** | |
| 1. Ambulation | |
| 2. Transferring | |
| 3. Running | |
| 4. Sports | |
| 5. Stairs/curb | |
| 6. Other | |
| **B. Perceived causes (accident/environmental-related)** | |
| 1. Collapse episode | |
| 2. Dizziness/vertigo | |
| 3. Balance/gait impairment | |
| 4. Other | |
| **C. Perceived causes (environmental factors)** | |
| 1. Wet surface | |
| 2. Uneven surface/steps | |
| 3. Objects on surface/rugs | |
| 4. External forces | |
| 5. Icy surfaces | |
| 6. Other | |
| **D. Injuries sustained from fall** | |
| 1. Fractures | |
| 2. Treated injury | |
| 3. Untreated injury | |
| 4. No injury | |

## B2: Physical Activity Scale for the Elderly (PASE) questionnaire

**Q1.** Over the past 7 days, how often did you participate in sitting activities such as reading, watching TV, or doing handcrafts?

**Q1b.** On average, how many hours per day did you engage in these sitting activities?

**Q2.** Over the past 7 days, how often did you take a walk outside your home or yard for any reason? For example, for fun or exercise, walking to work, walking the dog, walking in a mall, etc?

**Q2a.** On average, how many hours per day did you spend walking?

**Q3.** Over the past 7 days, how often did you engage in light sport or recreational activities such as bowling, golf with a cart, shuffleboard, fishing from a boat or pier or other similar activities?

**Q3b.** On average, how many hours per day did you engage in these light sport or recreational activities?

**Q4.** Over the past 7 days, how often did you engage in moderate sport or recreational activities such as doubles tennis, ballroom dancing, hunting, ice skating, golf without a cart, softball or other similar activities?

**Q4b.** On average, how many hours per day did you engage in these moderate sport or recreational activities?

**Q5.** Over the past 7 days, how often did you engage in strenuous sport or recreational activities such as jogging, swimming, cycling, singles tennis, aerobic dance, skiing (downhill or cross country or other similar activities?

**Q5b.** On average, how many hours per day did you engage in these strenuous activities?

**Q6.** Over the past 7 days, how often did you do any exercises specifically to increase muscle strength or endurance, such as lifting weights or pushups, etc?

**Q6a.** On average, how many hours per day did you engage in exercises to increase muscle strength or endurance, such as lifting weights, pushups, or physical therapy with weights, etc.?

**Q7.** During the past 7 days, have you done any light housework, such as dusting, washing or drying dishes, or ironing?

**Q8.** During the past 7 days, have you done any heavy housework or chores such as vacuuming, scrubbing floors, washing windows, or carrying wood?

**Q9a.** During the past 7 days, did you engage in home repairs like painting, wallpapering, electrical work, etc.?

**Q9b.** During the past 7 days, did you engage in lawn work or yard care, including snow or leaf removal, chopping wood, etc?

**Q9c.** During the past 7 days, did you engage in outdoor gardening?

**Q9d.** During the past 7 days, did you engage in caring for another person such as a child, dependent spouse, or another adult?

**Q10.** During the past 7 days, did you work for pay or as a volunteer?

**Q10a.** How many hours per week did you work for pay and/or as a volunteer?

**Q10b.** Which of the following categories best describes the amount of physical activity required on your job and/or volunteer work?

Category 1 ("Mainly sitting with slight arm movements") includes examples such as: office worker, watchmaker, seated assembly line worker, bus driver, etc.

Category 2 ("Sitting or standing with some walking") includes examples such as: cashier, general office worker, light tool and machinery worker.

Category 3 ("Walking, with some handling of materials generally weighing less than 50 pounds") includes examples such as: mailman, waiter/waitress, construction worker, heavy tool and machinery worker.

Category 4 ("Walking and heavy manual work often requiring handling of materials weighing over 50 pounds") includes examples such as: lumberjack, stonemason, farm or general labourer].

## B3. Self-reported questionnaire for MS symptoms

| | |
|---|---|
| **SHOULDER** | |
| **1** | Do you have pain during rotation of the arm? |
| **2** | Are you awakened by pain during the night? |
| **3** | Do you have pain on reaching objects above the head? |
| **4** | Do you have pain on lifting objects? |
| **5** | Do you have pain or soreness upon awakening that passes later on during the day? |
| **6** | Have you taken anti-inflammation drugs or pain-killers? |
| **ARM** | |
| **7** | Do you feel that you have less strength? |
| **8** | Dou you feel that one arm is weaker than the other? |
| **9** | Do you have pain at the maximum extension of the forearm? |
| **ELBOW** | |
| **10** | Do you have pain on lifting an object? |
| **11** | Do you have pain on hitting against a rigid object? |
| **12** | Have you taken anti-inflammation drugs or pain-killers? |
| **WRIST** | |
| **13** | Do you have pain on lifting an object? |
| **14** | Do you have pain on hitting against a rigid object? |
| **15** | Have you taken anti-inflammation drugs or pain-killers? |
| **HAND:** Do you feel "pins and needles"? If so, in which finger? | |
| **16** | I |
| **17** | II |
| **18** | III |
| **19** | IV |
| **20** | V |
| **SPINE: THORACO-CERVICAL** | |
| **21** | Do you have pain/tenderness/ pins and needles on turning your head from side to side? |
| **22** | Do you often have pain or headache or heaviness of the head or neck? |
| **23** | Do you have pain between the shoulder blades? |
| **24** | Do you feel it necessary to move your head from side to side to get moving and feel? |
| **25** | Do you have episodes of painful sudden acute stiffness of the neck? |
| **26** | Have you taken anti-inflammation drugs or pain-killers? |
| **SPINE: LUMBO-SACRAL** | |
| **27** | Do you have pain on bending to tie your shoe laces? |
| **28** | Do you have any back-pain on turning left or right? |
| **29** | Do you have a feeling of heaviness in your back on standing for long hours? |
| **30** | Do you have bothersome feeling when sitting still? Do you have to get up? |
| **31** | Did you have one episode of sudden intense back pain that leaves you unable to move? |
| **32** | Have you taken anti-inflammation drugs or pain-killers? |

| | |
|---|---|
| **HIP** | |
| **33** | Do you have pain on crossing your legs? |
| **34** | Do you have any pain when opening your legs to the maximum? |
| **35** | Do you often have pain from your buttocks along the length of the leg down to your ankles? |
| **36** | Have you taken a single dose of anti-inflammatory drugs or pain-killers? |
| **KNEE** | |
| **37** | Do you have pain in the knee in the act of sitting down or getting up? |
| **38** | Do you have pain in your knee after having walked a lot? |
| **39** | Is your knee often swollen at the end of the day? |
| **40** | Do you have pain in the "good" knee? |
| **41** | Do you have pain or a bothersome feeling as you kneel down? |
| **42** | When lying in bed, do you feel the need to move your legs, ones or more than once? |
| **43** | Have you taken a single dose of anti-inflammatory drugs or pain-killers? |
| **FOOT** | |
| **44** | Do you often feel a sensation of pins and needles that runs down to one or more toes? |
| **45** | Do you have any difficulty in standing on your toes? |
| **46** | Do you have any pain in your foot after walking for a long time? |
| **47** | Do you have pain on taking the first step in the morning? |
| **48** | Do you have any difficulty or pain when putting on stiff orthopaedic shoes? |
| **49** | Do you have pain under the heel when walking a lot? |
| **50** | Have you taken a single dose of anti-inflammatory drugs or pain-killers? |

## Appendix C: World Health Organization Trial Registration Data Set

1. **Primary Registry and Trial Identifying Number:** ClinicalTrials.gov; NCT02421393; URL https://clinicaltrials.gov/ct2/show/NCT02421393.
2. **Date of Registration in Primary Registry:** 20 April. 2014
3. **Secondary Identifying Numbers:** NA.
4. **Source(s) of Monetary or Material Support:** Metabolic Fitness Association O.N.L.U.S., Via Nomentana, 27 - 00015 Monterotondo, Rome, Italy; Phone +390690080260; Fax: +390690080235; e-mail: info@metabolicfitness.it.
5. **Primary Sponsor:** Metabolic Fitness Association O.N.L.U.S., Via Nomentana, 27 - 00015 Monterotondo, Rome, Italy; Phone +390690080260; Fax: +390690080235; e-mail: info@metabolicfitness.it.
6. **Secondary Sponsor(s):** European Foundation for the Study of Diabetes, Rheindorfer Weg 3 - 40591 Düsseldorf, Germany; Phone: +49 211 758469 0; Fax: +49 211 758 469 29; E-mail: foundation@easd.org.
7. **Contact for Public Queries: Stefano Balducci, MD,** Metabolic Fitness Association O.N.L.U.S., Via Nomentana, 27 - 00015 Monterotondo, Rome, Italy; Phone +390690080260; Fax: +390690080235; e-mail: sbalducci@esinet.it.
8. **Contact for Scientific Queries: Giuseppe Pugliese,** M.D., Ph.D., Department of Clinical and Molecular Medicine, "La Sapienza" University of Rome, Via di Grottarossa, 1035-1039 - 00189 Rome, Italy; Phone: +39-0633775440; Fax: +39-0633776327; E-mail: giuseppe.pugliese@uniroma1.it.
9. **Public Title:** The Study to Weigh the Effect of Exercise Training on BONE quality and strength (SWEET BONE) in type 2 diabetes.
10. **Scientific Title:** The Study to Weigh the Effect of Exercise Training on BONE quality and strength (SWEET BONE) in type 2 diabetes.
11. **Countries of Recruitment:** Italy.
12. **Health Condition(s) or Problem(s) Studied:** type 2 diabetes (T2D).
13. **Intervention:**
    a. Intervention arm
       - Name: Supervised exercise training.
       - Description: two weekly supervised mixed exercise training sessions for two years, on top of standard care.
    b. Standard care.
14. **Key Inclusion and Exclusion Criteria**
    a. Inclusion criteria: known T2D (defined by the ADA criteria) of at least 1-year duration. Additional requirements are age 40-80 years; BMI 27-40 kg/m$^2$; sedentary lifestyle (i.e., more than 8 hours/day spent in any waking behaviour characterized by an energy expenditure ≤1.5 METs while in a sitting or reclining posture) and physically inactivity (i.e., insufficient amounts of PA according to current guidelines) from at least 6 months; a Short Battery Performance Test score ≥4; ability to walk 1.6 Km without assistance; and eligibility after cardiologic evaluation.

b. Exclusion criteria: unable or unwilling to give informed consent or communicate with local study staff; current diagnosis of psychiatric disorder or hospitalization for depression in the past six months; self-reported alcohol or substance abuse within the past twelve months; self-reported inability to walk two blocks; musculoskeletal disorders or deformities that may interfere with participation in the intervention; history of central nervous dysfunction such as hemiparesis; myelopathies; cerebral ataxia; clinical evidence of vestibular dysfunction; postural hypotension defined as a fall in BP when changing position of >20 mmHg (systole) or >10 mmHg (diastole); currently pregnant or nursing; cancer requiring treatment in the past five years, except for cancers that have clearly been cured or in the opinion of the investigator carry an excellent prognosis (e.g., stage 1 cervical cancer); chronic obstructive pulmonary disease; end-stage liver disease; chronic diabetic complications (recent major acute cardiovascular event, including heart attack, stroke/transient ischemic attack(s), revascularization procedure, or participation in a cardiac rehabilitation program within the past three months; pre-proliferative and proliferative retinopathy; macroalbuminuria and/or eGFR < 45 ml/min/1.73 $m^2$; severe motor and sensory neuropathy; diabetic foot with history of ulcer); cardiovascular disease at cardiologic examination (history of cardiac arrest; history of pulmonary embolism in the past six months; unstable angina pectoris or angina pectoris at rest; resting HR <45 beats/min or >100 beats/min; complex ventricular arrhythmia at rest or with exercise; uncontrolled atrial fibrillation with HR >100 beats/min; NYHA Class III or IV congestive heart failure; acute myocarditis; pericarditis or hypertrophic myocardiopathy; left bundle branch block or cardiac pacemaker); treatment with anti-fracture agents, oestrogens, aromatase inhibitors, testosterone, corticosteroids and/or glitazones; previous documented non-traumatic fractures; spinal deformity index (SDI) >3 (and >2 in a single vertebra); and a T score <-2.5 at spine/hip at DXA; haemoglobin (Hb) $A_{1c}$ >9.0%; blood pressure (BP) >150/90 mmHg; vitamin D <10 ng/ml; conditions not specifically mentioned above at the discretion of the clinical site.

15. **Study Type**

a. Type of study: interventional.

b. Study design:

- Method of allocation: randomized
- Masking: no (assessor-blinded)
- Assignment: parallel
- Purpose: testing the efficacy of a specific exercise training program in improving bone quality and strength in patients with T2D

c. Phase: NA

d. Allocation concealment mechanism and sequence generation: centralized randomization stratified by age, gender, and type of diabetes treatment (non-insulin versus insulin therapy), using a permuted-block randomization software which randomly varies the block size.

15. **Date of First Enrolment:** November 1, 2018 (expected).

16. **Target Sample Size:** 200

17. **Recruitment Status: recruiting.**

16. **Primary Outcome(s)**

- Name: baseline to end-of-study change in Trabecular Bone Score (TBS);
- Method of measurement: spine dual-energy X-ray absorptiometry (DXA)-derived software-based measure;

- Time points: baseline and end-of-study.

17. **Key Secondary Outcomes**

    a. Name: baseline to end-of-study change in broadband ultrasound attenuation (BUA), speed of sound (SOS), and quantitative ultrasound index (QUI); methods of measurement: quantitative ultrasound (QUS); time points: baseline and end-of-study.

    b. Name: baseline to end-of-study change in multiple measured and calculated bone parameters; methods of measurement: peripheral quantitative computed tomography (pQCT); time points: baseline and end-of-study.

    c. Name: baseline to end-of-study change in bone mineral density (BMD) and other DEXA-derived measures; method of measurement: spine and hip DXA; time points: baseline and end-of-study.

    d. Name: baseline to end-of-study change in markers of bone turnover; method of measurement: immunochemical methods; time points: baseline and end-of-study.

    e. Name: baseline to end-of-study change in body composition; method of measurement: total body DXA; time points: baseline and end-of-study.

    f. Name: baseline to end-of-study change in muscle strength; methods of measurement: isometric muscle strength test; time points: baseline and end-of-study.

    g. Name: baseline to end-of-study change in muscle cross-sectional area; method of measurement: pQCT; time points: baseline and end-of-study.

    h. Name: baseline to end-of-study change in balance, gait and power; method of measurement: Short Battery Performance Test; time points: baseline and end-of-study.

    i. Name: number of falls; 17-item History of Falls questionnaire; time points: baseline and every 6 months thereafter for 7 years (2-year trial + 5-year post-trial follow-up).

    j. Name: symptomatic fractures; method of measurement: clinical and radiographic records; time points: baseline and every 6 months thereafter for 7 years (2-year trial + 5-year post-trial follow-up).

    k. Name: asymptomatic and symptomatic fractures; method of measurement: vertebral morphometry; time points: baseline and every 6 months thereafter for 7 years (2-year trial + 5-year post-trial follow-up).

## Appendix D: Informed consent

### Patient Information Sheet

### TITLE OF THE STUDY: The Study to Weigh the Effect of Exercise Training on BONE quality and strength (SWEET BONE) in type 2 diabetes

This study is registered at ClinicalTrial.gov as "Study to Weigh the Effect of Exercise Training on BONE quality and strength (SWEET-BONE) in type 2 diabetes: an exercise intervention program for reducing the risk of fractures "(N. NCT02421393, URL https://clinicaltrials.gov/ct2/show/NCT02421393)

**IDENTIFICATION OF THE STUDY**

Dear Sir/Madam,

The study, which your physician (diabetes specialist) is inviting you to participate in, aims to evaluate the effect of 2-year training consisting of supervised and combined aerobic and resistance exercise sessions in individuals with type 2 diabetes mellitus on:

- bone quality and mass;
- bone metabolism;
- muscle strength and mass;
- balance and gait;
- falls;
- symptomatic and asymptomatic fractures.

The hypothesis is that a specific exercise training program produces a significant improvement in the qualitative and quantitative bone parameters by influencing bone metabolism, with a consequent reduction in the risk of fractures and, in the long term, a significantly reduced number of fractures.

The research involves about 200 patients with type 2 diabetes.

During the study you will be assigned to one of the following two groups:

1. Exercise (EXE) group, which receives standard care and participates in two weekly mixed exercise training sessions for two years, supervised by an exercise specialist at the Metabolic Fitness Association.
2. Control (CON) group, which receives only standard care.

The study will have a duration of 2 years plus a 5-year post-trial follow-up, during which you will be subjected to 6-month monitoring visits. The parameters reported above will be assessed at the beginning and at the end of the 2-year period, except for falls and fractures, which will be assessed every 6 months for the entire 7 year period (2-year trial + 5-year post-trial follow-up).

**PROTECTION OF PERSONAL DATA:**

- All information concerning you, the collection and processing of which is connected and indispensable to the achievement of the objectives of this study, will be treated in a manner suitable to ensure

absolute confidentiality and security in accordance with the provisions for the protection of personal data and the right to privacy (Italian Data Protection Act, No. 675 of December 6, 1996 and subsequent amendments/additions).

- You will be identified by a code and the clinical information concerning you will not be disclosed without your written permission. The data collected will consist of your initials, date of birth, sex and otherwise sensitive clinical data as suitable to reveal your state of health.
- As a participant in the processing of your personal data, you will have full access, through your family doctor, to the information concerning you. You will also have the right to exercise all the rights of cancellation, transformation, integration, updating, correction and blocking of your data within the limits set out in art. 13 of the Italian Data Protection Act 675/96 mentioned above. You will not be charged any fee for the scheduled exams, the results of which will be promptly communicated to your family doctor.

**STUDY BENEFITS:**

- Upon agreeing to participate in this study, you might be assigned to follow a supervised exercise training program. Whatever group you are assigned to, you will be under strict control by a staff-member, medical or otherwise, specialized in the management of type 2 diabetes, including physical activity/exercise therapy.
- In addition, your doctor may become aware of the presence of cardiovascular risk factors or complications to be monitored.
- Finally, the knowledge acquired thanks to your participation will be useful both for you and for other patients.

**PARTICIPATION IN THE STUDY:**

- Your participation in this study is completely cost-free and, if you decide not to take part, you will still be assisted in the most appropriate medical treatment.
- We invite you to ask your family physician any question you deem appropriate. Your doctor will also ask you to sign and date the consent form for the processing of personal data to confirm that you have read all the information contained herein, which includes that you have understood the aims of the study and most importantly, that you have freely given your consent to the collection and processing of your personal data.

## Patient Consent Form

**TITLE OF THE STUDY: The Study to Weigh the Effect of Exercise Training on BONE quality and strength (SWEET BONE) in type 2 diabetes**

I, the undersigned _____ born in _____ on _____

and resident in _____

hereby declare, after reading the information, the following:

- to have read and understood the patient information sheet of the aforementioned study and to have had ample time and opportunity to ask questions and obtain satisfactory answers to the investigator;
- to have understood that my participation is voluntary and that I can withdraw from the study at any time, without having to explain or influence any future medical assistance in any way;
- to have understood that my personal data will be processed according to the regulations in force specified in the information sheet of the study and that I can exercise my rights by contacting the Data Controller at any time and in the manner specified in accordance with art. 7, Legislative Decree n. 196 of 30/06/2003, (so-called Privacy Code).

Following these statements, I declare that I, the undersigned, freely:

- accept to participate in the study mentioned above;
- consent to the processing of personal and sensitive data collected in the context of this study, in the terms and methods indicated and explained in the information, aware that anonymity in the treatment will be guaranteed;
- consent that the investigator and his collaborators, as expressly indicated in the informative report, collect and process the data deriving from the investigations for the express purpose of a scientific publication.

**Signature of the patient** **_____** **date _____**

**Surname and name of the patient** **_____**

**Signature of the investigator** **_____** **date _____**

**Surname and name of the investigator** **_____**