ONLINE SUPPLEMENTAL MATERIAL

Supplemental Table 1. Members of the Steering Committee of the CV-PREVITAL study

Institution	Member of the Steering Committee
Centro Cardiologico Monzino IRCCS	Giulio Pompilio, Damiano Baldassarre
Istituto Auxologico Italiano IRCCS	Gianfranco Parati
IRCCS Humanitas Research Hospital	Gianluigi Condorelli
Istituto di Ricerche Farmacologiche Mario Negri IRCCS	Giuseppe Remuzzi
IRCCS MultiMedica	Gianfranco Gensini
IRCCS Istituto Neurologico Mediterraneo NEUROMED	Luigi Frati
IRCCS Policlinico San Donato	Lorenzo Menicanti
Istituti Clinici Scientifici Maugeri IRCCS	Walter Ricciardi
IRCCS ISMETT (Mediterranean Institute for Transplantation and Advanced Specialized Therapies)	Pier Giulio Conaldi
IRCCS Ospedale Policlinico San Martino	Antonio Uccelli
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico	Fabio Blandini
Fondazione Policlinico Universitario Agostino Gemelli IRCCS	Giovanni Scambia
Fondazione IRCCS Policlinico San Matteo	Eloisa Arbustini
IRCCS San Raffaele	Massimo Fini
Consorzio Sanità (Co.S.)	Antonio Di Malta
Romeo and Enrica Invernizzi Foundation	Emilio Trabucchi

Baldassarre D, *et al. BMJ Open* 2023; 13:e072040. doi: 10.1136/bmjopen-2023-072040

Supplemental Table 2. List of operative units and enrolled cohorts

OPERATIVE UNITS	ENROLLED COHORTS
Consorzio Sanità (Co.S.)	50,000 subjects attending the ambulatory of the participating GPs
Centro Cardiologico Monzino IRCCS	5,000 subjects attending pharmacies of the Lombardy territory
Istituto Auxologico Italiano IRCCS	5,000 subjects attending the institute (including 1,500 subjects referred to the Sleep Medicine Center)
IRCCS Humanitas Research Hospital	2,000 subjects attending the institution
IRCCS MultiMedica	1,000 subjects with diabetes and 2,000 subjects from the general population
IRCCS Istituto Neurologico Mediterraneo NEUROMED	10,000 subjects from the NEUROMED clinical research centre
IRCCS Policlinico San Donato	1,000 subjects selected among its own employees
Istituti Clinici Scientifici Maugeri IRCCS	1,000 subjects selected among their own employees
IRCCS ISMETT (Mediterranean Institute for Transplantation and Advanced Specialized Therapies)	150 subjects included in a program of physical training and lifestyle modifications
IRCCS Ospedale Policlinico San Martino	2,000 male subjects from the Municipality of Genoa
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico	2,000 blood donors afferent to the Department of Transfusion Medicine and Hematology
Fondazione Policlinico Universitario Agostino Gemelli IRCCS	1,000 subjects attending to the outpatient clinics of the Non-Invasive Cardiology Diagnostic Unit, of the Centre for Hypertension, and of the Centre for Endocrine and Metabolic Diseases
Fondazione IRCCS Policlinico San Matteo	500 subjects selected among asymptomatic relatives of patients attending to the Polyclinic San Matteo for cardiology reasons plus 100 healthy individuals attending to the Genetics Unit of IRCCS San Matteo
IRCCS San Raffaele	150 subjects selected among its own employees
Istituto di Ricerche Farmacologiche Mario Negri IRCCS	Non-recruiting unit. Role: Monitoring center for the cohort of subjects recruited by GPs

GPs: general practitioners

STAFF TRAINING, STANDARD OPERATING PROCEDURES (SOPs) AND QUALITY CONTROL

CV-PREVITAL uses several training models for study staff, including web-based and on-site training. Operators involved in recruitment are also required to read a manual for data management before receiving the ID and password to access the CV-PREVITAL digital platform. Standard operating procedures (SOPs), which are available upon request, have also been implemented to ensure that all research activities are performed according to predetermined standards, definitions, and schedules.
Quality control activities include (a) disseminating SOPs developed to ensure data integrity, (b) implementing warning messages in the electronic "Case Report Form" (eCRF) when data input falls within an implausible range, and (c) implementing warning or halting messages when specific variables and/or questionnaires (or parts of them) are left unfilled in the eCRF. For quality control of the 7-year outcome assessment, a random sample of outcomes is reviewed and adjudicated by a centrally appointed panel of cardiologists. At year seven of the trial, if at least 10 composite specific outcomes (including at least 2 myocardial infarctions, 2 hospitalizations for angina, 2 strokes, 2 revascularizations, and 2 deaths) adjudicated locally in each recruiting center are validated with full agreement from the central panel of cardiologists, then local classification and adjudication does not require further central review. Otherwise, the procedure continues until local adjudication reaches full agreement with the central panel. In the event that a specific recruitment center records a total of less than 10 events, all events are adjudicated centrally. The quality control for the collection of data on 7-year vascular events, needed to avoid the "lost at follow-up bias", is warranted by active recalling of participants or their relatives in case of death. The quality control regarding the use of the app during follow up, including the participants' adherence to the proposed activities, is accomplished and verified by the app itself. Indeed, as described in the paragraph "Intervention", in addition to sending reminders, personalized motivational feedback, and messages based on task evaluation and periodic goal achievement (also exploiting the logic of gaming), the app also provides for logging of non-use or sub-optimal use of the app itself.

WEB BASED TRIAL MANAGEMENT

The hub for CV-PREVITAL data collection and storage is the IT platform of the Italian Cardiology Network (ICN), developed in collaboration with the Consortium of Bioengineering and Medical Informatics (Italian acronym: CBIM) of the Italian Ministry of Health and hosted in REDCap. This platform is integrated with the IT platform of Consorzio Sanità (Co.S.), which is the interface used by primary care physicians participating in the study, as well as with the CV-PREVITAL app database. All data collected by general practitioners (GPs) are entered directly into web-based forms and saved to a structured database of each local GPs cooperative. The data are then harmonized and transferred to the dataset of Co.S.. Data included in this dataset are then transferred to the REDCap dataset of the ICN managed by CBIM. Instead, all data collected from research hospitals (Italian acronym: IRCCS) and pharmacies are directly entered into web-based forms and saved into the structured database at CBIM. All of the web-based systems mentioned incorporate real-time data entry quality control, as well as informatics tools to verify eligibility for recruitment prior to randomization. Access to each portion of the various digital platforms that host the various datasets is protected with passwords and restricted to individuals with specific access privileges. Person identifying information is kept separate from all other information and linked only by a pseudo-anonymous study ID for each participant.

DETAILS ON RANDOMIZATION PROCEDURES

Modalities of randomization for GPs cohort

In the randomization modality for GPs cohort, sampling involves three hierarchical levels:

level 1: 50 CSPs (acronym of the Italian term Centri Sanitari Polifunzionali) i.e., fifty GPs health centers coordinated by Co.S., each including at least 3 practitioners.
level 2: Approximately 250 GPs, with an average of 5 GPs for each CSP.
level 3: 50,000 individuals to be enrolled (200 for each GP).

To reduce the risk of imbalance, randomization is performed by GP, stratifying by CSP. In each CSP, GPs assigned to the control group and GPs assigned to the intervention group are balanced. The randomization of GPs is centralized and managed by CBIM.

Modalities of randomization for IRCCSs Cohorts

In the case of the IRCCSs cohorts, individuals are randomized directly, with the exception of the one recruited in community pharmacies, where the procedure randomizes pharmacies and not individuals. For IRCCSs that randomize individuals, the randomization takes place without stratification by age and sex, to avoid unnecessarily lengthening the time required for participant enrollment. Potential discrepancies between IRCCSs cohorts (and/or sub-studies), in terms of distribution of age, sex and any other important covariates (geography, socioeconomic status, etc.), are handled by adopting a meta-analytic approach with individual participant data, with random effects in global analyses, and by stratifying for the appropriate subgroups in specific analyses. Randomization of the different cohorts enrolled in the various IRCCSs is also centralized, using the ICN IT platform to create specific randomization lists for each sub-study. The assignment of patients to the appropriate treatment arm is managed remotely and automatically at the time of patient inclusion in the study. This approach also allows for centralized real-time monitoring of enrollment progression. In case of a specific design (for instance, a 2x2 factorial), the randomization procedure ensures a balance of individuals in the two main treatment arms (mHealth vs. Usual care) and in the two specific secondary arms.

RISK SCORE USED AS PRIMARY OUTCOME

The score was constructed by analysing the combined impact of different modifiable factors on the risk of developing cardiovascular diseases (CVD) during the follow up of the MOLI-SANI study.[1 2] The analysis was conducted on n=21,806 MOLI-SANI participants free of personal history of CVD. The event considered was a combined outcome of cardiovascular death and nonfatal cardiovascular events. The number of observed events was n=816, with a median follow-up of 8.1 years of. The analysis model included the following covariates: age, sex, history of cancer at baseline, drug therapy for diabetes, hypertension, or dyslipidemia, BMI (4 categories), income (4 categories), and schooling (2 categories). The modifiable risk factor score included the following variables (all on a continuous scale): (1) the number of cigarettes (per day); (2) adherence to the Mediterranean diet (score from 0 to 9 points, calculated as in Trichopoulou et al.[3]); (3) mean arterial pressure (MAP) = (2*diastolic+systolic)/3; (4) relative fat mass (RFM) (proxy for percentage of adipose fat as in Woolcott et al.[4]); (5) blood glucose; (6) LDL cholesterol; (7) HDL cholesterol; (8) triglycerides; and (9) leisure-time physical activity. The above variables have been standardized to mean zero and standard deviation one, separately for men and women (with the exception of the number of cigarettes and Mediterranean diet adherence index, left in their original scales).

For each individual, a score of modifiable cardiovascular (CV) risk factors was obtained as a weighted sum of the following variables: number of cigarettes, score of adhesion to Mediterranean diet and z-values of LDL, HDL, triglycerides, mean arterial pressure, glucose, leisure time physical activity and relative fat mass. Weights were natural logarithms of the hazard ratio of each variable, as calculated in the fully adjusted model. Risk factors positively associated with the endpoint showed hazard ratio >1 and consequently they were summed up with positive weights. On the contrary, variables negatively associated with the endpoint entered the score with negative weights as a consequence of their hazard ratio in the range 0-1. By construction, the higher the score, the higher the magnitude of its association with the endpoint. To improve the interpretability of the score, we divided it by 0.06859, which is the natural logarithm of the hazard ratio for one year more of age as measured in the derivation cohort. In this way, one unit of the rescaled score resulted in being associated with the outcome as one year of age more at baseline. Practically, a 1-point increase in the score is equivalent (in terms of cardiovascular risk) to an increase of 1 year of age. As the score value increases, so does the cardiovascular risk. The median score value in the derivation cohort is -3. Therefore, a 33% reduction in the score is nearly equivalent to reducing the score by one unit, which corresponds to a decrease in cardiovascular risk equivalent to one year of age less at baseline. In the derivation cohort (Moli-sani population), one year more at baseline was associated with 6%

to 8% higher rate of cardiovascular events. Then, we believe that a gain of one year can be considered a clinically meaningful intervention effectiveness in the short term.

We provide here the association (hazard ratio) between age, sex, and all components of the Moli-sani Risk Score with the occurrence of fatal or non-fatal cardiovascular events, as observed in the Moli-sani (derivation) cohort.

Non-modifiable risk factors	**HR***	**95% CI**
Age (for 1 year more)	1.071	1.062 to 1.080
Men vs women	2.577	2.205 to 3.011
Modifiable risk factors		
No. of cigarettes (1-unit increase)	1.029	1.022 to 1.037
Mediterranean Diet score (1-point increase)	0.941	0.901 to 0.983
LDL, z-score (1-unit increase)	1.219	1.135 to 1.309
HDL, z-score (1-unit increase)	0.857	0.789 to 0.932
Triglycerides, z-score (1-unit increase)	1.015	0.941 to 1.096
Mean Arterial Pressure, z-score (1-unit increase)	1.204	1.125 to 1.289
Glucose, z-score (1-unit increase)	1.144	1.083 to 1.209
Leisure time physical activity, z-score (1-unit increase)	0.956	0.890 to 1.027
Relative Fat Mass, z-score (1-unit increase)	1.036	0.925 to 1.162

*HR means hazard ratio; CI means confidence interval; HR and 95%CI are calculated from a multivariable Cox survival regression including all the variables in the Table plus educational level (2-level variable), household income (4-level variable), body mass index (3-level variable), history of cancer (no/yes), diabetes (no/yes), hypertension (no/yes) and hyperlipidaemia (no/yes).

The score was then obtained following the formula:
Smoke_score = (number of cigarettes per day) * 0.029
Diet_med_score = (Mediterranean diet adherence score) * 0.061
LDL_score = (z-score of LDL) * 0.198
HDL_score = (z-score of HDL) * 0.154
Triglycerides_score = (triglycerides z-score) * 0.015
MAP_score = (z-score of MAP) * 0.186
Glucose_score = (z-score of glucose) * 0.135
Physical_activity_score = (z-score of leisure-time physical activity index) * 0.045
RFM_score = (z-score of relative fat mass index) * 0.036

SCORE_TOT =
(Smoke_score + LDL_score + Triglycerides_score + MAP_score + Glucose_score + RFM_score -
Diet_med_score - HDL_score - Physical_activity_score) / 0.06859

For the calculation of z-scores (z-score=(value-average) / standard deviation) it is possible to refer to the following values observed in the MOLI-SANI project (population aged ≥45 years):

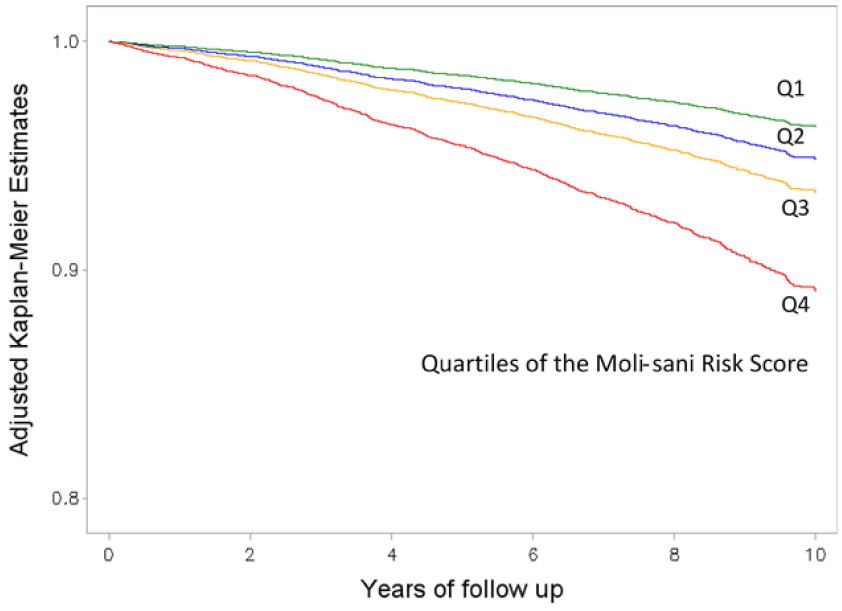
Variable	Mean	Standard deviation	Mean	Standard deviation
	MEN		WOMEN	
LDL (mg/dL)	130	35	136	36
HDL (mg/dL)	52	13	63	15
Triglycerides (mg/dL)	150	99	118	66
MAP (mmHg)	105	11	102	12
Blood Glucose (mg/dL)	107	28	98	23
Physical_activity (MET-hours/day)	4.6	4.7	2.7	3.2
RFM (%) (males)	29	3.6	42	5

MAP=(2*diastolic+systolic)/3
RFM=64 - (20 × height (cm)/waist circumference (cm)) for men and
RFM=76 - (20 × height (cm)/waist circumference (cm)) for women

Assessing physical activity (in leisure time) in terms of met-h/day can be challenging. Consider replacing this measure with a proxy based on a multi-level qualitative classification of such physical activity. For example, a 3-level classification: 'sedentary', 'moderately active', 'active' can be transformed into corresponding (approximate) z-scores = -1, 0, 1.

In the MOLI-SANI project, the score has median -5.0 and interquartile range 8.3 (min=-26.9, low risk and max=41.5, high risk). Each score point was associated (in the MOLI-SANI study) with a risk of MACE approximately equal to that of one additional year at baseline (HR for one score point: 1.071, 95%CI: 1.062 to 1.080).

Survival curves by score categories, as observed in the MOLI-SANI project, are shown below:



Quartiles	Median	Min-max	N	No. events	% events	HR*	95% CI
Q1	-9.8	-26.9 to -7.0	4164	114	2.74	1	(reference)
Q2	-5.0	-7.1 to -3.0	4164	164	3.94	1.40	1.10 to 1.79
Q3	-1.1	-3.1 to 1.2	4164	205	4.92	1.83	1.44 to 2.31
Q4	4.5	1.3 to 41.5	4164	333	8.00	3.18	2.54 to 3.97

Comprehensive data regarding the development and validation of the Moli-sani Risk Score are currently being reviewed for publication in a scientific peer-reviewed journal.

ANCILLARY STUDIES

The CV-PREVITAL study includes several ancillary studies, each with its own protocol. The objectives and outcomes of the ancillary studies are described below.

Ancillary study of Centro Cardiologico Monzino IRCCS

The ancillary study of the IRCCS Centro Cardiologico Monzino IRCCS (abbreviated as Monzino) aims to evaluate the hypothesis that the same mHealth intervention investigated in the parent study can improve metabolic balance in the short term and reduce the onset of type 2 diabetes in the long term in individuals at high risk of developing this disease due to pre-diabetes. To this end, 1,000 participants already enrolled in the parent study at the outpatient clinics of GPs or at pharmacies (including 200 subjects with a diagnosis of type 2 diabetes mellitus (T2DM), 400 subjects with a diagnosis of pre-diabetes and 400 normoglycemic individuals) equally divided into control and intervention groups, are invited to undergo an in-depth diabetological evaluation at Monzino. This evaluation includes a clinical visit, non-invasive diagnostic tests to assess carotid subclinical atherosclerosis (i.e., atherosclerotic plaque size, total plaque area, total plaque volume, intima-media thickness (IMT), interadventitia common carotid artery diameter (ICCAD), and wall echolucency), endothelial function (i.e., reactive hyperemia index), peripheral atherosclerosis (i.e., Ankle Brachial Index (ABI)), diabetic retinopathy (i.e., fundus retinography), and collection of blood and urine samples for biochemical analysis. These include OGTT (oral glucose tolerance test of fasting blood glucose (FPG) and 120 minutes after ingestion of 75 grams of glucose (2h PG)), HbA1c (by standardized HPLC method), insulinemia, fasting apolipoprotein B and lipoprotein(a), hs-CRP, microalbuminuria (Albumin/Creatinine ratio), creatinine and eGFR. Total cholesterol, HDL cholesterol, triglycerides, and calculated LDL cholesterol, which were already measured by point-of-care tests within the parent study, are re-measured with standard laboratory methods. After 12 months of follow-up, each individual in the Monzino sub-study is invited to attend to the same facility for repeating all the evaluations performed at baseline, except for the evaluations of carotid subclinical atherosclerosis, endothelial function, peripheral atherosclerosis and diabetic retinopathy. The proportion of subjects who change from a diagnosis of T2DM to a diagnosis of pre-diabetes or from a diagnosis of pre-diabetes to a diagnosis of normoglycemia, compared to the baseline examination is thus evaluated. After 7 years of follow-up, the occurrence of cardiovascular events and overt diabetes, depending on the length of time in pre-diabetes and the interaction of pre-diabetes with other risk factors (e.g. obesity, hypertension, hypertriglyceridemia, etc.), is also assessed. The sample size of this ancillary study was calculated based on the difference between groups in glucose response during OGTT. In the subsamples of normal (n=400) and prediabetic (n=400) subjects, a comparison of two groups of 200 subjects (App Vs. Usual care) ensures a significant evaluation ($p<0.017$, applying Bonferroni correction for 3 independent tests) of a between-group difference of approximately 32% of a standard deviation of blood glucose at two hours after the start of the test, with a statistical power of 80%. In the subsample of diabetic subjects (n=200), the comparison of two groups of 100 subjects (App Vs. Usual care) ensures the detection of a minimal difference of approximately 46% of a

standard deviation of blood glucose at two hours after the start of the test, again with 80% power and a p<0.017.

Ancillary study of Istituto Auxologico Italiano IRCCS

The ancillary study of the Istituto Auxologico Italiano IRCCS (abbreviated as Auxologico) enrols 5,000 individuals, divided into three sub-cohorts based on the presence or absence of hypertension, obesity, or sleep problems. In these individuals, in addition to the conventional cardiovascular risk factors included in the parent study, several supplementary variables are investigated. In the hypertensive subjects sub-cohort, the following parameters are evaluated: 24-hour systolic blood pressure (SBP); ambulatory blood pressure variables (i.e., 24-hour SBP, 24-hour diastolic blood pressure (DBP), day-time SBP, day-time DBP, night-time SBP, night-time DBP, SD 24-hour SBP, SD 24-hour DBP, SD day-time SBP, SD day-time DBP, SD night-time SBP, SD night-time DBP); dipping status (i.e., the difference between the mean SBP during the day and mean SBP during the night, expressed as a percentage of the daytime mean); 24-hour urinary sodium secretion; microalbuminuria; creatinine; eGFR; left ventricular hypertrophy (evaluated with the Sokolow index and Cornell product). In the obese/overweight subjects sub-cohort, the following parameters are evaluated: BMI; waist circumference; waist/hip ratio; fasting insulinemia and fasting blood glucose levels. Additional evaluation in subjects classified as both hypertensive and obese/overweight includes cardiovascular risk estimate based on clinical variables and biomarkers (Troponin I, cut-off of 0.008 ng/mL; hs-CRP, cut-off of 6.81 mg/L; N-terminal pro-BNP, cut-off of 187 pg/mL) and measurement of uric acid levels. In subjects with sleep problems attending the Center for Sleep Medicine, detailed information on the qualitative and quantitative characteristics of night sleep is recorded using the Pittsburgh Sleep Quality Index (PSQI) questionnaire. Other evaluations related to sleep complaint include the Epworth Sleepiness Scale (ESS) questionnaire [5 6] to assess the improvement in daytime sleepiness and the diagnosis of obstructive sleep apnea (OSA) by polysomnographic indices such as the apnea-hypopnea index (AHI) (<5/hour = normal OSA; 5–14.9/hour = mild OSA; 15–29.9/hour = moderate OSA; ≥30/hour = severe OSA). In subjects with OSA, differences in the usage of positive airway pressure (PAP) devices and in the daily usage of PAP treatment at 1 year after randomization between control and intervention groups are also evaluated.

After 12 months of follow-up, each individual enrolled in the Auxologico sub-study is invited to return to the same facility to repeat all the evaluations performed at baseline.

The primary outcome measures in the three sub-cohorts of the Auxologico ancillary study are as follows: 1) the difference in mean systolic 24-hour blood pressure at 12 months between the two study arms (App-based intervention vs. usual care); 2) the difference in mean BMI at 12 months between the two study arms; 3) the difference in sleep quality (mean score on the Pittsburgh questionnaire - PSQI) at 12 months between the two study arms.

A sample size of 506 hypertensive subjects (253 in each group) will allow detection of a 3 mmHg mean systolic 24-hour blood pressure difference between the intervention (APP) and control groups, assuming a first-type error rate of 5%, a power of 80%, and a standard deviation of 12 mmHg.[7] This sample size was calculated using a two-tailed t-test under the assumption of equal variances between groups. Assuming a dropout probability of 25%, the final sample size will consist of 676 subjects (338 in each group).

A sample size of 426 overweight or obese subjects (213 in each group) will allow detection of a 1.5 Kg/m^2 BMI difference between the intervention (APP) and control groups, assuming a first-type error rate of 5%, a power of 80%, and a standard deviation of 5.5 Kg/m^2.[8] This sample size was calculated using a two-tailed t-test under the assumption of equal variances between groups. Assuming a dropout probability of 25%, the final sample size will consist of 578 subjects (284 in each group). A sample size of 1,132 subjects with impaired sleep quality as per PSQI>5 (566 in each group) will allow detection of a 0.7 difference in PSQI score between the intervention (APP) and control groups, assuming a first-type error rate of 5%, a power of 80%, and a standard deviation of 4.2 points.[9] This sample size was calculated using a two-tailed t-test under the assumption of equal variances between groups. Assuming a dropout probability of 25%, the final sample size will consist of 1,510 subjects (775 in each group).

Ancillary study of IRCCS Humanitas Research Hospital

As an ancillary study, the IRCCS Humanitas Research Hospital (abbreviated as Humanitas) performs a quantitative evaluation of the coronary artery calcium (CAC) score through CT imaging in half of the participants. CAC score is calculated using the Agatston method and by determining the volume of calcium.[10] The study has a 2x2 factorial design: subjects are randomized 1:1 to receive either an app or usual care as in the parent study. Each subject is then further randomized 1:1 to receive either CT scanning on top of usual care or usual care alone.

After 12 months of follow-up, each individual is invited to attend the IRCCS Humanitas again, as in the parent study. A comparison of the mean change in lipid biomarkers from baseline to follow-up between the two groups (CT scan or usual care alone) is performed.

It is expected that patients randomized to CT scanning compared to usual care will experience a larger reduction in LDL-C levels from baseline; i.e., a difference in the mean reduction in LDL-C of 0.25 mmol/L (9.65 mg/dL), with an SD of 1 mmol/L (38.6 mg/dL). The rationale for this hypothesis is that the presence of a calcium score > zero will increase the likelihood of statin prescription and subject adherence.

To detect this difference, a total of 506 participants (253 in each group) will be required with 80% power, and a two-sided α of 0.05. However, based on a previous study on primary prevention performed at the same institution, considering that the prevalence of patients with a zero calcium score would be approximately 60%, the total number of participants will increase to 1,265. Considering an overall 5% dropout, the final total number of participants will be 1,328 (664 in each group).

Furthermore, at 12 months, the ability of SNPs identified in previous genome-wide association studies or newly identified in this study to predict severe coronary artery calcification is also assessed.

At 7 years, the incremental effectiveness (i.e., healthy quality-adjusted life years (QALYs)), and the incremental cost-effectiveness ratios (ICERs) of screening by CT scanning for CAC score are assessed.

Finally, major adverse cardiovascular and cerebrovascular events between subjects randomized to screening by CT scanning or traditional risk factor assessment alone are assessed.

Ancillary study of IRCCS MultiMedica

In its ancillary study, IRCCS MultiMedica (abbreviated as MultiMedica) performs additional investigations in 1,000 diabetic patients and in 2,000 individuals recruited from the general population. These investigations include: evaluation of organ damage (indexed by common carotid IMT), ABI, and endothelial function as assessed through ICAM and VCAM; quality of life, assessed by using the WHOQOL-Measuring Quality of Life questionnaire; psychological conditions, measured using the Mini Mental Status test; cardiovascular risk, measured by the "SCORE" (Systematic COronary Risk Evaluation) algorithm;[11] and hematochemical investigations, useful to define the condition of diabetes or dyslipidemia. Hematochemical and biochemical investigations carried out in diabetic subjects include: blood glucose, Brain Natriuretic Peptide (BNP), creatinine (eGFR), hs-CRP, interleukin 6 (IL-6), interleukin 1 beta (IL-1 beta), microalbuminuria. In addition to total cholesterol, HDL cholesterol, triglycerides and calculated LDL cholesterol measured within the procedures adopted for the parent study, additional variables measured in dyslipidemic individuals include: apolipoprotein AI, apolipoprotein B, lipoprotein(a), creatine phosphokinase (CPK), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT). After 12 months of follow-up, each individual is invited to return to IRCCS MultiMedica to repeat all the aforementioned evaluations. The mean change from baseline between the 2 groups is compared. The ancillary study also includes: multivariate analysis of baseline data for the identification of determinants and predisposing factors to the diabetes status, dyslipidemia and hypertension; the detection of causative mutations in case of suspected genetic disorders; the 12-month evaluation of CAC score in patients with suspected familial hypercholesterolemia; and the assessment of the onset of cardiovascular events, and new diagnosis of diabetes and hypertension in the 7-year follow-up period.

1,782 subjects will be needed to identify a significant reduction (alpha=0.01) in scores after one year of intervention, assuming a standard deviation of 5 and a statistical power of 95%. Assuming a dropout rate of about 10%, 2,000 patients will be recruited.

Ancillary study of IRCCS Istituto Neurologico Mediterraneo NEUROMED

In addition to the biochemical variables measured in the parent study, in the ancillary study of the IRCCS Istituto Neurologico Mediterraneo NEUROMED (abbreviated as NEUROMED) hs-CRP and creatinine (eGFR) are evaluated. Moreover, NEUROMED ancillary study includes the administration of supplementary questionnaires on dietary habits (to assess the proportion of subjects who change their consumption of ultra-processed foods, according to the NOVA classification[12]) and the evaluation of cognitive status by using the Montreal Cognitive Assessment (MOCA) test.[13] Finally, IRCCS NEUROMED analyses the determinants of dietary changes using multivariable approaches. After 12 months of follow-up, each individual is invited to return to IRCCS NEUROMED to repeat the aforementioned evaluations. The mean change from baseline between the 2 groups is compared. This ancillary study will be conducted in a subset (N=1,000) of the recruited population. This sample size is large enough to guarantee large power (power>90%; α=0.01) for testing the hypotheses of this ancillary study (assessment of determinants of dietary changes concerning the consumption of ultra-processed foods, and evaluation of cognitive status by the Montreal cognitive assessment test).

Ancillary study of IRCCS Policlinico San Donato

In the ancillary study, the IRCCS Policlinico San Donato (abbreviated as San Donato) performs additional investigations on 1,000 subjects selected among its own employees. At baseline, participants undergo: 1) a vascular investigation (carotid B-mode ultrasonography) to assess IMT, plaques size, presence/absence of atherosclerotic plaques, and total plaque area; 2) a trans-thoracic echocardiographic examination (TT-Echo) to assess relative wall thickness, E/A ratio, E/e' ratio, heart mass, end-diastolic and end-systolic volume, left atrial volume, Ejection Fraction (EF; %), maximal tricuspid regurgitation velocity (TRV max), and epicardial adipose tissue (EAT). Moreover, additional hematochemical analyses are performed, including NT-proBNP, as this biomarker has been inserted in the algorithm for the diagnosis of heart failure with preserved ejection fraction,[14] and TSH, to investigate the relationship between disthyroidism and cardiovascular disease. Finally, in order to refine the cardiovascular risk estimation, the ancillary study of San Donato evaluates other additional serum biomarkers in individuals with comorbidities, such as diabetes mellitus, overweight, obesity, abdominal obesity (number estimated=400 individuals). In particular, insulinemia, homocysteine, hs-CRP, Na^+, K^+, IL-6, and sRAGE are analysed.

After 12 months of follow-up, participants are invited to attend to IRCCS San Donato for assessing the mean change from baseline in NT-proBNP and TSH values. The value of ultrasound and transthoracic-echocardiographic variables as predictor of cardiovascular events is assessed at the end of the 7-years follow-up.

1,000 patients will be sufficient to estimate as significant a correlation coefficient (alpha=0.001, adjusted for Bonferroni to account for multiple comparisons) of 0.15, with a statistical power of 80%. Moreover, the same sample size will allow to assess as significant (alpha(two-sided)=0.05) a difference mean after 12 months from baseline of 0.10 standard deviations of the parameters considered, with a power of 80%. Finally, in the analyses to refine the cardiovascular risk, 400 patients will provide a significant correlation coefficient (alpha(two-sided)=0.01) of 0.20, with a statistical power of 80%.

Ancillary study of Istituti Clinici Scientifici Maugeri IRCCS

In the ancillary study of the IRCCS Clinical Scientific Institutes Maugeri (abbreviated as Maugeri), 1,000 individuals are categorized according to their cardiovascular risk. Subjects at intermediate/high risk undergo additional hematochemical analyses including blood glucose, uricemia, and microalbuminuria. In participants who need further risk stratification, additional tests to assess atherosclerotic organ damage are performed, including ABI, the CT CAC score and carotid artery ultrasound.

In all individuals, in addition to the usual care or mHealth intervention planned for the parent study, a personalized program of physical activity is also prescribed. In particular, for individuals classified at high-risk, an exercise test for silent ischemia screening is performed to obtain the prescriptive drivers needed to personalize the physical training intervention. Finally, in all participants at intermediate/high risk, a blood sample for genetic and epigenetic tests and for the evaluation of possible additional hematochemical factors predisposing to atherosclerotic diseases is collected.

Cardiovascular events, silent ischemia and change from baseline in ABI, CAC score and carotid imaging markers over a 7-year follow-up period, depending on the length of time in physical activities programs, are evaluated. The interaction of physical activity with other risk factors (e.g. obesity, hypertension, hypertriglyceridemia, etc.) is also performed to assess the relationship with carotid imaging markers. Assuming a prevalence of subjects at intermediate/high cardiovascular risk of about 15%, 150 patients will guarantee a significant correlation coefficient (alpha=0.01) of 0.30, with a statistical power of 80%. The other analysis will only be exploratory descriptive analysis for which the sample calculation was not done.

Ancillary study of IRCCS ISMETT (Mediterranean Institute for Transplantation and Advanced Specialized Therapies)

In its ancillary study, the IRCCS ISMETT (Mediterranean Institute for Transplantation and Advanced Specialized Therapies) (abbreviated as ISMETT) plans to conduct baseline and 12-month assessments, including: 1) a CT scan to assess CAC score; 2) a cardiac magnetic resonance to evaluate myocardial fibrosis; 3) an evaluation of a series of circulating biomarkers indicating cardiac stress and/or heart failure and kidney dysfunction, including creatinine, blood urea, nitrogen (Blood Urea Nitrogen, BUN), and hs-CRP. Other biomarkers tested include NT-proBNP, Na^+, K^+, homocysteine, iron, ferritin, transferrin, and complete blood count. The effect of specific cardiovascular risk factors (e.g. obesity, hypertension, diabetes etc.) on outcomes 1, 2 and 3 is also evaluated. The mean change from baseline between the 2 groups is compared. To assess as significant a difference (alpha(two-sided)=0.05) in mean change after 12 months from baseline of 0.22 standard deviations of the parameters considered with a power of 80%, 150 subjects are needed.

Ancillary study of IRCCS Ospedale Policlinico San Martino

In the ancillary study of the IRCCS Ospedale Policlinico San Martino (abbreviated as San Martino), 1,500 male individuals, recruited in the city of Genoa, undergo an echocolor Doppler examination for the early detection of abdominal aortic and iliac aneurysm. In an additional group of 500 male individuals, a color Doppler ultrasound of external carotid arteries is performed to evaluate the average IMT for the early diagnosis of carotid plaques and carotid stenosis. In such individuals, the risk stratification for cardiovascular disease is also evaluated. To ensure a 95% confidence interval of 18.8, 29.3, assuming a mean aortic diameter equal to 19.43 mm, 1500 subjects are needed[15].

Ancillary study of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

In the ancillary study of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (abbreviated as Ca' Granda), individuals with a cardiovascular risk >7.5% or with at least 3 metabolic risk factors selected among the 2,000 participants enrolled in their structure undergo: 1) an ultrasonographic scan to assess carotid subclinical atherosclerosis (indexed by plaque size, presence/absence of plaques, and IMT); 2) a non-invasive fibroscan analysis to assess the amount of hepatic fat/lipotoxicity (indexed by the CAP Score) and the hepatic fibrosis stage (indexed by the FIB-4 Index); 3) a series of blood chemistry tests, including microalbuminuria, AST, ALT, GGT, HbA1c, insulinemia, coagulation balance (i.e., von Willebrand Factor Antigen, Protein C, and Factor VIII), D-Dimer levels, and interleukin-32 (as a circulating biomarker of lipotoxicity). After 12 months of follow-up, each individual is invited to attend to IRCSS Ca' Granda again for the follow up visit. The mean change from baseline between the control and intervention groups is compared for all the variables mentioned above, except for coagulation balance and D-Dimer levels, which are measured only at baseline.

In addition, the characterization of the intestinal microbiome is performed in a subgroup of 200 individuals at baseline and after 7 years by: 1) a metagenomic analysis (taxonomic and functional), including the evaluation of serum levels of trimethylamine oxide (TMAO) and other metabolites of bacterial origin (branched-chain amino acid (BCAAs), aromatic amino acid (AAAs)), and 2) the interaction of the microbiome with classical and inherited risk factors. Finally, a genetic characterization is performed in the whole Ca' Granda cohort by Whole Exome Sequencing (WES) and genotyping (GWAS) for *PNPLA3 I148M, TM6SF2 E167K, GCKR P446L* and *MBOAT7* genetic variants influencing hepatic fat content (HFC).

A genetic risk score based on these variants (hepatic fat content-genetic risk score, HFC-GRS) is calculated, and the association of HFC-GRS with early cardiovascular damage (estimated by IMT) is evaluated. As we have preliminary data indicating that high HFC-GRS (above the median) is associated with a >3-fold higher

risk of developing NASH and clinically significant fibrosis, the power of the study to detect an impact of genetic scores on the risk of liver disease (NASH or clinically significant fibrosis) is >95% ($p<0.05$, two-tailed). Regarding the possibility of prospectively evaluating extra-hepatic outcomes, given the age range and the presence of metabolic risk factors, the cumulative incidence of major cardiovascular thrombotic events (death, myocardial infarction or cerebrovascular events, venous thromboembolism) is expected to be 3-4% in the cohort. The sample size has a >80% power to detect a hazard ratio of 1.8 of non-hepatic events, which is consistent with literature data, associated with genetically determined hepatic fat accumulation.

Ancillary study of Fondazione Policlinico Universitario Agostino Gemelli IRCCS

The additional investigations performed in the 1,000 individuals enrolled by the Fondazione Policlinico Universitario Agostino Gemelli IRCCS (abbreviated as Gemelli) include ultrasonographic scan of carotid arteries for evaluation of IMT, measurement of additional variables of lipid metabolism (Lp(a) and serum oxidized LDL levels), and inflammation (hs-CRP, IL1beta, IL-18, IL-6, IL-10, and TNF-alpha), and measurement of serum additional biochemical variables including human lipopolysaccharides (LPS), metabolite of bacterial origin and TMAO. Finally, this ancillary study also envisages the assessment of the intestinal microbiome composition with Next Generation Sequencing (NGS) technology and of a serum marker of intestinal permeability (zonulin).

After 12 months of follow-up, each individual is invited to attend the IRCSS Gemelli for repeating the aforementioned evaluations. The mean change from baseline between the control and intervention groups is compared. The assessment of cardiovascular events incidence over the 7-year follow-up period, depending on the significant biomarkers variation and microbiome composition detected, is also evaluated. The primary endpoint in this ancillary study is the mean change in compositional microbiome after treatment between the two subgroups, measured in terms of microbiome entropy, i.e., Shannon's alpha diversity index. Given the paucity of evidence on this topic and the already available sample size, a post-hoc power calculation is proposed, assuming 500 subjects per group, a two-sided 95% confidence interval with a significance level (type I error) of 0.05. Based on these assumptions, 1000 subjects, i.e., 500/group, are able to detect a small Cohen's d effect size equal to 0.2, with an estimated power of 0.8847885. The power estimate was computed with the "pwr" R package (https://CRAN.R-project.org/package=pwr), which was installed in the R environment v4.2.3 (CRAN ®, R Core 2022, Wien, Austria) (https://www.R-project.org/), by applying a two-sided, two-sample t test with effect size. The script is provided accordingly (https://github.com/piaclarapafundi/Italian-Cardiologic-Network-Ancillary-Study).

Ancillary study of Fondazione IRCCS Policlinico San Matteo

In its ancillary study, the Fondazione IRCCS Policlinico San Matteo (abbreviated as San Matteo) develops a multigene analysis panel that allows the identification of a genotype at risk of diabetes before the appearance of the clinical phenotype. To this end, 200 diabetic patients, 400 pre-diabetic subjects, and 400 normoglycaemic subjects (enrolled at IRCCS Monzino) and 100 healthy individuals (enrolled at the Genetics Unit of IRCCS San Matteo) are subjected to genetic testing using a multigene NGS panel. DNA is collected from white blood cells. The gene prevalence is calculated as the ratio between patients carrying pathogenic variants and all patients of the studied cohort. In addition, San Matteo ancillary study also aims to investigate the prevalence of likely pathogenic and pathogenic variants in genes related to familial hypercholesterolemia in subjects with a diagnosis of hypercholesterolemia. Finally, the ancillary study envisages the development of new monogenic/polygenic scores and the validation of existing scores for the assessment of the risk of developing diabetes, hypertension and hypercholesterolemia not present at baseline.

The sample size of 100 subjects enrolled at San Matteo is based on feasibility. The precision of the prevalence estimates given the sample size of 100 subjects is summarized in the table and calculated as half of the 95% confidence interval for different scenarios. No correction for multiple tests is applied (exploratory study). Assuming we analyse the 100 patients at San Matteo with the patients enrolled at IRCCS Monzino, a sample size of 1,000 patients estimates the confidence intervals as shown in the table.

Proportion	Binomial exact (95% confidence interval), n=100		Binomial exact (95% confidence interval), n=1000	
0.5	0.39832	0.60168	0.46855	0.53145
0.05	0.16432	0.11283	0.03733	0.06539
0.02	0.00243	0.07038	0.01226	0.03072
0.01	0.00025	0.05446	0.00480	0.01813

Ancillary study of IRCCS San Raffaele

In its ancillary study, the IRCCS San Raffaele (abbreviated as San Raffaele) recruits a cohort of 150 individuals aged ≥ 45 years selected among its employees. These individuals are included in a program of physical activity monitored and combined with nutrition education provided in the workplace, aimed at reducing the incidence of hyperlipidemia, overweight/obesity, and related risks such as the onset of T2DM and hypertension. In addition to the evaluations already planned in the parent study, the study foresees assessing the amount of daily physical activity through an accelerometer app, adherence to the Mediterranean diet by the Mediterranean Diet Scale (MDS) questionnaire[16] and complete blood count. All measurements are performed at 6 and 12 months from baseline, except the assessment of daily physical activity which is also performed at month 3. Comparison of the mean change from baseline between the 2 groups at the different time points is performed.

Assuming a CVD event incidence of 747.6/100,000 population, 125 subjects are needed to ensure 80% power and a maximum 95% confidence interval width of 3%, with an alpha of 0.05. Considering an estimated 20% dropout during the study, we will enroll a sample size of 150 total subjects (thus 75 per group).

Supplemental Table 3. Name of approving body and approval number/ID of CV-PREVITAL studies

	Approval Number	Board Name
Parent study	R1256/20-CCM 1319	Comitato Etico degli IRCCS Istituto Europeo di Oncologia e Centro Cardiologico Monzino
Ancillary studies of Monzino	R1579/21-CCM 1677; R1617/22-CCM 1723	Comitato Etico degli IRCCS Istituto Europeo di Oncologia e Centro Cardiologico Monzino
Ancillary study of Istituto Auxologico Italiano	2022_03_08_06	Comitato Etico dell'IRCCS Istituto Auxologico Italiano
Ancillary study of Humanitas	2860	Comitato Etico Indipendente dell'Istituto Clinico Humanitas
Ancillary study of MultiMedica	MM: 472.2021	Comitato Etico IRCCS MultiMedica - Sezione del Comitato Etico Centrale IRCCS Lombardia
Ancillary study of NEUROMED	Session of 28/09/2020	Comitato Etico dell'Istituto Neurologico Mediterraneo Neuromed
Ancillary study of San Donato	197/INT/2021	Comitato Etico IRCCS Ospedale San Raffaele
Ancillary study of Maugeri	2575 CE	Comitato Etico degli Istituti Clinici Scientifici Maugeri
Ancillary study of ISMETT	IRRB/16/22	Comitato Etico IRCCS Sicilia
		Sezione ISMETT IRCCS srl
Ancillary study of San Martino	173/2021	Comitato Etico Regionale della Liguria
Ancillary study of Ca' Granda	887_2020	Comitato Etico Milano Area 2
Ancillary study of Gemelli	3614	Comitato Etico della Fondazione Policlinico Universitario A. Gemelli IRCCS – Università Cattolica del Sacro Cuore
Ancillary studies of San Matteo	2022-3.11/91; 2022-3.11/493	Comitato Etico Pavia
Ancillary study of San Raffaele	21/21	Comitato Etico IRCCS San Raffale Roma

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