BMJ Open

Rationale and design of the CV-PREVITAL study: an Italian multiple cohort randomised controlled trial investigating innovative digital strategies in primary cardiovascular prevention

Damiano Baldassarre ,[1,2] Licia Iacoviello ,[3,4] Roberta Baetta,[1] Maria Carla Roncaglioni,[5] Gianluigi Condorelli,[6,7] Giuseppe Remuzzi ,[8] Gianfranco Gensini,[9] Luigi Frati,[10] Walter Ricciardi,[11,12] Pier Giulio Conaldi,[13] Antonio Uccelli,[14] Fabio Blandini,[15] Silvano Bosari,[15] Giovanni Scambia,[12,16] Massimo Fini,[17] Antonio Di Malta,[18] Mauro Amato,[1] Fabrizio Veglia,[19] Alice Bonomi,[1] Catherine Klersy,[20] Francesca Colazzo,[1] Martino Pengo,[21,22] Francesca Gorini,[21] Luciana Auteri,[21] Giuseppe Ferrante,[6,7] Marta Baviera,[5] Giuseppe Ambrosio ,[23] Alberico Catapano,[9,24] Alessandro Gialluisi,[3,4] Alexis Elias Malavazos,[25,26] Serenella Castelvecchio,[27] Massimiliano Marco Corsi-Romanelli,[28,29] Rosanna Cardani,[30] Maria Teresa La Rovere,[31] Valentina Agnese,[13] Bianca Pane,[14,32] Daniele Prati,[33] Laura Spinardi,[15] Giovanna Liuzzo,[12,34] Eloisa Arbustini,[35] Maurizio Volterrani,[36,37] Marco Visconti,[18] José Pablo Werba,[1] Stefano Genovese,[1] Grzegorz Bilo ,[21,22] Cecilia Invitti,[21] Anna Di Blasio,[21] Carolina Lombardi,[21,22] Andrea Faini,[21,38] Debora Rosa,[21] Luisa Ojeda-Fernández,[5] Andreana Foresta,[5] Amalia De Curtis,[3] Augusto Di Castelnuovo ,[39] Simonetta Scalvini,[40] Antonia Pierobon,[31] Alessandra Gorini,[41,42] Luca Valenti,[33,43] Livio Luzi,[9,29] Annarosa Racca,[44] Manuela Bandi,[44] Elena Tremoli,[19] Lorenzo Menicanti,[27] Gianfranco Parati,[21,22] Giulio Pompilio,[1,26] CV-PREVITAL Study Group[45]

To cite: Baldassarre D, Iacoviello L, Baetta R, *et al*. Rationale and design of the CV-PREVITAL study: an Italian multiple cohort randomised controlled trial investigating innovative digital strategies in primary cardiovascular prevention. *BMJ Open* 2023;**13**:e072040. doi:10.1136/bmjopen-2023-072040

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-072040).

DB and LI are joint first authors.

Received 18 January 2023

For numbered affiliations see end of article.

Correspondence to
Professor Damiano Baldassarre; damiano.baldassarre@cardiologicomonzino.it

ABSTRACT

Introduction Prevention of cardiovascular disease (CVD) is of key importance in reducing morbidity, disability and mortality worldwide. Observational studies suggest that digital health interventions can be an effective strategy to reduce cardiovascular (CV) risk. However, evidence from large randomised clinical trials is lacking.

Methods and analysis The CV-PREVITAL study is a multicentre, prospective, randomised, controlled, open-label interventional trial designed to compare the effectiveness of an educational and motivational mobile health (mHealth) intervention versus usual care in reducing CV risk. The intervention aims at improving diet, physical activity, sleep quality, psycho-behavioural aspects, as well as promoting smoking cessation and adherence to pharmacological treatment for CV risk factors. The trial aims to enrol approximately 80 000 subjects without overt CVDs referring to general practitioners' offices, community pharmacies or clinics of Scientific Institute for Research, Hospitalization and Health Care (Italian acronym IRCCS) affiliated with the Italian Cardiology Network. All participants are evaluated at baseline and after 12 months to assess the effectiveness of the intervention on short-term endpoints, namely improvement in CV risk score and reduction of major CV risk factors. Beyond the funded life of the study, a long-term (7 years) follow-up is also planned to assess the effectiveness of the intervention on the incidence of major adverse CV events. A series of ancillary studies designed to evaluate the effect of the mHealth intervention on additional risk biomarkers are also performed.

Ethics and dissemination This study received ethics approval from the ethics committee of the coordinating centre (Monzino Cardiology Center; R1256/20-CCM 1319) and from all other relevant IRBs and ethics committees. Findings are disseminated through scientific meetings and peer-reviewed journals and via social media. Partners are informed about the study's course and findings through regular meetings.

Trial registration number NCT05339841.

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death in developed countries.[1] In Italy, there are 136 353 deaths annually attributed to atherosclerotic CVD,

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The randomised controlled design of the study and the enrolment of a large population of participants (n~80 000) recruited in different real-world settings, including general medicine, community pharmacies and Scientific Institute for Research, Hospitalization and Health Care (IRCCS).
- ⇒ The adoption of a coordinated network strategy that also envisages the creation of an Information Technology (IT) infrastructure for communication among health operators.
- ⇒ The collection of biological samples for the multisite biobank of the Italian Cardiology Network, according to specific standard operating procedures for sample collection, storage and transfer.
- ⇒ The lack of standardisation of the equipment used for haematological testing and blood pressure measurement, due to the real-world nature of the study, is a possible limitation of the trial.
- ⇒ Due to the nature of the intervention, the trial personnel and participants are not blinded to the treatment allocation.

with acute coronary syndromes and ischaemic strokes accounting for about 22% of total deaths.[2] CVDs are also among the major causes of chronic disability, affecting millions of people worldwide.

CVDs are, to a large extent, preventable. Prevention of CVD is of key importance, not only to reduce morbidity, disability and mortality, but also to increase the years of healthy living among the growing elderly population, thus contributing to alleviate the socioeconomic burden associated with cardiovascular (CV) events. However, according to European data,[3] only a small percentage of the healthcare budget is allocated to preventive measures. In this context, there is an urgent need for exploring innovative approaches to better address the challenge of CVD prevention. Internet-based tools and smartphone applications have the potential to play a significant role in CVD prevention by enabling remote lifestyle monitoring, diagnosis, self-management of CV risk factors, medication adherence, education and psychological support. Preliminary evidence suggests that digital health interventions can be an easy-to-implement and cost-effective strategy to reduce CV risk in primary prevention.[4] However, more robust evidence is still required, which can only be provided by large controlled trials.

In response to this need, and driven by a specific mandate from the Italian Parliament (Law No. 136, 17 December 2018, and Law No. 145, 30 December 2018), the Italian Cardiology Network (ICN), a network of Scientific Institute for Research, Hospitalization and Health Care (Italian acronym IRCCS) engaged in the CV field promoted by the Ministry of Health, launched the 'Digital Strategies in Primary Cardiovascular Prevention in the Italian Population (CV-PREVITAL)' study in 2020.

CV-PREVITAL is a multicentre, prospective, randomised, controlled, open-label interventional trial that aims to compare the effectiveness of an educational and motivational mobile health (mHealth) intervention with that of usual care in primary CV prevention. The main hypothesis of the study is that digital technologies can be used efficiently for improving the control of CV risk factors and detrimental lifestyles, thereby reducing CVD incidence and mortality, compared with usual care. The trial also includes several ancillary studies. The purpose of this report is to provide a comprehensive description of the project background and of the study protocol, which is also publicly available at www.clinicaltrials.gov.

METHODS AND ANALYSIS

The study protocol adheres to 'The Standard Protocol Items: Recommendations for Intervention Trials 2013 statement'[5] (online supplemental file 1).

Trial organisation

CV-PREVITAL consists of a large clinical trial (the parent study) and of a series of ancillary studies. The organisational structure of CV-PREVITAL is presented in figure 1. The organisational structure includes several integrated committees: the Steering Committee (see also online supplemental table 1); the Central Management Committee (based at the Monzino Cardiology Center) responsible for organising and coordinating the entire study; the Scientific Coordination Committee and nine technical committees (TCs). The TCs are tasked with coordinating specific activities in various areas, including clinics, haematological analysis, socioeconomic status assessment, non-invasive diagnostic techniques, genetic analysis, statistics, artificial intelligence, mHealth, eHealth, technology platforms and technology transfer.

The list of operative units and their role in the study are shown in online supplemental table 2. A part from the Institute of Pharmacological Research Mario Negri IRCCS, which acts as the monitoring centre for the cohort of subjects recruited by general practitioners (GPs), all other IRCCSs participate as recruiting centres. The working group also includes Consorzio Sanità (Co.S.), a consortium of cooperatives of GPs working in the National Health Service.

Study data are collected and managed using REDCap electronic data capture tools hosted at the Consortium of Bioengineering and Medical Informatics.[6 7]

Trial design

CV-PREVITAL is a multicentre, prospective, parallel-arm, randomised, open-label interventional study. It aims to recruit approximately 80 000 participants (aged ≥45 years) nationwide. Of these, 50 000 subjects are selected among those who daily access the participanting GPs offices. Additionally, to evaluate the effectiveness of the mHealth intervention in settings other than primary care, several specific cohorts are enrolled by IRCCSs (online supplemental table 2). These cohorts consist of approximately 34 000 subjects from outpatient clinics, diagnostic centres, blood donor centres, company cohorts, the general population and pharmacies. The actual study start date (first participant enrolled) is 10 June 2022; the estimated completion date is June 2029.

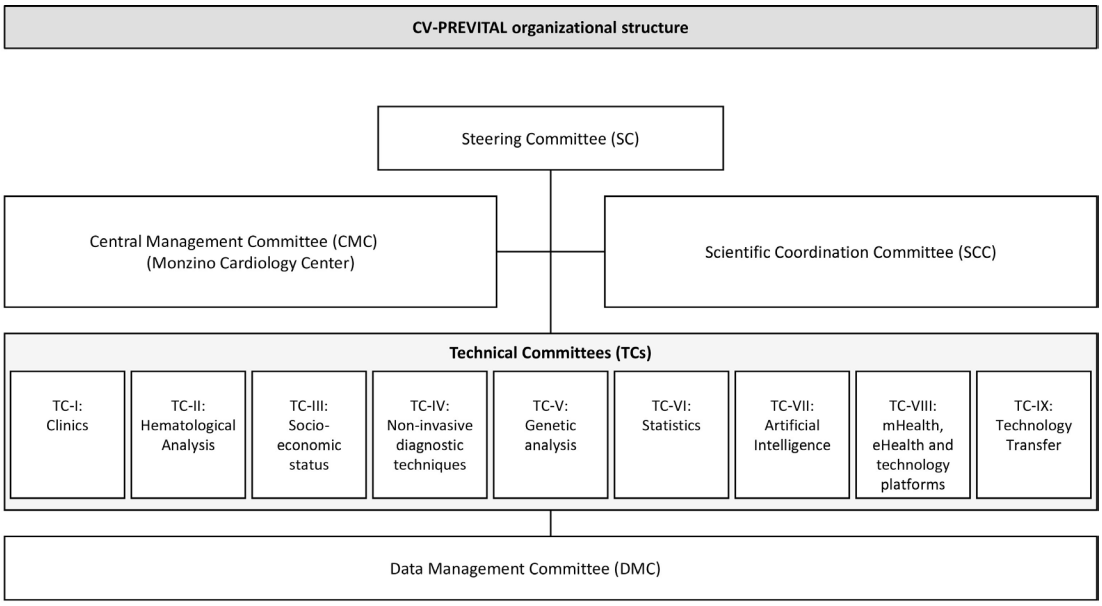


Figure 1 CV-PREVITAL organisational structure.

The full list of study sites is available on ClinicalTrials.gov. A structured summary of the trial based on the WHO Trial Registration Data Set is provided in online supplemental file 2. The data flow of CV-PREVITAL is illustrated in figure 2.

Eligibility

Participants of both sexes are eligible to participate in the study if they meet the following criteria: (a) they are in primary CV prevention, (b) they are ≥45 years old, (c) they possess a smartphone and (d) they have provided their informed consent by signing the relevant documents. Individuals who meet any of the following conditions are not eligible for the study: (a) informed consent not signed, (b) age lower than 45 years, (c) history of overt CVD (myocardial infarction (MI), angina pectoris, stroke, transient ischaemic attack (TIA), aortic aneurysm or arteriopathy obliterating lower limb pathologies, or congestive heart failure (NYHA Class III–IV)). Prior to randomisation, eligible participants are asked by the study investigators to sign the informed consent forms (online supplemental file 3). To promote participation across all recruitment settings, leaflets and posters promoting the study and explanatory videos emphasising the importance of proper management of CV risk factors have been realised. The number of screened individuals who are deemed ineligible is centrally recorded in the ICN database.

Randomisation

To assess the effectiveness of the intervention, the participants are allocated randomly in a 1:1 fashion into two groups: (1) the control group, receiving conventional care (usual care); and (2) the intervention group, receiving mHealth intervention in addition to usual care (mHealth group). Randomisation is carried out in three different ways depending on whether the participants are enrolled by GPs, by community pharmacies or IRCCSs. For participants enrolled by GPs, the randomisation procedure ensures that the number of physicians assigned to the control group is balanced with the number assigned to the intervention group within each group practice (referred to as Centro Sanitario Polifunzionale). For participants enrolled by community pharmacies, the randomisation procedure ensures that the number of pharmacies assigned to the control group is balanced with the number assigned to the intervention group in each geographic area. For participants enrolled by IRCCSs, the procedure directly randomises the participants themselves. The randomisation process is carried out by means of a central randomisation service developed in-house. Allocation concealment is ensured, as the randomisation code is not revealed until the participant is recruited and baseline measurements are completed. Additional details are provided in the online supplemental material.

Intervention

At baseline, participants allocated to the mHealth group receive, in addition to usual care, a smartphone application (CV-PREVITAL app) designed for managing a personalised primary CV prevention programme. The app serves the following purposes: (a) education on CV risk, remote monitoring and self-management of CV risk factors, (b) education on and remote monitoring and self-management of psycho-behavioural variables and (c) detection and/or modification of harmful lifestyles. The CV risk factors monitored by the app include high blood pressure, dyslipidaemia, diabetes mellitus, obesity, abdominal obesity and sleep disorders. Psycho-behavioural variables include stress, depression, anxiety and factors related to aspects of the human sphere relevant for patients' empowerment, such as risk propensity, self-efficacy and locus of control. Harmful lifestyles include unhealthy diet, excessive alcohol intake, smoking habits and

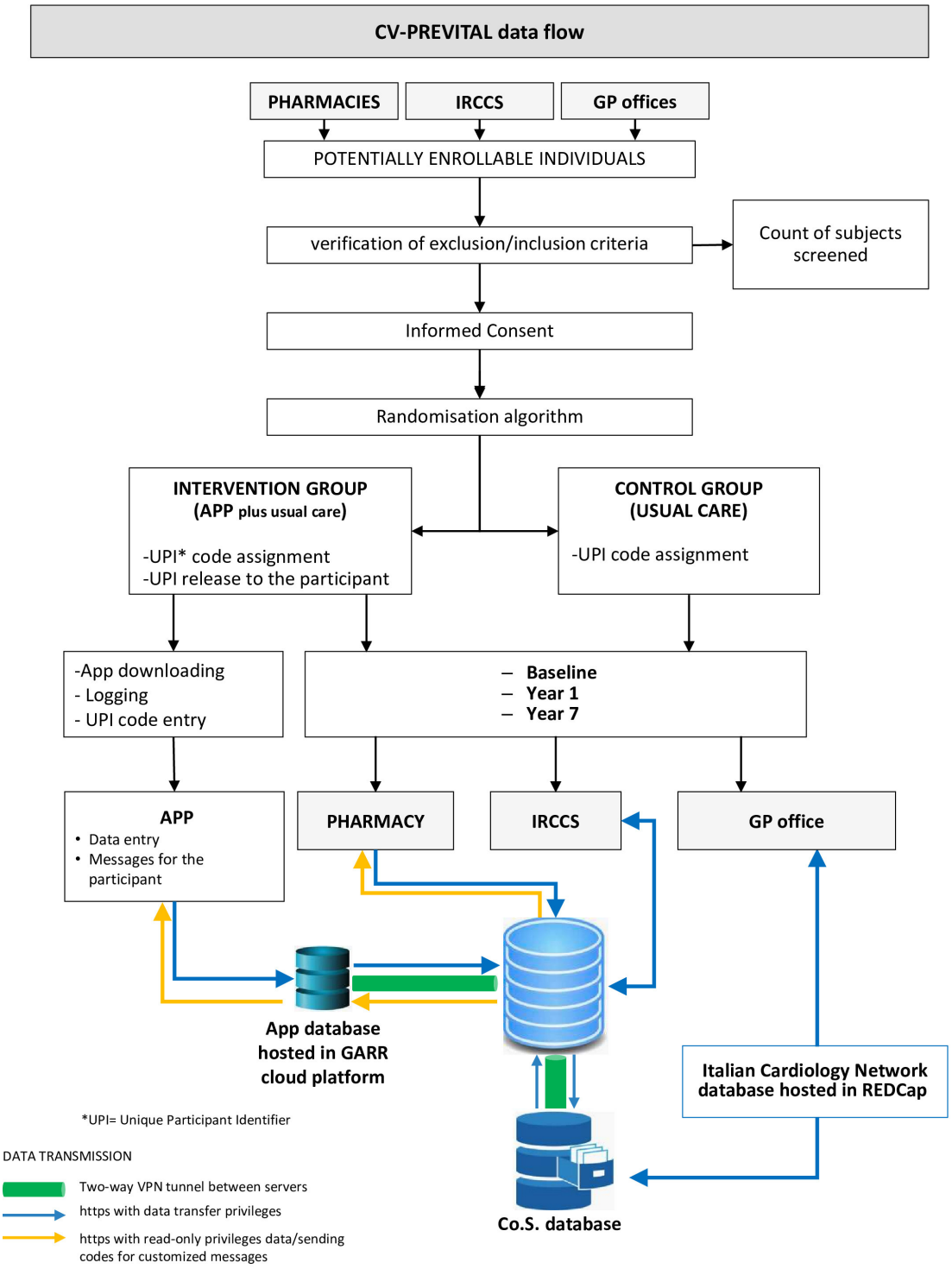


Figure 2 CV-PREVITAL data flow. Co.S., Consorzio Sanità; GARR, Gruppo per l'Armonizzazione della Rete della Ricerca; GP, general practitioner; IRCCS, Scientific Institute for Research, Hospitalization and Health Care (Istituto di Ricovero e Cura a Carattere Scientifico in Italian language); VPN, Virtual Private Network.

a sedentary lifestyle. The app is organised in several educational sections and tools for monitoring the variables under consideration, allowing participants to track their progress over time. It delivers personalised educational contents and provides guided access to different sections based on the participant's profile (eg, subjects with hypertension or hypercholesterolemia or diabetes and so on). Profiling is performed through specific algorithms according to data collected at baseline (see below), which are recorded in a pseudonymised form on the ICN platform database. Lifestyle monitoring is carried out through active participation, where participants periodically provide information relevant to their health, such as dietary habits, assumption of medications, specific anthropometric parameters, sleep quality and level of physical activity practiced. The app may integrate with native wellness apps to automatically track step counts

and sleep duration with the user's permission. The app also provides reminders, personalised motivational feedback and evaluation of tasks and goal achievements on a periodic basis. These elements are implemented using a gamification logic,[8] that is, an approach that seeks to create experiences reminiscent of gaming and that implies not only a combination of concepts such as rewards (eg, points, achievement badges and challenges), but also the use of narrative storylines, avatar-based self-representation and onboarding tutorials. Gamification logic has been proposed for a twofold purpose: to make study participation and data compilation tasks more enjoyable, and to encourage long-term commitment to tasks that may be perceived as boring or demotivating over time. The ultimate goal is to help users complete the required tasks, improve health literacy and adhesion to healthy behaviours and/or maintaining healthy habits. Data collected through the app during the follow-up period are transmitted to the ICN database. This allows the treating doctor to access the information and personalise further prevention activities based on the collected data.

Control group

Participants allocated to the control group are followed by the conventional approach (usual care) based on regular visits respecting the usual schedule dictated by the rules of general practice. As a part of the baseline assessment, they receive counselling and are encouraged to maintain or improve their current physical activity level, dietary habits, medical adherence and so on depending on their individual goals and needs.

Hypotheses and outcomes

The primary hypothesis of the trial is that a personalised intervention of CV primary prevention based on mHealth technology can be more effective than usual care in controlling conventional risk factors and harmful lifestyles in the short term and in reducing vascular events in the long term. The primary outcome used to measure the efficacy of the mHealth intervention at short term (12 months) is the change in a risk score developed specifically for the Italian population. The score, referred to as the 'modified Moli-Sani score' (details in online supplemental material), was created by analysing the combined impact of different modifiable risk factors on the risk of developing CVD during the follow-up of the Moli-Sani study, which collects data from the general population of Molise, a region in south-central Italy.[9 10] An improvement of one unit (approximately 33% reduction) in the modified Moli-Sani score between the baseline and final assessment in the intervention group (App), compared with the score change observed in the control group (Usual care), is indicative of a clinically meaningful intervention effectiveness in the short term. This is because, according to the construction of the Moli-Sani risk score, a one-point improvement in the Moli-Sani risk score is equivalent (in terms of CV risk) to an increase of 1 year of age. The primary outcome used to measure the efficacy of the mHealth intervention in the long term (7 years) includes major adverse cardiovascular events (MACE), that is, CV death, MI, stroke, TIA, peripheral artery disease, new diagnoses of angina, hospitalisations for CVD and need for revascularisation.

Several short-term secondary outcomes are also prespecified. These include: (a) a combined endpoint including the simultaneous change in hypertension, diabetes and hypercholesterolemia; (b) the change in at least one of the risk factors considered in the score; (c) the percentage of subjects who agree to complete questionnaires; (d) the percentage of subjects who interrupts the use of the app during the follow-up and (e) adherence to recommended therapies.

Besides these clinical outcomes, other outputs of the project include the development and validation of a new algorithm for estimating CV risk, the estimation of the costs and effectiveness of the intervention and the identification of new socioeconomic and behavioural risk factors.

Measurements performed at baseline and follow-up

At baseline, subjects identified as potentially eligible for recruitment receive information material and consent forms for study participation. Those who agree to participate are invited to complete a series of questionnaires. Questionnaires can be completed in two ways: (a) on-site by a direct access to an electronic 'Case Report Form' (eCRF), with the assistance of a healthcare professional; or (b) remotely via web access to the eCRF, with the help of computer tutorials or phone assistance, after having provided a digital informed consent and using a secure access. The remote option was provided to cope with the limitations due to the COVID-19 pandemic, which required social distancing to limit the spread of SARS-CoV-2.

Self-report questionnaires administered at baseline cover the following areas:

1. Family and personal history of diseases (cardiovascular and cerebrovascular disease; metabolic disease).
2. Ethnicity, socioeconomic status and marital status.
3. Smoking habits.
4. Alcohol consumption (PREDIMED questionnaire).[11]
5. Adherence to Mediterranean diet (PREDIMED questionnaire)[11] and Moli-Sani questionnaire—an adaptation of the MEDAS questionnaire.[12]
6. Salt consumption (MiniSal questionnaire).[13]
7. Physical activity (IPAQ—International Physical Activity Questionnaire).[14]
8. Personal history of sleep disorder and sleep quality (PSQI—Pittsburgh Sleep Quality Index).[15]
9. Psycho-behavioural factors:
   9.1 Perceived stress (PSS—Perceived Stress Scale).[16]
   9.2 Anxiety and depression (PHQ 4 questionnaire).[17]
   9.3 Self-efficacy (GSE—General Self-Efficacy Scale).[18]
   9.4 Locus of control (Multidimensional Health Locus of Control Scale).[19]
   9.5 Risk propensity (RPS—Risk Propensity Scale).[20]
10. Personal history of COVID-19.

Baseline evaluation is completed by healthcare professionals (nurses, physicians or pharmacists) with the

collection of the following data: (a) ongoing pharmacological treatments (chronic therapies); (b) personal history of organ damage from diabetes and hypertension; (c) measurements of anthropometric parameters (weight, height, body mass index, waist circumference,[21] blood pressure and heart rate) and (d) biochemical variables (total, low-density lipoprotein and high-density lipoprotein cholesterol, triglycerides and glycated haemoglobin) assessed by point-of-care testing or by standard laboratory methods. Based on these data, by using validated algorithms a series of risk scores are estimated, including scores assessing the risk of developing metabolic diseases such as diabetes (Findrisc),[22] and hypertension,[23] and a score assessing the risk of developing vascular events (the modified Moli-Sani score). Other risk algorithms, such as those developed within the 'Progetto Cuore' framework,[24] the European and the American risk algorithms (ie, SCORE-Risk[25] and Framingham Risk Score,[26] respectively) and the ASCVD (ie, the score proposed within the American College of Cardiology/American Heart Association Task Force on Practice guidelines),[27] are also calculated for comparison.

At the 12-month follow-up, participants are invited to return to the recruitment centre to complete the baseline questionnaires again and to repeat the anthropometric and biochemical measurements made during the first assessment. At the 7-year follow-up, participants are contacted to monitor the occurrence of new MACE. In the case of fatal events, information is obtained by contacting the participant's family.

All follow-up visits adhere to routine clinical practice for CV prevention. Reasons for discontinuation are documented using a dedicated eCRF form.

A schematic diagram illustrating the data collected at the three time points of the study protocol (baseline, 12 months and 7 years) is shown in online supplemental file 4.

Sample size

The sample size has been calculated based on the long-term endpoint (ie, incidence of CV events). Using data from the IMPROVE study, which included approximately 1000 Italians (around 50% men and 50% women) aged 55–79 years with a 7-year follow-up (Italian groups of the IMPROVE study),[28] the annual incidence of MACE was estimated. With an assumed incidence rate of 0.0116/year, it was projected that with a sample size of 50 000 participants, with an approximately equal distribution of men and women, a total of 3921 events would occur over 7 years. This sample size was determined to be sufficient to detect as statistically significant (alpha=0.05) and with a power of 80% an 8.5% reduction in MACE incidence in the intervention group compared with the usual care group, with an HR of 0.915. Additionally, on the basis of the data of the Moli-Sani study, which included 21 806 subjects with a median follow-up of 8.2 years and 862 events, the incidence rate is 0.0048 and the expected number of events in the CV-PREVITAL population is 1687. This sample size provides a power of 80% to detect as significant (alpha=0.05) a 12.8% reduction in MACE incidence in the intervention group compared with the usual care group, with an HR of 0.872. Based on past experience of prevention studies with very long follow-ups (≥5 years), for example, IMPROVE, the number of lost at follow-up is particularly high (even >50%). In order to take account of such a potentially high rate of loss to follow-up, the calculated sample size (n=50 000) was increased by approximately 60% to a final number of ~80 000. It is worth noting that being calculated on the vascular events at 7 years, this sample size yields a very high power (>95%) to detect even very small differences in short-term endpoints, in both risk scores and single risk factors (eg, <1 mg/dL for total cholesterol and blood glucose, and 1 mm Hg for systolic blood pressure). So, all the results obtained derived from a sample sufficiently powered (1–β=80%) to perform also sex stratified analyses. Results obtained from different cohorts, such as those enrolled by GPs and various IRCCSs, are combined using a meta-analytic approach to ensure a comprehensive analysis.

Statistical analysis

Continuous data will be presented as means and SDs and as medians and IQRs, categorical data as frequencies and %.

Three classes of pre-specified statistical analyses have been planned. The first class involves analysing variables collected at enrolment to estimate the baseline prevalence of different risk factors and conditions among the recruited cohorts. The second class focuses on variables collected at the end of the short-term follow-up (12 months) to assess the effectiveness of the intervention (App vs Usual care) on CV risk. The third class of analyses pertains to variables collected at the end of the long-term follow-up (7 years) to assess the effectiveness of the intervention on the incidence of fatal and non-fatal CV events.

Cross-sectional analyses on data collected at baseline will be carried out using logistic regression and general linear models (GLMs). The short-term primary endpoint, that is, the change in CV risk score in the two treatment arms, will be analysed with GLMs adjusting for potential confounders possibly unbalanced between the two groups. Secondary endpoints, that is, changes in the level of individual risk factors, will be analysed with GLMs and Bonferroni correction will be applied to account for the number of tests performed. The long-term primary endpoint, that is, the incidence of fatal and nonfatal CV events, will be analysed by Cox regression models adjusting for potential confounders. As long-term secondary endpoints, new risk algorithms will be developed using Cox models and validated using Receiver-operating characteristic (ROC) curve analysis and reclassification techniques. Results generalisability will be tested with cross-validation approaches. Subgroup analyses stratified by gender are also planned.

Missing outcomes for the primary endpoint will be imputed using multiple imputation, and a sensitivity analysis on the imputed data will be performed. Drop-outs will not be replaced.

The efficacy analyses will be performed according to the intention to treat principle on the full analysis set (ITT analysis). A sensitivity analysis will also be performed in the population with adherence to protocol (Per-protocol (PP) analysis).

Cost-effectiveness assessment

In the assessment of cost-effectiveness for different screening scenarios, the economic aspects of digital-health interventions are recognised as complex due to their nature as 'complex interventions in a complex system'. Instead, in the intervention involving health professionals the costs are relatively limited and include: (a) cost of implementing and mainteining the Information Technology (IT) platform required for the intervention; (b) cost for developing the smartphone application that, once implemented, has virtually negligible installation costs and (c) cost of the time spent by health professionals for training, using the IT platform, and engaging and educating the participants. For an analytical evaluation of the economic aspects of the intervention, two approaches are applied: cost/efficacy analysis (CEA) and cost/utility analysis (CUA). CEA is the simplest and most frequently used form of evaluation in health economics. It aims to estimate the relationship between the costs of the resources used and the effectiveness achieved through their use. Effectiveness is estimated using a single indicator in two ways: first, as the number of participants who achieve the target in the main risk factors (hypertension, diabetes and hypercholesterolemia); and second, as the number of CV events (both fatal and non-fatal) avoided during the 7-year follow-up, relative to the incurred costs. CUA, on the other hand, considers not only the duration, but also the quality of life that participants experience as a result of the intervention. Quality-adjusted life years (QALYs) are used as summary measures to comprehensively assess the overall health and well-being of the individuals. To estimate QALYs, validated instruments such as WHO Quality Of Life or similar tools will be used and administered during the follow-up period.

Web-based trial management

To establish an effective communication network between GPs and physicians from the IRCCSs, all the data collected are stored in the IT platform of the ICN, as shown in figure 2. This platform is integrated with the Co.S. IT platform, which is the interface used by GPs participating in the study (figure 2). Additionally, the ICN database communicates with the mHealth interface (App for smartphones) dedicated to the population, which serves for both educational purposes and additional data collection (figure 2).

To ensure data protection and comply with security recommendations specified by the National Institute of Standards and Technology[29] and European data protection regulations,[30] various measures have been implemented. These measures are designed to safeguard the confidentiality, integrity and availability of the collected data. A detailed description of the web-based system for data management and the specific data protection measures implemented is provided in the online supplemental material.

Staff training, standard operating procedures (SOPs) and quality control

A detailed description of models for staff training, standard operating procedures (SOPs; available on request) and quality control activities is reported in the online supplemental material.

Ancillary studies (CV-PREVITAL sub-studies)

CV-PREVITAL also includes a series of ancillary studies that are conducted by the various IRCCSs already participating in the parent study. Ancillary studies are designed to evaluate a series of additional risk biomarkers in groups or selected sub-groups included in the parent study. A detailed description of the specific variables evaluated in each ancillary study is reported in the online supplemental material.

The steering committee reviewed all the ancillary study protocols to ensure that the specific objectives did not duplicate or interfere with those of the parent study and that all the adopted procedures were consistent with those established in the main protocol. Beyond the specific aims of single sub-studies, a particularly relevant goal, common to all the sub-studies, is the collection of biological samples (eg, serum, plasma, DNA or RNA) for the multisite biobank of the ICN. For this purpose, the research consortium developed specific SOPs for collection, storage and samples transfer, for example, towards centres acting as core lab. A brief description of the plan for collection, processing and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies is provided in online supplemental file 5. A biobank informed consent is obtained to specifically address the collection of these samples.

Patient and public involvement

Patients and/or the public are not involved in the design, or conduct, or reporting, or dissemination plans of this research.

ETHICS AND DISSEMINATION

The CV-PREVITAL study has been approved by all relevant IRBs and ethics committees. Their list and the study approval number-IDs are provided in online supplemental table 3. Any protocol amendment is promptly reported to all relevant parties (namely, investigators, ethical committees/IRBs, ClinicalTrials.gov). Personal data are processed in compliance with the provisions

set out in Regulation (UE) 2016/679 (the 'GDPR') and in Legislative Decree. 196/2003 (Personal Data Protection Code, added by the Legislative Decree 101/2018). Personal information is available to researchers using password-protected files. In addition, all data for presentations are anonymised and aggregated, so the participants' identity is not revealed in any way. CV-PREVITAL results will be disseminated at conferences, through publication in peer-reviewed journals and through other channels (eg, web sites of the ICN and of all the hospital involved, social media) in order to reach a diverse community of researchers, GPs, pharmacists and other stakeholders, including citizen and policymakers.

DISCUSSION

To the best of our knowledge, this is the first randomised, controlled trial designed to evaluate the effects of an individualised digital intervention delivered through an app containing tools for education on CV risk, remote monitoring and self-management of CV risk factors, detection and/or modification of harmful lifestyles, and patient empowerment.

Preliminary data show that smartphone applications might actually have a great potential in the remote monitoring and self-management of CV risk factors and in improving therapy adherence in hypertensive, diabetic and dyslipidemic patients.[31 32] However, more evidence is needed to confirm their effectiveness in primary CV prevention programmes. CV-PREVITAL, by collecting information in a prospective, randomised and controlled way on a large-scale, has the potential to provide strong evidence to support policy makers in making informed decisions about strategic planning and resources allocation in primary CV prevention.

If the proposed intervention proves to be workable and successful, the study will provide robust evidence that digital medicine can be a useful strategy to engage, motivate and empower people towards primary prevention of CVD. In addition, due to the large sample size and the different types of cohorts involved, the study has also the potential to generate reliable evidence for implementing digital technology-based CV primary prevention programmes not only in general or specialist medicine, but also in other settings such as occupational medicine, blood donors centres and community pharmacies.

A significant strength of the CV-PREVITAL study design is the adoption of a coordinated network strategy involving IRCCSs with proven experience in primary prevention programmes, epidemiology and biomedical statistics, along with a large number of GPs spread throughout the national territory. We expect that such strategy, which also envisages the creation of an IT infrastructure for communication among GPs and IRCCSs, may provide the basis for their permanent collaboration, increase the opportunity for future real-world research and enhances knowledge transfer among healthcare professionals.

The participation of a large number of pharmacies is another significant strength, considering their wide distribution and frequent access by citizens, which makes them capable of taking an active role as an outpost of the national health systems for the delivery of health services and the implementation of primary prevention programmes. In this regard, it is worth mentioning that it is estimated that approximately 4 000 000 people enter the ~20 000 pharmacies existing in Italy every day.[33]

Another important strength of the study is that it allows to make inference on (a) the level of adherence to the digital prevention programmes, (b) the rate of drop-outs associated with this type of programmes in different cohorts and in different age and sex classes and (c) the barriers to participation based on participants' feedbacks. These insights are crucial for decision makers to understand and address barriers that can hinder the successful implementation of digital health in primary prevention of CVD, including digital literacy, internet access, concerns about privacy and data security, and perceptions of digital approaches' usefulness.

A last important aspect of the CV-PREVITAL study is that it was designed in the pre-COVID-19 era, but is in fact being carried out during the pandemic. While this presented challenges, it also provided new opportunities to highlight the usefulness of digital tools and accelerate their adoption in remote monitoring and CVD management worldwide.[34]

A possible limitation of the study is the lack of standardised equipment for haematological testing and blood pressure measurement. However, blood pressure measurement devices validated according to internationally acknowledged validation protocols are used.[35] Although aware of the inevitable increase in variability of measurements associated to this type of choice, the decision was made to obtain data better reflecting what happens in real-world prevention programmes.

Overall, the CV-PREVITAL study holds promise to contribute significant evidence and insights into the effectiveness and implementation of digital interventions in primary CV prevention.

Author affiliations
[1]Centro Cardiologico Monzino IRCCS, Milan, Italy
[2]Department of Medical Biotechnology and Translational Medicine, Università degli Studi di Milano, Milan, Italy
[3]Department of Epidemiology and Prevention, IRCCS Istituto Neurologico Mediterraneo NEUROMED, Pozzilli, Italy
[4]Research Center in Epidemiology and Preventive Medicine (EPIMED), Varese, Italy
[5]Laboratory of Cardiovascular Prevention, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy
[6]Department of Cardiovascular Medicine, IRCCS-Humanitas Research Hospital, Rozzano, Italy
[7]Department of Biomedical Sciences, Humanitas University, Milan, Italy
[8]Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy

[9]IRCCS Multimedica, Milan, Italy
[10]IRCCS Istituto Neurologico Mediterraneo NEUROMED, Pozzilli, Italy
[11]Istituti Clinici Scientifici Maugeri IRCCS Pavia, Pavia, Italy
[12]Università Cattolica del Sacro Cuore - Campus di Roma, Rome, Italy
[13]IRCCS ISMETT (Mediterranean Institute for Transplantation and Advanced Specialized Therapies), Palermo, Italy
[14]IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[15]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[16]Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[17]IRCCS San Raffaele, Rome, Italy
[18]Co.S. (Consorzio Sanità) Study Center, Italy, Soresina, Italy
[19]Maria Cecilia Hospital, GVM Care & Research, Cotignola, Ravenna, Italy
[20]Unit of Clinical Epidemiology & Biostatistic, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[21]Istituto Auxologico Italiano IRCCS, Milan, Italy
[22]Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy
[23]Cardiology, University of Perugia School of Medicine, Perugia, Italy
[24]Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, Milan, Italy
[25]Endocrinology Unit, Clinical Nutrition and Cardiovascular Prevention Service, IRCCS Policlinico San Donato, San Donato Milanese, Italy
[26]Department of Biomedical Surgical and Dental Sciences, Università degli Studi di Milano, Milan, Italy
[27]Department of Cardiac Surgery, IRCCS Policlinico San Donato, San Donato Milanese, Italy
[28]UOC SMEL-1, IRCCS POLICLINICO SAN DONATO, San Donato Milanese, Italy
[29]Department of Health and Biomedical Sciences, Università degli Studi di Milano, Milan, Italy
[30]BioCor Biobank, UOC SMEL-1 of Clinical Pathology, IRCCS-Policlinico San Donato, San Donato Milanese, Italy
[31]Istituti Clinici Scientifici Maugeri IRCCS Montescano, Montescano, Italy
[32]Dipartimento di Scienze Chirurgiche e Diagnostiche Integrate, Università degli Studi di Genova, Genoa, Italy
[33]Department of Transfusion Medicine and Haematology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[34]Dipartimento di Scienze Cardiovascolari, Fondazione Policlinico Gemelli IRCCS, Rome, Italy
[35]Centro Malattie Genetiche Cardiovascolari - Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[36]Cardio Pulmonary Department, IRCCS San Raffaele, Rome, Italy
[37]Exercise Science and Medicine, San Raffaele Open University, Rome, Italy
[38]Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Milan, Italy
[39]Mediterranea Cardiocentro, Naples, Italy
[40]Istituti Clinici Scientifici Maugeri IRCCS Lumezzane, Lumezzane, Italy
[41]Istituti Clinici Scientifici Maugeri IRCCS Milano, Milan, Italy
[42]Dipartimento di Scienze Cliniche e di Comunità, Università degli Studi di Milano, Milan, Italy
[43]Dipartimento Fisiopatologia e Trapianti, Università degli Studi di Milano, Milan, Italy
[44]Federfarma Lombardia & Fondazione Guido Muralti, Milan, Italy
[45]Italian Cardiology Network, Milan, Italy

Acknowledgements This manuscript is dedicated to the memory of Professor Alberto Zanchetti, who passed away on 24 March 2018, and Professor Luigi Rossi Bernardi, who passed away on 16 December 2019, whose thoughts and experiences have deeply inspired the study. The authors wish to thank Ms Manuela Pettignano (Centro Cardiologico Monzino IRCCS) for her valuable support in preparing the manuscript.

Collaborators CV-PREVITAL Study Group: Giulio Pompilio, Damiano Baldassarre, Roberta Baetta, Mauro Amato, José Pablo Werba, Stefano Genovese, Gualtiero Colombo, Chiara Vavassori, Maria Luisa Biondi, Beatrice Frigerio, Alessio Ravani, Daniela Sansaro, Daniela Coggi, Alessandra Romandini, Monica Giroli, Mattia Giuliani, Alice Bonomi, Maurizio Rondinelli, Catia Trudu, Carmen Cinieri, Massimo Monturano, Francesca Colazzo (Centro Cardiologico Monzino IRCCS). Gianfranco Parati, Cecilia Invitti, Grzegorz Bilo, Martino Pengo, Francesca Gorini, Luciana Auteri, Andrea Faini, Carolina Lombardi, Anna Di Blasio, Debora Rosa, Camilla Torlasco, Luisa Gilardini, Davide Soranna, Antonella Zambon, Elisa Perger, Lucia Zanotti, Luigi Badano, Lidia Cova, Davide Gentilini, Luca Grappiolo (Istituto Auxologico Italiano IRCCS). Gianluigi Condorelli, Giuseppe Ferrante, Laura Papa, Victor Savevski, Francesca Ieva, Ignazio Romano (IRCCS Humanitas Research Hospital). Giuseppe Remuzzi, Maria Carla Roncaglioni, Marta Baviera, Luisa Ojeda, Andreana Foresta, Fiorenza Clerici, Angela Palumbo (Istituto di Ricerche Farmacologiche Mario Negri IRCCS). Gian Franco Gensini, Giuseppe Ambrosio, Alberico Catapano, Roberto Mattioli, Ermanno Longhi, Livio Luzi, Lorenzo Giovanni Mantovani, Fabiana Madotto (IRCCS MultiMedica). Luigi Frati, Licia Iacoviello, Augusto Di Castelnuovo, Alessandro Gialluisi, Amalia De Curtis, Marialaura Bonaccio, Francesco Gianfagna, Anwal Ghulam, Sara Magnacca, Fabrizia Noro, Simona Costanzo, Simona Esposito, Sabatino Orlandi, Mariarosaria Persichillo, Francesca Bracone, Teresa Panzera, Emilia Ruggiero, Roberta Parisi, Sabrina Franciosa, Martina Morelli, Fiorella De Rita, Chiara Cerletti, Giovanni de Gaetano, Maria Benedetta Donati (IRCCS Istituto Neurologico Mediterraneo NEUROMED). Lorenzo Menicanti, Serenella Castelvecchio, Alexis Elias Malavazos, Massimiliano Marco Corsi Romanelli, Rosanna Cardani, Ambra Cerri, Carola Dubini, Manuel Bruno Trevisan, Laura Valentina Renna, Valentina Milani, Sara Boveri, Paola Giubbilini, Lucia Ramputi, Irene Baroni, Giada De Angeli (IRCCS Policlinico San Donato). Walter Ricciardi, Maria Teresa La Rovere, Simonetta Scalvini, Antonia Pierobon, Alessandra Gorini, Francesca Olmetti, Maurizio Bussotti, Carlo Gaetano, Paola Baiardi, Tiziana Bachetti, Martina Balbi, Laura Comini, Monica Lorenzoni, Adriana Olivares, Egidio Traversi, Camilla Garrè, Riccardo Sideri (Istituti Clinici Scientifici Maugeri IRCCS). Pier Giulio Conaldi, Valentina Agnese, Francesco Clemenza, Giovanni Gentile, Giuseppe Caruana, Nicola Cuscino, Gabriele Di Gesaro, Alessio Greco, Italia Loddo, Fabio Tuzzolino (IRCCS ISMETT (Mediterranean Institute for Transplantation and Advanced Specialized Therapies)). Antonio Uccelli, Bianca Pane, Domenico Palombo, Giovanni Spinella, Gaddiel Mozzetta, Pietro Ameri, Gabriele Zoppoli, Alice Finotello, Italo Porto, Giovanni Pratesi (IRCCS Ospedale Policlinico San Martino). Fabio Blandini, Daniele Prati, Luca Valenti, Laura Spinardi, Margherita Clerici, Serena Pelusi, Cristiana Bianco, Rossana Carpani, Giulia Periti, Sara Margarita (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico). Giovanni Scambia, Giovanna Liuzzo, Gaetano Antonio Lanza, Anna Severino, Daniela Pedicino, Domenico D'Amario, Alessia D'Aiello, Ramona Vinci, Alice Bonanni, Mattia Brecciaroli, Simone Filomia, Roberta Pastorino, Stefania Boccia, Andrea Urbani, Maurizio Sanguinetti, Angelo Santoliquido, Luca Proto, Dalila Tarquini, Maria Chiara Grimaldi (Fondazione Policlinico Universitario Agostino Gemelli IRCCS). Eloisa Arbustini, Catherine Klersy, Sergio Leonardi, Arianna Elia, Alessia Currao, Mario Urtis, Alessandro Di Toro, Lorenzo Giuliani (Fondazione IRCCS Policlinico San Matteo). Massimo Fini, Maurizio Volterrani, Giuseppe Caminiti, Federica Marcolongo, Barbara Sposato, Fiorella Guadagni, Valentina Morsella, Angelica Marziale (IRCCS San Raffaele). Antonio Di Malta, Marco Visconti (Consorzio Sanità (Co.S.)). Annarosa Racca, Manuela Bandi, Giulia Protti (Federfarma Lombardia & Fondazione Guido Muralti).

Contributors GPo, DB, RB, MA, PW, SG, GCol, CV, MLB, BF, ARa, DSa, DC, ARo, MGir, MGiu, ABono, MR, CTr, CCi, MMon, FCo, GPa, CI, GB, MPen, FGo, LA, AFa, CL, ADiB, DR, CTo, LGi, DSo, AZ, EP, LZ, LB, LCov, DG, LGr, GCon, GF, LPa, VS, FI, IR, GR, MCR, MBav, LOF, AFo, FCler, APa, GFG, GA, ACa, RM, EL, LL, LGM, FMad, LF, LI, ADiC, AGi, ADeC, MBo, FGi, AGh, SMag, FN, SCo, SE, SO, MPer, FBr, TP, ER, RPar, SFr, MMor, FD, CCe, GDeG, MBD, LM, SCa, AEM, MMC, RCard, ACe, CD, MBT, LVR, VMi, SBov, PG, LR, IB, GDeA, WR, MTLR, SS, APi, AGo, FO, MBu, CGae, PB, TB, MBal, LCom, ML, AO, ET, CGar, RS, PGC, VA, FClem, GG, GCar, NC, GDiG, AGr, IL, FT, AUc, BP, DPa, GSp, GM, PA, GZ, AFi, IP, GPra, FBI, DPr, LV, LS, MC, SP, CB, RCarp, GPe, SMar, GSc, GL, GAL, ASe, DPe, DD, AD'Ai, RV, ABona, MBr, SFi, RPas, SBoc, AUr, MS, ASa, LPr, DT, MCG, EA, CK, SL, AE, ACu, MU, ADiT, LG, MF, MVo, GCam, FMar, BS, FGu, VMo, ADM, ADiM, MVi, ARac, MBan, GPro, ETre, FV, SBos substantially contributed to the conception of the work and final approval of the version to be published. DB, GPa, CI, GB, MPen, GCon, GF, MCR, GFG, GA, ACa, LF, LI, ADiC, LM, MTL, PGC, GL, EA, MVo, ADiM, MVi, ETre, FV contributed to the design of the work. DB, RB, MA, SG, GCol, CV, MLB, BF, ARa, DSa, DC, ARo, CTr, CCi, GB, MPen, FGo, ADiB, DR, GF, LPa, IR, ACa, ADeC, SMag, SCo, MPer, FBr, TP, ER, RPar, SCa, RCard, CD, LVR, LR, GDeA, MTL, SS, TB, MBal, LCom, ML, AO, ET, CGar, RS, VA, GDiG, GM, PA, DPr, LV, SP, CB, RCarp, GPe, SMar, GL, ASe, DPe, AD'Ai, LPr, DT, MCG, EA, SL, AE, ACu, MU, ADiT, MVo, FGu, VMo, GPro contributed to the acquisition of data. DB, MA, ABono, DSo, GF, FI, LGM, ADiC, VMi, SBov, PB, FT, RPas, SBoc, CK, FV contributed to the statistical advice. DB, RB, ABono, MPen, GF, MCR, ACa, SCa, MTL, BP, DPr, LV, GL, EA, MVo, FV contributed to the drafting of the work. GPo, DB, RB, MA, PW, DC, ABono, GPa, MPen, FGo, GCon, GF, MCR, MBav, LOF, AFo, ACa, LI, ADiC, SCa, MTL, AGo, VA, AUc, BP, GM, DPr, LV, GL, EA, CK, MVo, FV contributed to revising the work critically for important intellectual content. DB, RB, MA contributed to the agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. GPa and GPo are joint last authors.

Funding The CV-PREVITAL study is carried out through funding by the Italian Ministry of Health (Ministero della Salute), Project Code RCR-2019-23669116_001. The finantial support includes the cost of developing the app used in the study. The app was built with the technical collaboration of a mobile solutions provider (YouCo s.r.l.) selected through a European tender carried out under Article 60 of Legislative Decree 50/2016 as amended. Ownership of the app is held by the Italian Cardiology Network. Funding source (Italian Ministry of Health) and technical partner (YouCo) are not involved in study execution, data analyses and interpretation, or decision to submit results.

Competing interests Authors and collaborators disclosed the relationships/activities/interests reported below. Grants or contracts from any entity: GSc, ACa, DPr, PW, ADiC, LV, LB, FCler, APa, LGM; Consulting fees: GSc, GL, SG, LV, LL, LGM, SL, IP; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: GSc, GA, ACa, DPr, GL, PW, SG, LV, LL, GPa, LB, LGi, EP, PA; Support for attending meetings and/or travel: DPr, LV, LL, EP, PA; Patents planned, issued or pending: LL, CGae; Participation on a Data Safety Monitoring Board or Advisory Board: GA, DPr, SG, LV, LL, LB, PA; Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid: GA, LV; Receipt of equipment, materials, drugs, medical writing, gifts or other services: LB, PA. Details are available in the individual ICMJE online disclosure forms (available upon request).

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Comitato Etico degli IRCCS Istituto Europeo di Oncologia e Centro Cardiologico Monzino (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 dell'IRCCS Istituto Auxologico Italiano (Ancillary study of Istituto Auxologico Italiano; 2022_03_08_06); Comitato Etico Indipendente dell'Istituto Clinico Humanitas (Ancillary study of Humanitas; 2860); Comitato Etico IRCCS Multimedica - Sezione del Comitato Etico Centrale IRCCS Lombardia (Ancillary study of Multimedica; MM: 472.2021); Comitato Etico dell'Istituto Neurologico Mediterraneo Neuromed (Ancillary study of Neuromed; Session of 28/09/2020); Comitato Etico IRCCS Ospedale San Raffaele (Ancillary study of San Donato; 197/INT/2021); Comitato Etico degli Istituti Clinici Scientifici Maugeri IRCCS (Ancillary study of Maugeri; 2575 CE); Comitato Etico IRCCS Sicilia Sezione ISMETT IRCCS srl (Ancillary study of ISMETT; IRRB/16/22); Comitato Etico Regionale della Liguria (Ancillary study of San Martino; 173/2021); Comitato Etico Milano Area 2 (Ancillary study of Ca' Granda; 887_2020); Comitato Etico della Fondazione Policlinico Universitario A. Gemelli IRCCS - Università Cattolica del Sacro Cuore (Ancillary study of Gemelli; 3614); Comitato Etico Pavia (Ancillary studies of San Matteo; 2022-3.11/91; 2022-3.11/493); Comitato Etico IRCCS San Raffale Roma (Ancillary study of San Raffaele; 21/21). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs

Damiano Baldassarre http://orcid.org/0000-0002-2766-8882
Licia Iacoviello http://orcid.org/0000-0003-0514-5885
Giuseppe Remuzzi http://orcid.org/0000-0002-6194-3446
Giuseppe Ambrosio http://orcid.org/0000-0002-9677-980X
Grzegorz Bilo http://orcid.org/0000-0002-5104-9176
Augusto Di Castelnuovo http://orcid.org/0000-0001-9767-7998

REFERENCES

1 Virani SS, Alonso A, Benjamin EJ, *et al*. Heart disease and stroke statistics-2020 update: a report from the American heart association. *Circulation* 2020;141:e139–596.
2 European Commission. State of health in the EU – Italy, country health profile. 2021. Available: https://www.euro.who.int/__data/assets/pdf_file/0008/355985/Health-Profile-Italy-Eng.pdf
3 Healthcare expenditure Statistics: Eurostat (Hlth_Sha11_Hc). 2019. Available: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Healthcare_expenditure_statistics#Healthcare_expenditure_by_function
4 Widmer RJ, Collins NM, Collins CS, *et al*. Digital health interventions for the prevention of cardiovascular disease: a systematic review and meta-analysis. *Mayo Clin Proc* 2015;90:469–80.
5 Chan A-W, Tetzlaff JM, Altman DG, *et al*. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
6 Harris PA, Taylor R, Minor BL, *et al*. The redcap consortium: building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
7 Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (Redcap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
8 Sardi L, Idri A, Fernández-Alemán JL. A systematic review of gamification in E-health. *J Biomed Inform* 2017;71:31–48.
9 Di Castelnuovo A, Costanzo S, Persichillo M, *et al*. Distribution of short and lifetime risks for cardiovascular disease in Italians. *Eur J Prev Cardiol* 2012;19:723–30.
10 Salvetti M, Paini A, Di Castelnuovo A, *et al*. Correction of QRS voltage for body mass index does not improve the prediction of fatal and nonfatal cardiovascular events. The Moli-Sani study. *Nutr Metab Cardiovasc Dis* 2020;30:426–33.
11 Martínez-González MA, García-Arellano A, Toledo E, *et al*. A 14-item mediterranean diet assessment tool and obesity indexes among high-risk subjects: the PREDIMED trial. *PLoS One* 2012;7:e43134.
12 Schröder H, Fitó M, Estruch R, *et al*. A short screener is valid for assessing mediterranean diet adherence among older Spanish men and women. *J Nutr* 2011;141:1140–5.
13 D'Elia L, Manfredi M, Strazzullo P, *et al*. Validation of an easy questionnaire on the assessment of salt habit: the MINISAL-SIIA study program. *Eur J Clin Nutr* 2019;73:793–800.
14 Mannocci A, Di Thiene D, Del Cimmuto A, *et al*. International physical activity questionnaire: validation and assessment in an Italian sample. *Int J Public Health* 2010;7:369–76.
15 Buysse DJ, Reynolds CF III, Monk TH, *et al*. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Research* 1989;28:193–213.
16 Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983;24:385–96.
17 Kroenke K, Spitzer RL, Williams JBW, *et al*. An ultra-brief screening scale for anxiety and depression: the PHQ-4. *Psychosomatics* 2009;50:613–21.
18 Zotti AM, Balestroni G, Cerutti P, *et al*. Application of the general perceived self-efficacy scale in cardiovascular rehabilitation. *Monaldi Arch Chest Dis* 2007;68:178–83.
19 Gala C, Musicco F, Durbano F, *et al*. Italian validation of the multidimensional scale of "health locus of control. *New Trends Exp Clin Psychiat* 1995;11:79–86. Available: https://csrc.nist.gov/CSRC/media/Publications/sp/800-155/draft/documents/draft-SP800-155_Dec2011.pdf
20 Meertens RM, Lion R. Measuring an individual's tendency to take risks: the risk propensity scale1. *J Appl Social Pyschol* 2008;38:1506–20.
21 Neeland IJ, Ross R, Després J-P, *et al*. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. *Lancet Diabetes Endocrinol* 2019;7:715–25.
22 Wilson PWF, Meigs JB, Sullivan L, *et al*. Prediction of incident diabetes mellitus in middle-aged adults: the Framingham offspring study. *Arch Intern Med* 2007;167:1068–74.
23 Parikh NI, Pencina MJ, Wang TJ, *et al*. A risk score for predicting near-term incidence of hypertension: the Framingham heart study. *Ann Intern Med* 2008;148:102–10.
24 Palmieri L, Panico S, Vanuzzo D, *et al*. Evaluation of the global cardiovascular absolute risk: the progetto CUORE individual score. *Ann Ist Super Sanita* 2004;40:393–9.
25 Conroy RM, Pyörälä K, Fitzgerald AP, *et al*. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;24:987–1003.

26 D'Agostino RB, Vasan RS, Pencina MJ, *et al*. General cardiovascular risk profile for use in primary care: the Framingham heart study. *Circulation* 2008;117:743–53.
27 Goff DC, Lloyd-Jones DM, Bennett G, *et al*. ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American college of cardiology/American heart association task force on practice guidelines. *Circulation* 2014;129:S49–73.
28 Baldassarre D, Nyyssönen K, Rauramaa R, *et al*. Cross-sectional analysis of baseline data to identify the major determinants of carotid intima-media thickness in a European population: the IMPROVE study. *Eur Heart J* 2010;31:614–22.
29 Regenscheid A, Scarfone K. *BIOS integrity measurement guidelines (draft) recommendations of the National institute of standards and technology. NIST National institute of standards and technology (US Department of commerce) (Special Publication 800-155*).
30 Regulation (EU) 2016/679 of the European parliament and of the council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing directive 95/46/EC (General data protection regulation) (text with EEA relevance) OJ L 119 27.04.2016 [P. 1, CELEX]; 2016. Available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32016R0679OJ
31 Ramachandran A, Snehalatha C, Ram J, *et al*. Effectiveness of mobile phone messaging in prevention of type 2 diabetes by lifestyle modification in men in India: a prospective, parallel-group, randomised controlled trial. *Lancet Diabetes Endocrinol* 2013;1:191–8.
32 Albini F, Xiaoqiu L, Torlasco C, *et al*. An ICT and mobile health integrated approach to optimize patients' education on hypertension and its management by physicians: the patients optimal strategy of Treatment(POST) pilot study. *Annu Int Conf IEEE Eng Med Biol Soc* 2016;2016:517–20.
33 Cossolo M. La Farmacia Italiana 2020/2021. n.d. Available: https://www.federfarma.it/Documenti/farmacia_italiana2020-2021.aspx
34 Cowie MR, Lam CSP. Remote monitoring and digital health tools in CVD management. *Nat Rev Cardiol* 2021;18:457–8.
35 Stergiou GS, Alpert B, Mieke S, *et al*. A universal standard for the validation of blood pressure measuring devices: association for the advancement of medical instrumentation/European society of hypertension/international organization for standardization (AAMI/ESH/ISO). *J Hypertens* 2018;36:472–8.

Online Supplemental file 1. SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Online Supplemental file 2
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	9, 10
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 8, 9
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	10
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	2, 3, Online Supplemental Material
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2

	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	2, 3
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	2, 3, Online Supplemental Material
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	3
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	3-5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5-7, Online Supplemental Material

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Online Supplemental file 4
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6, Online Supplemental Material
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	3
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	3, Online Supplemental Material
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	3, Online Supplemental Material
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	3, Online Supplemental Material
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5, 6
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7, Online Supplemental Material
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6, 7
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	6, 7
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A

Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10, Online Supplemental Material
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	7
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	3
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	10
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2, 8
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Online Supplemental file 3*
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Online Supplemental file 5

*Online Supplemental file 3 is the informed consent form (written in Italian language, followed by the English version) in use by the cohort enrolled by general practitioners. Each ancillary study has its own informed consent form (available on request).

Online Supplemental file 2. SPIRIT Item 2b: All items from the World Health Organization Trial Registration Data Set

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT05339841
Date of registration in primary registry	21 April, 2022
Secondary identifying numbers	R1256/20-CCM 1319; RCR-2019-23669116_001
Source(s) of monetary or material support	Italian Ministry of Health
Primary sponsor	Monzino Cardiology Center IRCCS
Secondary sponsor(s)	none
Contact for public queries	Damiano Baldassarre (damiano.baldassarre@cardiologicomonzino.it); Roberta Baetta (roberta.baetta@cardiologicomonzino.it)
Contact for scientific queries	Principal Investigators: Giulio Pompilio, Centro Cardiologico Monzino IRCCS (giulio.pompilio@cardiologicomonzino.it); Gianfranco Parati, Istituto Auxologico Italiano IRCCS (parati@auxologico.it) Scientific contact: studiocvprevital@retecardiologica.it
Public title	Italian Digital Primary Cardiovascular Prevention Study (CV-PREVITAL)
Scientific title	Digital Strategies in Primary Cardiovascular Prevention in the Italian Population
Countries of recruitment	Italy
Health condition(s) or problem(s) studied	Subjects in primary cardiovascular prevention
Intervention(s)	Intervention group: subjects assigned to a mobile health application (mHealth) app that delivers a personalized digital health support program based on periodic messages with advice, motivational reminders and support to improve lifestyle habits and risk factor control
	Control group: subjects assigned to usual care
Key inclusion and exclusion criteria	Ages eligible for study: ≥45 years; Sexes eligible for study: both; Accepts healthy volunteers: yes
	Inclusion criteria: adult subjects (≥45 years) consenting to participate in the study and using a smartphone
	Exclusion criteria: current or previous cardiovascular disease (personal history of myocardial infarction, angina pectoris, arterial revascularization procedures, stroke, transient ischemic attack, peripheral artery disease); Psychiatric disorders; Participation in other clinical trials
Study type	Interventional (mobile health application vs usual care)
	Allocation: randomized; Intervention model: parallel assignment; Masking: none (Open Label);

	Primary purpose: cardiovascular disease prevention
	Phase: not applicable
Date of first enrolment	June 10, 2022
Target sample size	82,800
Recruitment status	Recruiting
Primary outcome(s)	• Short term (month 12): change in cardiovascular risk • Long term (year 7): between groups difference in the incidence of vascular events
Key secondary outcomes	• Change of a combined endpoint including hypertension, diabetes, hypercholesterolemia [month 12] • Systolic and diastolic blood pressure (mmHg) [month 12] • HDL-C, LDL-C, and triglycerides (mg/dL) [month 12] • HbA1c (%) [month 12] • Body weight (kg) [month 12] • Physical activity (IPAQ questionnaire) [month 12] • Mediterranean diet adherence (PREDIMED questionnaire) [month 12] • Mediterranean diet adherence (Moli-Sani questionnaire) [month 12] • Smoking status [month 12] • Alcohol intake [month 12] • Salt intake (MiniSal questionnaire) [month 12] • Stress (Perceived Stress Scale; PSS) [month 12] • Psychological distress (PHQ 4 questionnaire) [month 12] • Anxiety (PHQ 4 questionnaire) [month 12] • Depression (PHQ 4 questionnaire) [month 12] • Multidimensional Health Locus of Control Scale (MHLCS) - Internality [month 12] • Multidimensional Health Locus of Control Scale (MHLCS) - Powerful Others Externality [month 12] • Multidimensional Health Locus of Control Scale (MHLCS) - Chance Externality [month 12] • General Self Efficacy (GSE Scale) [month 12] • Risk propensity (RPS Scale) [month 12] • Sleep quality (Pittsburgh Sleep Quality Index) [month 12] • Subjects' adherence to data recording [month 12] • Interruptions in the use of the mHealth App [month 12] • Adherence to recommended therapies [month 12] • Cost/effectiveness of intervention [year 7] • House ownership as socioeconomic status indicator [year 7]

	• Type of residence as socioeconomic status indicator [year 7] • Education as socioeconomic status indicator [year 7] • Employment status as socioeconomic status indicator [year 7] • Type of profession as socioeconomic status indicator [year 7] • Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) - history of hospitalization (questionnaire) [year 7] • Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) - history of symptoms (questionnaire) [year 7] • Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) - history of asymptomatic disease (questionnaire) [year 7] • Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) - history of vaccination (questionnaire) [year 7]

Online Supplemental file 3 - Informed consent materials
(Italian and English version)

Studio CV PREVITAL Versione 2.0 del 31.05.2021

MODULO DI INFORMAZIONE PER IL PAZIENTE

Studio CV PREVITAL

Strategie di Prevenzione primaria cardiovascolare nella popolazione italiana

Invito a partecipare allo studio CV PREVITAL
Gentile Signora/e la invitiamo a partecipare alla Ricerca CV PREVITAL.

Cos'è lo studio CV PREVITAL?
Lo studio CV PREVITAL è una ricerca collaborativa condotta da Medici di Famiglia, che si svolge a livello nazionale con l'obiettivo di migliorare la prevenzione primaria cardiovascolare in Italia.
Lo studio CV PREVITAL è promosso dal Ministero della Salute che riconosce nella prevenzione l'arma più efficace per ridurre l'insorgenza delle malattie cardiovascolari.

Perché è importante lo studio CV PREVITAL?
Attualmente, la prevenzione rappresenta la strategia più importante di intervento per diminuire l'incidenza di malattie cardiovascolari quali l'infarto del miocardio e l'ictus cerebrale. Identificare precocemente i soggetti a rischio di sviluppare queste malattie, e informare adeguatamente le persone interessate su come adottare stili di vita "sani" si sono dimostrate strategie molto efficaci per contrastare l'insorgenza di ipertensione, di diabete e di ipercolesterolemia che insieme al fumo e all'obesità rappresentano i principali fattori di rischio per l'insorgenza delle malattie cardiovascolari.
In questo contesto le tecnologie digitali stanno dimostrando un grande potenziale nel miglioramento della salute pubblica ed individuale, in quanto possono essere utilizzati come strumenti di supporto al medico per la gestione dei fattori di rischio.
Infatti negli ultimi anni si sta diffondendo sempre di più l'espressione "mobile-health" o "m-health", con cui si indica l'insieme di tecnologie (cellulari e smartphone, tablet, dispositivi digitali) applicate in ambito medico-sanitario, che stanno dimostrando un grande potenziale nel miglioramento della salute pubblica ed individuale.

Obiettivo dello studio
L'obiettivo dello studio è quello di valutare l'efficacia di un intervento di m-health nella riduzione dei principali fattori di rischio cardiovascolari e nell'insorgenza a lungo termine delle principali malattie cardiovascolari. L'intervento consiste nell'uso di un'applicazione, scaricabile sul proprio smartphone, che invierà dei messaggi educativi e formativi personalizzati, e permetterà il monitoraggio e l'auto-controllo dei principali fattori di rischio cardiovascolari e degli stili di vita.

In che cosa consiste lo studio
Lo studio coinvolgerà circa 250 Medici di Famiglia, distribuiti in diverse regioni di Italia e in totale verranno inclusi 50.000 soggetti.

Il suo medico verificherà che lei abbia i requisiti per partecipare allo studio e in caso positivo la inviterà ad aderire allo stesso firmando il consenso allegato.

Studio CV PREVITAL
Versione 2.0 del 31.05.2021

Lo studio CV PREVITAL è uno studio clinico randomizzato non farmacologico, dove i medici partecipanti saranno divisi casualmente in due gruppi:

1. gruppo di controllo
2. gruppo di intervento

I medici del "gruppo di controllo" gestiranno i propri pazienti secondo la normale pratica clinica (usal care), al meglio delle conoscenze attualmente disponibili.

I medici del "gruppo di intervento", in aggiunta a quanto previsto dalla normale pratica clinica, seguiranno i pazienti anche avvalendosi del supporto di una App che i partecipanti potranno scaricare sul proprio smartphone attraverso un link dedicato.

Lo studio clinico randomizzato è il metodo più appropriato, scientificamente riconosciuto, per poter valutare l'efficacia di interventi volti a modificare una condizione clinica. Nel caso del presente studio, l'uso della App per migliorare il controllo dei fattori di rischio cardiovascolare.

Che cosa comporta l'adesione allo studio CV PREVITAL?
Se dovesse decidere di partecipare a questo studio, il suo medico Le proporrà una serie di domande volte a valutare lo stato della sua salute cardiovascolare. In particolare sarà invitato a compilare, con l'aiuto di personale infermieristico e/o di tutorial digitali, alcuni questionari riguardanti le abitudini alimentari, l'attività fisica, l'abitudine al fumo e fattori psico-sociali e comportamentali. Le saranno inoltre misurati i livelli di colesterolo totale, LDL, HDL e l'emoglobina glicata mediante una goccia di sangue ottenuta grazie ad un prelievo capillare (piccola puntura sul dito). Infine, saranno effettuate le misurazioni di pressione arteriosa, peso, altezza e circonferenza vita. Il tutto sarà ripetuto dopo 12 mesi.

Il suo medico e il personale infermieristico La seguiranno mettendo in atto tutte le conoscenze disponibili per migliorare il suo profilo di rischio cardiovascolare. Se il suo medico fa parte del gruppo di intervento, Le verrà anche spiegato come utilizzare una specifica App. Questa servirà a raccogliere ulteriori dati nel periodo intercorrente fra l'incontro iniziale e quello a 12 mesi. Durante questo periodo, Le saranno inviati dei promemoria al fine di ricordarle di rispondere a delle semplici domande riguardanti le sue abitudini. Le sue risposte permetteranno sia di personalizzare i messaggi educativi che riceverà per aiutarla a migliorare il suo stile di vita, sia di valutare l'efficacia di questi interventi educazionali. Inoltre, se durante l'incontro basale si fosse riscontrata la presenza di uno o più fattori di rischio cardiovascolari, quali ad esempio ipertensione, diabete o ipercolesterolemia, le sarà chiesto di inserire, ad intervalli regolari, alcuni dati numerici (esempio: pressione arteriosa, emoglobina glicata, ecc.) che saranno utili per valutare l'andamento di questi fattori di rischio nel tempo e l'efficacia delle strategie educazionali messe in atto.
Dopo 7 anni Lei sarà ricontattato dal suo medico per verificare se nell'arco di questo tempo siano comparsi eventi vascolari maggiori (es infarto miocardico e ictus), o nuove diagnosi di angina e di arteriopatie periferiche, e/o se sia stato ospedalizzato per malattie cardiovascolari.

Quali sono i rischi e i benefici per chi partecipa allo studio?
Lo studio non La espone ad alcun tipo di rischio in quanto prevede soltanto l'utilizzo di una semplice App e non implica interventi di carattere invasivo. Anche i prelievi di sangue ai quali sarà sottoposto in occasione dell'incontro iniziale e di quello a 12 mesi, essendo effettuati attraverso una puntura sul dito (prelievo capillare) non la esporranno a rischi aggiuntivi. La partecipazione allo studio potrebbe invece comportare dei benefici. Ad esempio, conoscere meglio i propri fattori di rischio ed avere la possibilità di tenerli sotto controllo in modo più efficiente dovrebbe ridurre la velocità di insorgenza o di progressione delle malattie cardiovascolari in generale, e la probabilità di sviluppare eventi clinici acuti (ad es. un infarto) in particolare.

Il rifiuto a partecipare allo studio compromette in qualche modo il rapporto con il medico?
Assolutamente no, la partecipazione allo studio è volontaria e Lei è libero di ritirare il consenso in qualsiasi momento senza che Le sia richiesta alcuna motivazione. Il rapporto con il suo medico non sarà in alcun modo compromesso.

La partecipazione è gratuita o è remunerata?
La partecipazione allo studio è totalmente gratuita e non è previsto alcun compenso.

Uso dei dati
I Suoi dati verranno usati in ottemperanza alla normativa vigente in materia di tutela del trattamento dei dati personali. A tal fine, è prevista una specifica informativa che Le sarà fornita contestualmente alla proposta di adesione allo studio.

Approvazione dello studio
Lo studio è stato approvato dal Ministero della Salute, dal Comitato Etico Coordinatore e dai Comitati Etici locali di riferimento per i Medici che partecipano allo studio.

Studio CV PREVITAL
Versione 2.0 del 31.05.2021

DICHIARAZIONE DI CONSENSO

Studio CV PREVITAL
Strategie di Prevenzione primaria cardiovascolare nella popolazione italiana

Ho letto e compreso il modulo informativo per il paziente e il mio medico curante ha risposto a tutte le mie domande relative allo studio.

Ho avuto tempo per decidere se partecipare allo studio e sono consapevole che la mia partecipazione è completamente volontaria.

Sono consapevole che posso ritirarmi dallo studio in qualsiasi momento e senza l'obbligo di motivare la mia decisione.

Do, pertanto, il mio consenso a partecipare allo studio CV PREVITAL

Nome/Cognome del paziente	**Firma**	**Data**

Nome/Cognome dello sperimentatore responsabile	**Firma**	**Data**

Nome/Cognome del testimone	**Firma**	**Data**

INFORMATIVA PER IL TRATTAMENTO DEI DATI PERSONALI

Titolo dello studio:
Strategie di prevenzione primaria cardiovascolare nella popolazione italiana – CV PREVITAL

Promotore: IRCCS Centro Cardiologico Monzino

Categorie di dati oggetto del trattamento
Lo studio comporta l'acquisizione e l'utilizzo di informazioni considerate "dati personali" (quali: età, sesso, etnia, stato civile, stato socio-economico), incluse informazioni inerenti lo stato di salute, lo stile di vita, la storia familiare, considerate "dati particolari", e come tali sottoposte alla normativa vigente in materia di protezione dei dati personali:

- Regolamento Generale sulla Protezione dei Dati - UE 679/2016
- Codice in Materia di Protezione dei Dati Personali - D.lgs. n° 101/2018
- Regole deontologiche per trattamenti a fini statistici o di ricerca scientifica – 2018
- Provvedimento - 2018, che individua:
  Prescrizioni relative al trattamento dei dati personali effettuato per scopi di ricerca scientifica
  Prescrizioni relative al trattamento dei dati genetici per clinica e ricerca scientifica

Finalità del trattamento
I dati sopra descritti saranno trattati per consentire lo svolgimento dello studio CV PREVITAL e di tutte le relative operazioni ed attività connesse

Base giuridica del trattamento
Il consenso informato costituisce la base giuridica per il trattamento dei Suoi dati per gli scopi descritti nel modulo informativo. In assenza di consenso firmato non potremo utilizzare i Suoi dati per la conduzione e le analisi dello Studio.
Potrà interrompere la Sua partecipazione in qualsiasi momento e senza fornire alcuna motivazione; in tal caso, i Suoi dati saranno trattati come descritto nel modulo informativo dello Studio. Non saranno raccolti ulteriori dati che La riguardano, ferma restando l'utilizzazione di quelli eventualmente già raccolti per determinare, senza alterarli, i risultati della ricerca.

Natura del conferimento dei dati
La partecipazione alla sperimentazione avviene su base volontaria, pertanto, il conferimento dei dati personali è assolutamente volontario, nel senso che Lei potrà decidere di non conferire i Suoi dati personali e, quindi, di non partecipare allo Studio.

Modalità di Trattamento dei dati
Le finalità sopra indicate prevedono lo svolgimento del trattamento dei dati personali mediante strumenti manuali ed informatici con logiche strettamente correlate alle finalità stesse e, comunque, in modo da garantire la sicurezza e la riservatezza dei dati stessi.
I dati raccolti per i fini dello studio CV PREVITAL saranno gestiti in forma codificata.

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

Il medico che La seguirà nello studio, La identificherà con un codice che non permetterà di risalire direttamente alla Sua identità, se non presso lo studio medico partecipante.
I dati che La riguardano, raccolti nel corso dello studio, ad eccezione del Suo nominativo e il suo telefono, saranno trasmessi al Promotore in qualità di Titolare dei dati e ai Responsabili del trattamento dei dati prima elencati, e dagli stessi registrati, elaborati e conservati. I dati che Lei inserirà tramite la stazione intermodale multifunzione (totem multimediale presente nell'ambulatorio del suo medico) o da remoto (via internet) e i dati che inserirà tramite la App (se il suo medico fa parte del gruppo di intervento), saranno memorizzati in un database cloud e resi disponibili, in forma pseudonimizzata, alla piattaforma informatica della Rete Cardiologica.
Soltanto il medico, il personale responsabile del monitoraggio dello Studio *(Istituto di Ricerche Farmacologiche Mario Negri IRCCS)* e il personale delegato dalle Autorità Competenti per attività di verifica, potranno collegare questo codice al Suo nominativo quando necessario.

Ambito di comunicazione dei dati
La Sua partecipazione allo studio CV PREVITAL implica che, in conformità alla normativa sulle sperimentazioni cliniche dei medicinali, soltanto il personale incaricato delle attività di monitoraggio, il Comitato etico e le autorità sanitarie italiane e straniere potranno conoscere i dati che La riguardano, contenuti anche nella Sua documentazione clinica originale, con modalità tali da garantire la riservatezza della Sua identità.
La diffusione dei dati scientifici risultanti dalle analisi dei dati dello studio CV PREVITAL, potrà avvenire solo in forma anonima e per sole finalità scientifiche. In pratica, i risultati delle ricerche scientifiche, potranno essere presentati in forma aggregata nell'ambito di Convegni o pubblicati su riviste specializzate senza mai permettere la precisa identificazione dei pazienti.
Se previsto dal protocollo, i Suoi dati personali potranno essere trasferiti a Centri esterni per le finalità previste dal protocollo, designati dai Titolari quali "Responsabili del trattamento".
Potrà conoscere l'elenco aggiornato dei Responsabili del Trattamento, inviando una comunicazione al Responsabile della protezione dei dati (DPO) del Promotore.

In linea generale, la informiamo che ai sensi della normativa vigente, le informazioni, potranno essere condivise con altri enti e istituti di ricerca, con associazioni e altri organismi pubblici e privati aventi finalità di ricerca.
Nello specifico, lo studio CV PREVITAL è parte integrante di un più vasto progetto sviluppato con il Ministero della Salute, su indicazione del Parlamento per migliorare le strategie di prevenzione primaria cardiovascolare nella popolazione italiana, che coinvolge, Medici di Medicina Generale (MMG), Farmacie, IRCCS della Rete Cardiovascolare, la Società Italiana per la Salute Digitale e la Telemedicina e la Fondazione Romeo e Enrica Invernizzi.
Pertanto le informazioni dello studio CV PREVITAL potranno essere condivise con altri Istituti o Enti che partecipano al più vasto progetto di ricerca, fatte salve le garanzie dei sui diritti in materia di protezione dei dati personali.
Qualora dalle indagini effettuate per fini di ricerca in ambito scientifico conseguano informazioni, anche inattese, in grado di arrecare un beneficio concreto e diretto in termini di terapia o di prevenzione o in funzione di consapevoli scelte riproduttive, tali informazioni potranno essere comunicate a terzi su Sua autorizzazione, tranne eccezioni previste dalla normativa vigente.

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

Politica in materia di conservazione dei dati personali

I dati personali raccolti nell'ambito dello studio CV PREVITAL saranno conservati presso lo studio medico del Suo MMG, il Promotore e le strutture coinvolte nello Studio, per un periodo minimo di 7 anni dopo la conclusione dello Studio o per un periodo più lungo, se necessario, in base ad ulteriori requisiti di legge. Il periodo massimo di conservazione dei dati è di 25 anni dopo la conclusione dello studio.

Titolare e Responsabile della Protezione dei dati: Il Promotore che ha commissionato lo studio CV PREVITAL e il suo MMG, in qualità di Titolari del Trattamento, e l'Istituto di Ricerche Farmacologiche Mario Negri IRCCS e il Consorzio Sanità (Co.S.), in qualità di Responsabili del Trattamento, ciascuno per gli ambiti di propria competenza e in accordo alle responsabilità previste dalle norme di Buona Pratica Clinica (D.L. 211/2003), dal Regolamento UE 2016/679 del Parlamento e del Consiglio Europeo relativo alla protezione delle persone fisiche con riguardo al trattamento dei dati personali, nonché alla libera circolazione di tali dati (di seguito GDPR), dal D.lgs. 196/03 integrato dal dall'Autorizzazione generale n.9/2016 al trattamento dei dati personali effettuato a scopi di ricerca scientifica del 15 dicembre 2016 e dalla Delibera del Garante per le "Linee guida per i trattamenti di dati personali nell'ambito delle sperimentazioni cliniche di medicinali" del 24 luglio 2008 e successive modifiche, tratteranno i suoi dati personali, soltanto nella misura in cui sono indispensabili in relazione all'obiettivo dello Studio e per le finalità di seguito indicate.

La informiamo che i Titolari, ai sensi dell'articolo 37 del GDPR EU 2016/679, hanno proceduto ad individuare e nominare il Responsabile della Protezione dei dati (anche "*Data Protection Officer*" o "DPO":

Dati di contatto DPO del MMG:
[...]

Dati di contatto DPO del Promotore:
[...]

Diritti dell'Interessato

Diritto di accesso ai dati

Può chiedere di consultare le informazioni che sono state raccolte su di Lei. Tuttavia, per salvaguardare l'integrità scientifica dello studio, potrebbe non essere possibile accedere ad alcuni dati prima della conclusione dello studio stesso.

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

Diritto di rettifica ai dati
Può richiedere la modifica dei dati che La riguardano, qualora fossero errati o incompleti. Durante la valutazione di tale richiesta, ha il diritto di limitare il trattamento dei dati che La riguardano.

Diritto di portabilità dei dati
Può richiedere il trasferimento dei dati che La riguardano a Lei stesso o a qualcun altro in un formato comunemente utilizzato (cartaceo o elettronico).

Diritto di cancellazione dei dati
Può ritirare il consenso in qualsiasi momento senza darne motivazione alcuna. Può ritirare il consenso per la partecipazione allo studio e/o ai follow up successivi, anche senza ritirare il consenso per il trattamento dei dati. Qualora cambiasse idea sul trattamento dei Suoi dati, non sarà possibile rimuovere le informazioni personali già elaborate per lo studio prima del Suo ritiro (coperte dal consenso originale). In seguito, al ritiro del consenso al trattamento dei Suoi dati non verrebbero acquisite ulteriori informazioni che La riguardano.

Diritto di reclamo
Può presentare un reclamo presso l'autorità incaricata della protezione dei dati:
Garante della privacy, E-mail: garante@garanteprivacy.it Sito web: http://www.garanteprivacy.it

In merito all'esercizio di tali diritti, potrà rivolgersi direttamente al suo medico di medicina generale o, per il suo tramite, al Responsabile della protezione dei dati (DPO) del Promotore.

Definizioni

- Dato personale: qualsiasi informazione riguardante una persona fisica identificata o identificabile («interessato»); si considera identificabile la persona fisica che può essere identificata, direttamente o indirettamente, con particolare riferimento a un identificativo come il nome, un numero di identificazione, dati relativi all'ubicazione, un identificativo online o a uno o più elementi caratteristici della sua identità fisica, fisiologica, genetica, psichica, economica, culturale o sociale.

- Dati particolari: dati personali che rivelino l'origine razziale o etnica, le opinioni politiche, le convinzioni religiose o filosofiche, o l'appartenenza sindacale; i dati genetici, i dati biometrici intesi a identificare in modo univoco una persona fisica, i dati relativi alla salute o alla vita sessuale o all'orientamento sessuale della persona.

- Dati relativi alla salute: i dati personali attinenti alla salute fisica o mentale di una persona fisica, compresa la prestazione di servizi di assistenza sanitaria, che rivelano informazioni relative al suo stato di salute; quali ad esempio i dati relativi ad attività di ricovero, visite specialistiche ambulatoriali, consumo di farmaci e prestazioni di tipo socio-sanitario

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

Consenso al trattamento dei dati personali
ai sensi del GDPR UE 2016/679

Preso atto dell'informativa di cui all'art. 13 del GDPR UE 2016/679, il sottoscritto_____,
nato a_____, il_____,
in qualità di interessato

☐ dà il proprio consenso ☐ nega il proprio consenso
al trattamento dei dati per finalità relative allo studio clinico "Strategie di prevenzione primaria cardiovascolare nella popolazione italiana – CV PREVITAL"

☐ dà il proprio consenso ☐ nega il proprio consenso
affinché i risultati delle analisi e di eventuali scoperte inattese che emergano durante le attività di sperimentazione siano comunicate a:

☐ me medesimo

☐ familiare (Cognome e nome _____)

☐ convivente /coniuge (Cognome e nome _____)

☐ medico di famiglia (Cognome e nome _____)

Nome/Cognome del paziente	**Firma**	**Data**

Nome/Cognome del Medico di Medicina Generale responsabile	**Firma**	**Data**

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

CV PREVITAL Study Version 2.0 of 31.05.2021

PATIENT INFORMATION FORM

CV PREVITAL Study

Digital Strategies in Primary Cardiovascular Prevention in the Italian Population

Invitation to participate in the CV PREVITAL Study
Dear Madam(s), we invite you to participate in the CV PREVITAL Study.

What is the CV PREVITAL Study?
The CV PREVITAL study is a collaborative research conducted by Family Physicians, which takes place nationwide with the aim of improving primary cardiovascular prevention in Italy.
The CV PREVITAL study is promoted by the Ministry of Health, which recognises prevention as the most effective weapon for reducing the occurrence of cardiovascular disease.

Why is the CV PREVITAL Study important?
Currently, prevention is the most important intervention strategy to decrease the incidence of cardiovascular diseases such as myocardial infarction and stroke. Identifying at an early stage those at risk of developing these diseases, and adequately informing those concerned on how to adopt 'healthy' lifestyles have proved to be very effective strategies for combating the onset of hypertension, diabetes and hypercholesterolaemia, which together with smoking and obesity represent the main risk factors for the onset of cardiovascular diseases.
In this context, digital technologies are showing great potential in improving public and individual health, as they can be used as tools to support the physician in managing risk factors.
Indeed, in recent years, the term 'mobile-health' or 'm-health' has become increasingly popular, denoting the set of technologies (mobile phones and smartphones, tablets, digital devices) applied in the medical-health field, which are showing great potential in improving public and individual health.

Objective of the study
The objective of the study is to evaluate the effectiveness of an m-health intervention in reducing the main cardiovascular risk factors and the long-term occurrence of major cardiovascular diseases. The intervention consists of the use of a smartphone application (App), which will send personalised educational and training messages, and will allow monitoring and self-monitoring of the main cardiovascular risk factors and lifestyles.

What the study consists of
The study will involve about 250 Family Physicians, distributed in different regions of Italy, and in total 50,000 subjects will be included.

Your doctor will check that you are eligible to participate in the study and if so, will invite you to join the study by signing the attached consent.

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

CV PREVITAL Study
Version 2.0 of 31.05.2021

The CV PREVITAL study is a non-pharmacological randomised clinical trial, where participating physicians will be randomly divided into two groups:

1. control group
2. intervention group

The doctors in the 'control group' will manage their patients according to normal clinical practice (usal care), to the best of currently available knowledge.

The doctors in the 'intervention group', in addition to normal clinical practice, will also follow the patients with the support of an App that participants can download to their smartphones via a dedicated link.

The randomised clinical trial is the most appropriate, scientifically recognised method for evaluating the effectiveness of interventions aimed at modifying a clinical condition. In the case of the present study, the use of the App to improve the control of cardiovascular risk factors.

What does joining the CV PREVITAL study entail?
Should you decide to participate in this study, your doctor will ask you a series of questions aimed at assessing the state of your cardiovascular health. In particular, you will be invited to fill out, with the help of nurses and/or digital tutorials, questionnaires concerning your eating habits, physical activity, smoking habits and psycho-social and behavioural factors. You will also have your total cholesterol, LDL, HDL and glycated haemoglobin levels measured on a drop of blood obtained through a capillary sampling (small prick on the finger). Finally, blood pressure, weight, height and waist circumference measurements will be taken. This will be repeated after 12 months.

Your doctor and nursing staff will support you by implementing all available knowledge to improve your cardiovascular risk profile. If your doctor is part of the intervention group, you will also be taught how to use a specific App. This will be used to collect further data in the period between the initial evaluation and the 12-month evaluation. During this period, reminders will be sent to remind you to answer simple questions about your habits. Your answers will make it possible both to personalise the educational messages you receive to help you improving your lifestyle and to evaluate the effectiveness of these educational interventions. Moreover, if one or more cardiovascular risk factors, such as hypertension, diabetes, or hypercholesterolemia, were found to be present during the baseline evaluation, you will be asked to enter, at regular intervals, some numerical data (e.g. blood pressure, glycated haemoglobin, etc.) which will be useful for assessing the trend of these risk factors over time and the effectiveness of the educational strategies implemented.
After 7 years, you will be contacted again by your doctor to check whether any major vascular events (e.g. myocardial infarction and stroke) or new diagnoses of angina and peripheral arterial disease have occurred during this time, and/or whether you have been hospitalised for cardiovascular diseases.

What are the risks and benefits for those participating in the study?
The study does not expose you to any kind of risk as it involves only the use of a simple App and does not involve any invasive intervention. Even the blood sampling that you will be subjected to in occasion of the initial evaluation and at the 12-month evaluating, being performed through a prick on

the finger (capillary sampling), will not expose you to any additional risk. On the other hand, participation in the study could bring benefits. For example, knowing your own risk factors better and being able to control them more efficiently should reduce the rate of onset or progression of cardiovascular disease in general, and the likelihood of developing acute clinical events (e.g. a heart attack) in particular.

Does refusal to participate in the study in any way compromise the relationship with the doctor?
Absolutely not, participation in the study is voluntary and you are free to withdraw your consent at any time without being asked for a reason. Your relationship with your doctor will not be affected in any way.

Is participation free or is it remunerated?
Participation in the study is totally free of charge and there is no fee.

Use of data
Your data will be used in accordance with current legislation on the protection of personal data. To this end, a specific information notice will be provided to you together with the proposal to join the study.

Approval of the study
The study was approved by the Ministry of Health, the Coordinating Ethics Committee and the relevant local Ethics Committees.

CV PREVITAL Study
Version 2.0 of 31.05.2021

DECLARATION OF CONSENT

CV PREVITAL study
Digital Strategies in Primary Cardiovascular Prevention in the Italian Population

I read and understood the patient information form and my attending physician answered all my questions regarding the study.

I have had time to decide whether to participate in the study and I am aware that my participation is completely voluntary.

I am aware that I can withdraw from the study at any time and without having to justify my decision.

I therefore give my consent to participate in the CV PREVITAL study

Name/Surname of patient	**Signature**	**Date**

Name/Surname of the responsible investigator	**Signature**	**Date**

Name/Surname of witness	**Signature**	**Date**

INFORMATION FOR THE PROCESSING OF PERSONAL DATA

Title of the study:
Strategies for primary cardiovascular prevention in the Italian population – CV PREVITAL

Promoter: IRCCS Monzino Cardiology Center

Categories of data subject to processing
The study involves the acquisition and use of information considered "personal data" (such as: age, gender, ethnicity, marital status, socio-economic status), including information pertaining to health status, lifestyle, family history, considered "special data", and as such subject to current data protection regulations:

- Regolamento Generale sulla Protezione dei Dati - UE 679/2016
- Codice in Materia di Protezione dei Dati Personali - D.lgs. n° 101/2018
- Regole deontologiche per trattamenti a fini statistici o di ricerca scientifica – 2018
- Provvedimento - 2018, che individua:
  Prescrizioni relative al trattamento dei dati personali effettuato per scopi di ricerca scientifica
  Prescrizioni relative al trattamento dei dati genetici per clinica e ricerca scientifica

Purpose of processing
The data described above will be processed to enable the performance of the CV PREVITAL study and all related operations and activities

Legal basis for processing
Informed consent is the legal basis for processing your data for the purposes described in the information form. Without signed consent, we will not be able to use your data for the conduct and analysis of the Study.
You may discontinue your participation at any time and without giving any reason; in this case, your data will be processed as described in the Study's information form. No further data concerning you will be collected, without prejudice to the use of any data already collected to determine, without altering them, the results of the research.

Nature of provision of data
Participation in the trial is on a voluntary basis, therefore, the provision of personal data is completely voluntary, meaning that you may decide not to provide your personal data and, therefore, not to participate in the Study.

Methods of Data Processing
The above-mentioned purposes involve the conduct of the processing of personal data using manual and computerized tools with logic strictly related to the purposes themselves and, in any case, in such a way as to ensure the security and confidentiality of the data.
Data collected for the purposes of the CV PREVITAL study will be handled in coded form.

The physician who will follow you to the study will identify you with a code that will not allow your identity to be traced directly, except to the participating physician's office.
The data about you collected during the study, with the exception of your name and your phone, will be transmitted to the Promoter as the Data Controller and the Data Processors listed above, and recorded, processed and stored by them. The data that you enter via the multifunctional intermodal station (multimedia totem in your doctor's office) or remotely (via the Internet) and the data that you enter via the App (if your doctor is part of the intervention group), will be stored in a cloud database and made available, in pseudonymized form, to the Cardiology Network IT platform.
Only the physician, the personnel responsible for monitoring the Study (*Istituto di Ricerche Farmacologiche Mario Negri IRCCS*) and the personnel delegated by the Competent Authorities for verification activities will be able to link this code to your name when necessary.

Scope of data reporting
Your participation in the CV PREVITAL study implies that, in accordance with the regulations on clinical trials of medicinal products, only the personnel in charge of monitoring activities, the Ethics Committee and the Italian and foreign health authorities will be able to know the data concerning you, also contained in your original clinical documentation, in such a way as to guarantee the confidentiality of your identity.
Dissemination of scientific data resulting from the analysis of data from the CV PREVITAL study, may be done only anonymously and for scientific purposes only. In practice, the results of scientific research, may be presented in aggregate form at Conferences or published in peer-reviewed journals without ever allowing the precise identification of patients.
If provided for in the protocol, your personal data may be transferred to external Centers for the purposes provided for in the protocol, designated by the Holders as “Data Processors”.
You can find out the updated list of Data Processors by sending a communication to the Data Protection Officer (DPO) of the Promoter.

In general, we inform you that in accordance with current regulations, information, may be shared with other research organizations and institutes, associations, and other public and private bodies having research purposes.
Specifically, the CV PREVITAL study is an integral part of a larger project developed with the Ministry of Health at the direction of Parliament to improve primary cardiovascular prevention strategies in the Italian population, involving, General Practitioners (GPs), Pharmacies, Cardiovascular Network IRCCSs, the Italian Society for Digital Health and Telemedicine, and the Romeo and Enrica Invernizzi Foundation.
Therefore, information from the CV PREVITAL study may be shared with other Institutes or Entities participating in the larger research project, subject to the safeguards of his or her data protection rights.
If the investigations carried out for scientific research purposes result in information, even unexpected information, capable of providing a concrete and direct benefit in terms of therapy or prevention or as a function of conscious reproductive choices, such information may be disclosed to third parties upon your authorization, except for exceptions provided for in the regulations in force.

Policy on the retention of personal data
Personal data collected as part of the CV PREVITAL study will be retained at the medical office of your GP, the Promoter, and the facilities involved in the Study, for a minimum period of 7 years after

the conclusion of the Study or for a longer period, if necessary, according to additional legal requirements. The maximum data retention period is 25 years after the conclusion of the Study.

Owner and Data Protection Officer: The Promoter who commissioned the study CV PREVITAL and its GP, as Data Controllers, and the Istituto di Ricerche Farmacologiche Mario Negri IRCCS and Consorzio Sanità (Co.S.), as Data Processors, each for the areas of their competence and in accordance with the responsibilities provided by the rules of Good Clinical Practice (D. L. 211/2003), by the EU Regulation 2016/679 of the European Parliament and Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data (hereinafter GDPR), by the Legislative Decree 196/03 supplemented by the General Authorization n.9 /2016 to the processing of personal data carried out for the purpose of scientific research of December 15, 2016 and by the Resolution of the Guarantor for "Guidelines for the processing of personal data in the context of clinical trials of medicinal products" of July 24, 2008 and subsequent amendments, will process your personal data, only to the extent that they are indispensable in relation to the objective of the Study and for the purposes set out below.

We inform you that the Data Controllers, in accordance with Article 37 of the GDPR EU 2016/679, have proceeded to identify and appoint a Data Protection Officer (also "Data Protection Officer" or "DPO":

MMG DPO contact details:
[...]

Promoter's DPO contact details:
[...]

Rights of the Interested Party

Right of access to data
You may ask to see the information that has been collected about you. However, in order to safeguard the scientific integrity of the study, it may not be possible to access some data before the conclusion of the study.

Right to rectification of data
You may request that data concerning you be amended if it is incorrect or incomplete. While such a request is being considered, you have the right to restrict the processing of data about you.

Right to data portability

You can request the transfer of data about you to yourself or someone else in a commonly used format (paper or electronic).

Right to cancel data
May withdraw consent at any time without giving any reason. You may withdraw consent for participation in the study and/or subsequent follow-ups, even without withdrawing consent for data processing. Should you change your mind about processing your data, it will not be possible to remove the personal information already processed for the study before your withdrawal (covered by the original consent). Thereafter, upon withdrawal of consent to process your data, no further information about you would be acquired.

Right of complaint
Can file a complaint with the data protection authority:
Privacy Guarantor, E-mail: garante@garanteprivacy.it Web site: http://www.garanteprivacy.it

Regarding the exercise of these rights, you may contact your general practitioner directly or, through him or her, the Promoter's Data Protection Officer (DPO).

Definitions

- Personal data means any information relating to an identified or identifiable natural person ("data subject"); an identifiable person is one who can be identified, directly or indirectly, by reference in particular to an identifier such as a name, an identification number, location data, an online identifier, or to one or more features of his or her physical, physiological, genetic, mental, economic, cultural or social identity.

- Special data: personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, or trade union membership; genetic data, biometric data intended to uniquely identify a natural person, data relating to a person's health or sex life or sexual orientation.

- Health-related data: personal data pertaining to a natural person's physical or mental health, including the provision of health care services, that reveal information related to his or her health status; such as data related to hospitalization activities, outpatient specialist visits, drug consumption, and social and health services

Consent to the processing of personal data
in accordance with GDPR EU 2016/679

Having acknowledged the information referred to in Article 13 of the GDPR EU 2016/679, I, the undersigned_____,
born in _____, date_____,
as the person concerned

☐ gives consent ☐ denies consent
to the processing of data for purposes related to the clinical study "Primary cardiovascular prevention strategies in the Italian population – CV PREVITAL"

☐ gives consent ☐ denies consent
so that the results of analyses and any unexpected findings that emerge during experimental activities are communicated to:

☐ myself

☐ family member (Surname and name _____)

☐ cohabitant /spouse (Surname and name _____)

☐ general practitioner (Surname and name _____)

Patient Name/Surname	**Signature**	**Date**

Name/Surname of the Physician of General Practitioner in charge	**Signature**	**Date**

Online Supplemental file 4. SPIRIT Item 13: Participant timeline

TIMEPOINT	**T0 baseline**	**T1 month 12**	**T2 year 7**
Eligibility screen Informed consent Allocation	√		
Administration of self-report questionnaires covering the following areas: 1. family and personal history of diseases (cardio- and cerebrovascular disease; metabolic disease) 2. ethnicity, socio-economic status and marital status 3. smoking habits 4. alcohol consumption (PREDIMED questionnaire[8]) 5. adherence to Mediterranean diet (PREDIMED questionnaire[8] and Moli-Sani questionnaire–an adaptation of the MEDAS questionnaire[9]) 6. salt consumption (MiniSal questionnaire[10]) 7. physical activity (IPAQ–International Physical Activity Questionnaire[11]) 8. personal history of sleep disorder and sleep quality (PSQI–Pittsburgh Sleep Quality Index[12]) 9. psycho-behavioral factors: 9.1 perceived stress (PSS–Perceived Stress Scale) 9.2 anxiety and depression (PHQ 4–Patient Health Questionnaire 4) 9.3 self-efficacy (GSE–General Self-Efficacy Scale) 9.4 locus of control (Multidimensional Health Locus of Control Scale) 9.5 risk propensity (RPS–Risk Propensity Scale) 10. personal history of COVID-19 disease	√	√	
Measurement of systolic and diastolic blood pressure	√	√	
Measurement of weight, height, waist circumference	√	√	
Assessment of total cholesterol, HDL-C, triglycerides, calculated LDL-C, glycated hemoglobin	√	√	
Cardiovascular risk score calculation	√	√	
App delivery (intervention group only)	√		
Collection of data on occurrence of cardiovascular events		√	√

Online Supplemental file 5: Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies

In the CV-PREVITAL Study, each IRCCS recruits a number of participants to whom, in addition to the questionnaires, samples of biological material (blood, saliva or feces) are taken. The biological material collected is stored in the cryospaces dedicated by each IRCCS to the Widespread Biobank of the Italian Cardiology Network. In order to harmonize the collection and storage of samples, Standard Operating Procedures (SOPs) has been created for the Widespread Biobank and shared among the participating centers for the management of the sample from the patient recruitment and signing phase of the informed consent, to the collection and storage of biological samples and possible redistribution of the aliquots. The harmonization of sample collection also includes the use of the same container for sample collection, the same cryovials for storage, and the same codes for pseudonymization of samples. All aliquots are stored in cryotubes with QR Code to facilitate the distribution and sharing of samples among the recruiting centers of the CV-PREVITAL study or with other national or international institutes.

SOPs for blood derivates

All Cell Pellet (ACP) and plasma EDTA

In order to optimize the blood collection, ACP and plasma EDTA are obtained from the same collection tube. The venous sampling is carried out using K3EDTA tubes. Blood is processed within 2 hours from collection. Tubes are centrifuged without brake at 3000rpm at RT (18–22 °C) for 15 minutes to separate the plasma from the cells. Using a micropipette, plasma is divided into at least 3x300 microliter aliquots in cryotubes and then transferred to -80 °C for storage as soon as possible. After removing the residual plasma, the tube is inverted two or three times to homogenize the sample. ACP is divided in 3x300-microliter aliquots in cryotubes and transferred to a -80 °C for storage as soon as possible.

Serum

The venous sampling is carried out using tubes with coagulation activator and gel separator. Blood is processed within 2 hours from collection and allowed to clot for a minimum of 15-20 minutes at RT (18-22°C) or until the clot is completely formed. Tubes are centrifuged at 3000rpm at RT (18–22 °C) for 15 minutes to separate serum from the cells. Using a micropipette, serum is collected without touching the separator gel with the pipette tip and divided into at least 3x300-microliter aliquots in cryotubes. Aliquots are transfer red to a -80 °C freezer for storage as soon as possible.

Whole blood for total RNA extraction

The venous sampling is carried out using Tempus Blood RNA Tube (Applied Biosystems). Immediately after filling the Tempus tube, the blood is stabilized by vigorously shaking or vertexing the tube for 10-12 seconds. Samples are maintained at +4 °C for a maximum of 24 hours and then stored at -80 °C.

Saliva Samples

Saliva is collected using Salivette Cortisol tube (Sardstedt) and the collection is carried out by the subject participant to the project according to the manufacturer's instructions.
Harvesting must be done in the morning and it is recommended:

- for at least 2 hours before harvesting:
  - not to eat
  - not to drink
  - not to smoke
  - not to take chewing gum

- to brush teeth at least 2 hours before the start of the harvest
- to avoid the use of cosmetic products for lips.

Samples are maintained at +4 °C and centrifuged within 1 hour from collection without brake at 3000rpm at RT for 15 minutes. Using a micropipette, the sample is divided into at least 3x300 microliter aliquots in cryotubes and stored at -80 °C within 2 hours from collection.

Stool Samples

Stool sample is collected using DANASTOOL Sample Collection MICROBIOME Kit (DANAGEN) and the collection was carried out by the subject participant to the project according to the manufacturer's instructions.

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):

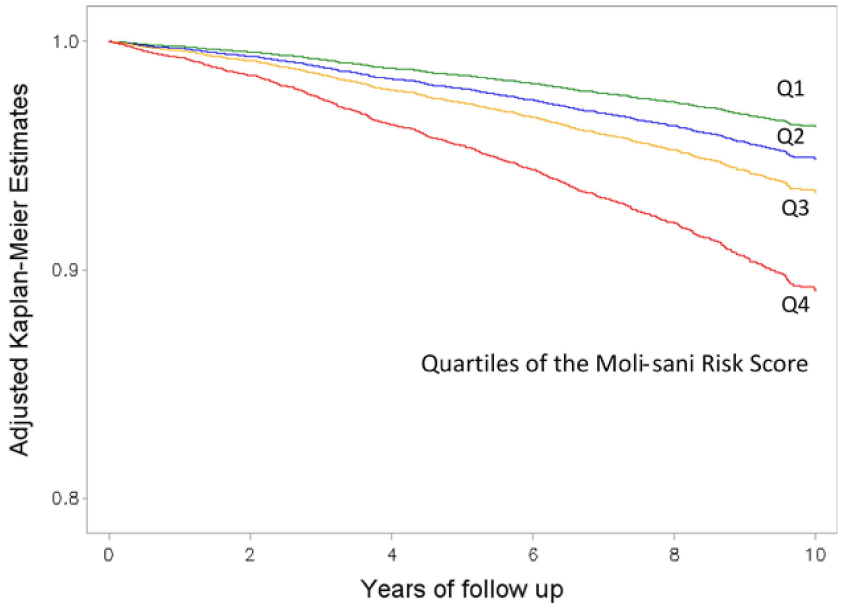
Variable	Mean	Standard deviation	Mean	Standard deviation
	MEN		WOMEN	
LDL (mg/dL)	130	35	136	36
HDL (mg/dL)	52	13	63	15
Triglycerides (mg/dL)	150	99	118	66
MAP (mmHg)	105	11	102	12
Blood Glucose (mg/dL)	107	28	98	23
Physical_activity (MET-hours/day)	4.6	4.7	2.7	3.2
RFM (%) (males)	29	3.6	42	5

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

CV-PREVITAL Study Group

Centro Cardiologico Monzino IRCCS
Giulio Pompilio, Damiano Baldassarre, Roberta Baetta, Mauro Amato, José Pablo Werba, Stefano Genovese, Gualtiero Colombo, Chiara Vavassori, Maria Luisa Biondi, Beatrice Frigerio, Alessio Ravani, Daniela Sansaro, Daniela Coggi, Alessandra Romandini, Monica Giroli, Mattia Giuliani, Alice Bonomi, Maurizio Rondinelli, Catia Trudu, Carmen Cinieri, Massimo Monturano, Francesca Colazzo.

Istituto Auxologico Italiano IRCCS
Gianfranco Parati, Cecilia Invitti, Grzegorz Bilo, Martino Pengo, Francesca Gorini, Luciana Auteri, Andrea Faini, Carolina Lombardi, Anna Di Blasio, Debora Rosa, Camilla Torlasco, Luisa Gilardini, Davide Soranna, Antonella Zambon, Elisa Perger, Lucia Zanotti, Luigi Badano, Lidia Cova, Davide Gentilini, Luca Grappiolo.

IRCCS Humanitas Research Hospital
Gianluigi Condorelli, Giuseppe Ferrante, Laura Papa, Victor Savevski, Francesca Ieva, Ignazio Romano.

Istituto di Ricerche Farmacologiche Mario Negri IRCCS
Giuseppe Remuzzi, Maria Carla Roncaglioni, Marta Baviera, Luisa Ojeda, Andreana Foresta, Fiorenza Clerici, Angela Palumbo.

IRCCS MultiMedica
Gian Franco Gensini, Giuseppe Ambrosio, Alberico Catapano, Roberto Mattioli, Ermanno Longhi, Livio Luzi, Lorenzo Giovanni Mantovani, Fabiana Madotto.

IRCCS Istituto Neurologico Mediterraneo NEUROMED
Luigi Frati, Licia Iacoviello, Augusto Di Castelnuovo, Alessandro Gialluisi, Amalia De Curtis, Marialaura Bonaccio, Francesco Gianfagna, Anwal Ghulam, Sara Magnacca, Fabrizia Noro, Simona Costanzo, Simona Esposito, Sabatino Orlandi, Mariarosaria Persichillo, Francesca Bracone, Teresa Panzera, Emilia Ruggiero, Roberta Parisi, Sabrina Franciosa, Martina Morelli, Fiorella De Rita, Chiara Cerletti, Giovanni de Gaetano, Maria Benedetta Donati.

IRCCS Policlinico San Donato
Lorenzo Menicanti, Serenella Castelvecchio, Alexis Elias Malavazos, Massimiliano Marco Corsi Romanelli, Rosanna Cardani, Ambra Cerri, Carola Dubini, Manuel Bruno Trevisan, Laura Valentina Renna, Valentina Milani, Sara Boveri, Paola Giubbilini, Lucia Ramputi, Irene Baroni, Giada DeAngeli.

Istituti Clinici Scientifici Maugeri IRCCS
Walter Ricciardi, Maria Teresa La Rovere, Simonetta Scalvini, Antonia Pierobon, Alessandra Gorini, Francesca Olmetti, Maurizio Bussotti, Carlo Gaetano, Paola Baiardi, Tiziana Bachetti, Martina Balbi, Laura Comini, Monica Lorenzoni, Adriana Olivares, Egidio Traversi, Camilla Garrè, Riccardo Sideri.

IRCCS ISMETT (Mediterranean Institute for Transplantation and Advanced Specialized Therapies)
Pier Giulio Conaldi, Valentina Agnese, Francesco Clemenza, Giovanni Gentile, Giuseppe Caruana, Nicola Cuscino, Gabriele Di Gesaro, Alessio Greco, Italia Loddo, Fabio Tuzzolino.

IRCCS Ospedale Policlinico San Martino
Antonio Uccelli, Bianca Pane, Domenico Palombo, Giovanni Spinella, Gaddiel Mozzetta, Pietro Ameri, Gabriele Zoppoli, Alice Finotello, Italo Porto, Giovanni Pratesi.

Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
Fabio Blandini, Daniele Prati, Luca Valenti, Laura Spinardi, Margherita Clerici, Serena Pelusi, Cristiana Bianco, Rossana Carpani, Giulia Periti, Sara Margarita.

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Giovanni Scambia, Giovanna Liuzzo, Gaetano Antonio Lanza, Anna Severino, Daniela Pedicino, Domenico D'Amario, Alessia D'Aiello, Ramona Vinci, Alice Bonanni, Mattia Brecciaroli, Simone Filomia, Roberta Pastorino, Stefania Boccia, Andrea Urbani, Maurizio Sanguinetti, Angelo Santoliquido, Luca Proto, Dalila Tarquini, Maria Chiara Grimaldi.

Fondazione IRCCS Policlinico San Matteo
Eloisa Arbustini, Catherine Klersy, Sergio Leonardi, Arianna Elia, Alessia Currao, Mario Urtis, Alessandro Di Toro, Lorenzo Giuliani.

IRCCS San Raffaele
Massimo Fini, Maurizio Volterrani, Giuseppe Caminiti, Federica Marcolongo, Barbara Sposato, Fiorella Guadagni, Valentina Morsella, Angelica Marziale.

Consorzio Sanità (Co.S.)
Antonio Di Malta, Marco Visconti.

Federfarma Lombardia & Fondazione Guido Muralti
Annarosa Racca, Manuela Bandi, Giulia Protti.

Supplemental References

1. Di Castelnuovo A, Costanzo S, Persichillo M, et al. Distribution of short and lifetime risks for cardiovascular disease in Italians. *Eur J Prev Cardiol* 2012;19(4):723-30. doi: 10.1177/1741826711410820 [published Online First: 2011/05/17]
2. Salvetti M, Paini A, Di Castelnuovo A, et al. Correction of QRS voltage for body mass index does not improve the prediction of fatal and nonfatal cardiovascular events. The Moli-sani study. *Nutr Metab Cardiovasc Dis* 2020;30(3):426-33. doi: 10.1016/j.numecd.2019.10.013 [published Online First: 2019/12/04]
3. Trichopoulou A, Costacou T, Bamia C, et al. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med* 2003;348(26):2599-608. doi: 10.1056/NEJMoa025039 [published Online First: 2003/06/27]
4. Woolcott OO, Bergman RN. Defining cutoffs to diagnose obesity using the relative fat mass (RFM): Association with mortality in NHANES 1999-2014. *Int J Obes (Lond)* 2020;44(6):1301-10. doi: 10.1038/s41366-019-0516-8 [published Online First: 2020/01/09]
5. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14(6):540-5. doi: 10.1093/sleep/14.6.540 [published Online First: 1991/12/01]
6. Vignatelli L, Plazzi G, Barbato A, et al. Italian version of the Epworth sleepiness scale: external validity. *Neurol Sci* 2003;23(6):295-300. doi: 10.1007/s100720300004 [published Online First: 2003/03/08]
7. Pierdomenico SD, Di Nicola M, Esposito AL, et al. Prognostic value of different indices of blood pressure variability in hypertensive patients. *Am J Hypertens* 2009;22(8):842-7. doi: 10.1038/ajh.2009.103 [published Online First: 2009/06/06]
8. Ash S, Reeves M, Bauer J, et al. A randomised control trial comparing lifestyle groups, individual counselling and written information in the management of weight and health outcomes over 12 months. *Int J Obes (Lond)* 2006;30(10):1557-64. doi: 10.1038/sj.ijo.0803263 [published Online First: 2006/03/15]
9. Grima NA, Rajaratnam SMW, Mansfield D, et al. Efficacy of melatonin for sleep disturbance following traumatic brain injury: a randomised controlled trial. *BMC Med* 2018;16(1):8. doi: 10.1186/s12916-017-0995-1 [published Online First: 2018/01/20]
10. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. *Journal of the American College of Cardiology* 1990;15(4):827-32. doi: 10.1016/0735-1097(90)90282-t [published Online First: 1990/03/15]
11. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;24(11):987-1003. doi: 10.1016/s0195-668x(03)00114-3 [published Online First: 2003/06/06]
12. Monteiro CA, Cannon G, Levy R, et al. NOVA. The star shines bright. Food classification. Public Health. *World Nutr* 2016;7:28-38.
13. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53(4):695-9. doi: 10.1111/j.1532-5415.2005.53221.x [published Online First: 2005/04/09]
14. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;42(36):3599-726. doi: 10.1093/eurheartj/ehab368 [published Online First: 2021/08/28]
15. Mola AG, Diaz CT, Martins GG, et al. Editor's Choice - Systematic Review and Meta-Analysis of Normal Infrarenal Aortic Diameter in the General Worldwide Population and Changes in Recent Decades. *Eur J Vasc Endovasc Surg* 2022;64(1):4-14. doi: 10.1016/j.ejvs.2022.04.014 [published Online First: 2022/04/29]
16. Panagiotakos DB, Pitsavos C, Stefanadis C. Dietary patterns: a Mediterranean diet score and its relation to clinical and biological markers of cardiovascular disease risk. *Nutr Metab Cardiovasc Dis* 2006;16(8):559-68. doi: 10.1016/j.numecd.2005.08.006 [published Online First: 2006/11/28]