ISRCTN12085208 https://doi.org/10.1186/ISRCTN12085208

The effect of a low-calorie Mediterranean diet, intermittent fasting, and natural senolytics on aging markers in participants with low and high vascular risk

Submission date
04/01/2026

Recruitment status
Recruiting

Registration date
22/01/2026

Overall study status
Ongoing

Last Edited
22/01/2026

Condition category
Signs and Symptoms

[_] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
This randomized clinical trial was designed to evaluate the effects of a low-calorie Mediterranean diet combined with intermittent fasting and the natural senolytic fisetin on biomarkers of aging, compared with the traditional MedDiet in 4,000 adults without established CVD, but at either high or very high vs. low or moderate CVD risk, stratified into two age groups (50 + 5 and 80 + 5 years), with 1,000 participants per intervention group. Primary aging-related outcomes will include senescent cell burden, inflammatory markers, DNA methylation patterns, and indices of mitochondrial dysfunction. In addition, the progression of subclinical arteriosclerosis will be assessed using carotid ultrasound, pulse wave velocity, endothelial function testing, and traditional cardiovascular risk factors.

The primary objective of the study is to determine whether optimization of healthy lifestyle behaviors, including diet, physical activity, and emotional well-being, when combined with a natural senolytic intervention can delay biological aging and reduce the incidence of age-related conditions, such as CVD, dementia, sarcopenia, and frailty.

Who can participate?
Participants receiving care within the network of Primary Care Centers affiliated with Hospital Clínic in Barcelona in two age groups: 50 ± 5 years and 80 ± 5 years, from the following sources: Hospital Clinic Outpatient clinics, Primary Care Centers affiliated with Hospital Clinic, and Participants from previously completed studies conducted by the research group, including PREDIMED and PREDIMED-Plus.

What does the study involve?
Participants will be randomly allocated into two groups:
Intervention group: Low-calorie Mediterranean diet + intermittent fasting + a natural supplement called fisetin.
Control group: Standard Mediterranean diet + placebo.

The study will last at least 2 years, with regular check-ups and support. Participants will have health checks, blood tests, and lifestyle assessments at the start and during follow-up visits. The study will track diet, physical activity, body composition, heart health, and markers of aging. Safety will be monitored throughout.

The goal is to see if combining diet, fasting, and fisetin can slow aging and reduce risk of heart disease and other age-related conditions.

What are the possible benefits and risks of participating?
Possible Benefits:
i. Health Improvement: Participants may experience improvements in markers of aging, including cardiovascular health parameters (blood pressure, cholesterol levels, and overall heart function), cognitive function, body weight and adiposity, and frailty
ii. Access to Treatment: Participants may gain access to fisetin or dietary interventions that are not widely available to the public, which could provide health benefits.
iii. Monitoring and Support: Regular health assessments during the trial may lead to better monitoring of cardiovascular health, diet, and lifestyle, along with guidance from healthcare professionals.
iv. Contributing to Science: By participating, individuals contribute to valuable research that may lead to a better understanding of dietary impacts on cardiovascular health, potentially benefiting others in the future.
v. Potential for Education: Participants often receive information and educational materials about cardiovascular health, cognitive function, adiposity and nutrition, which can foster healthier lifestyle choices.

Possible Risks:
i. Side Effects: Dietary changes and fisetin may cause side effects, such as gastrointestinal issues, allergic reactions, or interactions with other medications.
ii. Inconvenience: Participation in trials often requires regular visits, dietary adherence, or lifestyle changes, which can be time-consuming and may lead to stress.
iii. Uncertain Outcomes: The effects of the dietary treatment may vary among individuals, and there is a possibility of not experiencing any benefits.
iv. Confidentiality Concerns: While trials follow strict protocols to protect privacy, there is always a risk of data breaches regarding personal health information.
v. Placebo Effect: As the trial includes a control group receiving a placebo, participants may experience no benefit if assigned to that group.

Where is the study run from?
Instituto de Salud Carlos III, Barcelona.

When is the study starting and how long is it expected to run for?
January 2026 to January 2030.

Who is funding the study?
1. Instituto de Salud Carlos III, Barcelona.
2. Hospital Clínic de Barcelona, Barcelona.

Who is the main contact?
Prof Ramon Estruch, restruch@clinic.cat

Contact information

Type(s)
Scientific, Principal investigator, Public

Contact name
Prof Ramon Estruch

ORCID ID
https://orcid.org/0000-0003-1260-4445

Contact details
Fundació de Recerca Clínic Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)
Villarroel, 170
Barcelona
Spain
08036
+34619761420
RESTRUCH@clinic.cat

Additional identifiers

Study information

Scientific Title
Effect of intervention with a low-calorie Mediterranean diet, intermittent fasting, and natural senolytics on aging markers in subjects with low and high vascular risk

Acronym
ELDERDIET

Study objectives
Specific Objectives
a. Biological aging and senescence
To evaluate the effect of the combined intervention (hypocaloric MedDiet, intermittent fasting, and fisetin supplementation) on markers of cellular senescence and biological aging, including senescent cell burden, inflammatory markers, mitochondrial dysfunction, progenitor cell depletion, telomere length, and DNA methylation, compared with a hypocaloric MedDiet alone, in participants with high or very high and low or moderate cardiovascular risk across both age groups.
b. Subclinical cardiovascular disease
To assess the effect of the combined intervention on subclinical CVD, evaluated using imaging and functional vascular techniques, compared with a hypocaloric MedDiet alone, in participants with high or very high vs. low or moderate cardiovascular risk across both age groups.
c. Physical function and frailty
To evaluate the effect of the combined intervention on physical function, including sarcopenia and frailty status, compared with a hypocaloric MedDiet alone, in participants with high or very high and low or moderate cardiovascular risk across both age groups.
d. Advanced glycation end-products.
To assess the effect of the combined intervention on skin levels of advanced glycation end-products (AGEs), measured by skin autofluorescence, compared with a hypocaloric MedDiet

alone, in participants with high or very high and low or moderate cardiovascular risk across both age groups.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 20/11/2025, Comité de Ética de la Investigación con medicamentos del Hospital Clínic de Barcelona (Villarroel, 170, Barcelona, 08036, Spain; +34932275400; proceic@clinic.cat), ref: HCB/2025/1093

Primary study design
Interventional

Allocation
Randomized controlled trial

Masking
Blinded (masking used)

Control
Placebo

Assignment
Parallel

Purpose
Treatment

Study type(s)

Health condition(s) or problem(s) studied
Prevention of aging in patients with low to very high cardiovascular risk

Interventions
All participants will undergo a standardized medical and lifestyle assessment, including detailed information on alcohol consumption, smoking status, and dietary patterns.
• Randomization
Randomization will be performed using a computer-generated random number sequence. Odd numbers will designate control and even numbers will designate the intervention. The sequence will be blocked in groups of 20.
• Control Group
Participants randomized to the control group will follow a hypocaloric Mediterranean diet. They will receive standardized dietary counselling and general exercise recommendations aimed at promoting a healthy lifestyle. Follow-up assessments will be conducted at 3 months and subsequently every 6 months to monitor adherence and reinforce lifestyle guidance.
• Intervention Group
Participants randomized to the intervention group will follow a hypocaloric Mediterranean diet combined with a 14/10 intermittent fasting regimen, under the supervision of a trained study dietitian. Follow-up visits will be conducted at 3 months and subsequently every 6 months to promote adherence to dietary intervention and to provide standardized exercise

recommendations aimed at increasing physical activity.
In addition, participants in the intervention group will receive a nutritional supplement containing the natural senolytic compound fisetin, administered at a dose of 20 mg/kg/day for two consecutive days each month, supplied as 150 mg tablets. Participants assigned to the intervention group will comprise approximately 50% of the total study population and will be selected though the randomization procedure described above.
• Concomitant medication
All participants will continue their usual pharmacological treatments as prescribed by their primary care or specialist physicians. Study investigators will not modify, discontinue, or interfere with ongoing medical therapies.

Intervention Type
Mixed

Primary outcome(s)
1. Markers of cellular aging: Senescent Cell Burden measured using β-galactosidase expression in PBMC by flow cytometry at baseline, 1 and 2 years

2. Markers of cellular aging: Mitochondrial function - Oxygen Consumption Rate measured using a Seahorse XF analyzer at baseline, 1 and 2 years

3. Markers of cellular aging: Oxidative Stress and Redox Balance measured using TBARS and TAC by spectrophotometry at baseline, 1 and 2 years

4. Markers of cellular aging: Circulating Mitochondrial DNA (mtDNA) measured using Quantitative real-time PCR (qRT-PCR) targeting the mitochondrial 12S rRNA gene at baseline, 1 and 2 years

5. Markers of cellular aging: Endothelial Progenitor Cells measured using Flow cytometry at baseline, 1 and 2 years

Key secondary outcome(s))
1. Body Composition Assessment measured using Dual-Energy X-ray Absorptiometry (DEXA) at baseline, 1 and 2 years

2. 24-Hour Ambulatory Blood Pressure Monitoring (ABPM) measured using Spacelabs 90207 /90217 device at baseline, 1 and 2 years

3. Carotid Vascular Wall and Atherosclerotic Plaque Measurements measured using 2D and 3D Carotid ultrasound at baseline, 1 and 2 years

4. Echocardiography measurements measured using 2D and 3D B-mode transthoracic echocardiography at baseline, 1 and 2 years

5. Safety Assessment measured using standardized questionnaires at baseline, 1 and 2 years

6. Clinical Events measured using data collected from monitoring of all-cause mortality, specific mortality, cardiovascular events, diabetes mellitus, cognitive impairment, dementia and cancer at baseline, 1, 2 and 5 years

Completion date

01/01/2030

Eligibility

Key inclusion criteria
Participants will be eligible for inclusion if they meet the following criteria:
1. Age: 50 ± 5 years or 80 ± 5 years.
2. Absence of established CVD, as define below.
3. Ability and willingness to comply with the study procedures and provide written informed consent

Participants will be categorized at baseline into “high or very high vascular risk (H-VHVR) or “low-moderate vascular risk” (L-MVR) groups in accordance to accordance with the European Society of Cardiology (ESC) prevention guidelines and the SCORE 2 framework.

High and Very High Vascular Risk (H/VHVR) Group
Participants will be classified as H-VHVR if they meet at least one of the following criteria:
1. Diabetes mellitus for > 10 years, with or without of target organ damage (TOD), or Diabetes with > 1 additional major cardiovascular risk factor.
2. Severe hypertension: Blood pressure > 180/110 mm Hg, or requirement for > 3 antihypertensive drugs to achieve blood pressure control.
3. Severe Dyslipidemia: Untreated LDL cholesterol > 190 mg/dL (> 4.9 mmol/L), or current treatment with high-intensity statins with > 1 additional lipid-lowering therapy.
4. Moderate-to-severe renal disease Estimated glomerular filtration rate (eGFR) <60 mL/min/1. 73 m2 (CKD stage > 3)
5. Current cigarette smoking.
6. Family history of premature CVD. First-degree relative with CVD onset <55 years in men or <65 years in women.

Low and Moderate Vascular Risk (L-MVR) Group
Participants aged 50 ± 5 years or 80 ± 5 years who do not meet any of the above vascular risk criteria will be classified as having low-to-moderate vascular risk, corresponding to SCORE 2 estimates below the high-risk threshold for their age and geographic region.

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
45 years

Upper age limit
85 years

Sex
All

Total final enrolment
0

Key exclusion criteria
Participants will be excluded from the study if they present with any chronic condition associated with a senescent phenotype or other condition that could interfere with the intervention or outcome assessment, including:
1. Established cardiovascular disease (CVD): History of ischemic heart disease, stroke, or peripheral arterial disease.
2. Chronic kidney disease: Estimated glomerular filtration rate (GFR) < 60 mL/min/1.73 m2.
3. Chronic obstructive pulmonary disease (COPD): GOLD stage >2B.
4. Acute or chronic heart failure within the previous 12 months: Diagnosed according to Framingham criteria.
5. Idiopathic pulmonary fibrosis.
6. Hematologic or solid organ cancer diagnosed within the past five years.
7. History of osteoporotic fracture, including femoral, radial, or vertebral compression fractures.
8. Liver cirrhosis.
9. Cognitive impairment of any etiology, defined as a Global Deterioration Scale (GDS) > 4.
10. Human immunodeficiency virus (HIV) infection.
11. Frailty, defined as a FRAIL score > 3 points and/or a VIG-Frail index > 0.2.
12. Systemic autoimmune disease.
13. Current treatment with anticoagulant therapy, due to potential interactions with fisetin.
14. Food allergies or intolerances that preclude adherence to the Mediterranean diet.

Date of first enrolment
01/01/2026

Date of final enrolment
01/01/2028

Locations

Countries of recruitment
Spain

Sponsor information

Organisation
Instituto de Salud Carlos III

ROR
https://ror.org/00ca2c886

Funder(s)

Funder type

Funder Name
Hospital Clínic de Barcelona

Alternative Name(s)
Hospital Clínic of Barcelona, HCB

Funding Body Type
Government organisation

Funding Body Subtype
Other non-profit organizations

Location
Spain

Funder Name
Instituto de Salud Carlos III

Alternative Name(s)
SaludISCIII, InstitutodeSaludCarlosIII, Instituto de Salud Carlos III | Madrid, Spain, Carlos III Institute of Health, Institute of Health Carlos III, Carlos III Health Institute, La misión del Instituto de Salud Carlos III (ISCIII), ISCIII

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Spain

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file			05/01/2026	No	No
Statistical Analysis Plan			05/01/2026	No	No