Trials

STUDY PROTOCOL

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A multicomponent personalized prevention program in the primary care setting: a randomized clinical trial in older people with noncommunicable chronic diseases (Primacare_P3 study)

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Abstract

Background Multicomponent interventions based on a comprehensive geriatric assessment (CGA) could promote active aging and improve health status in older people with Noncommunicable Chronic Diseases (NCDs), but conflicting evidences are available.

Aim To evaluate the efficacy of a CGA-based multicomponent personalized preventive program (PPP) in reducing unplanned hospitalization rates during 12-month follow-up in community-dwelling older people with NCDs.

Materials and methods In this randomized clinical trial (RCT), 1216 older adults recruited by 33 general practitioners (GPs) will be randomly allocated to intervention group (IG) or usual care control group (CG). The IG will receive a multicomponent PPP developed on the findings of the CGA-based Multidimensional Prognostic Index short-form (Brief-MPI), including structured interventions to improve functional, physical, cognitive, and nutritional status, to monitor NCDs and vaccinations, and to prevent social isolation. Participants in the CG will receive usual care. Brief-MPI, resilience, and health-related quality of life will be assessed after 6 and 12 months. Moreover, saliva samples will be collected at baseline in IG to measure biomarkers of oxidative stress, inflammatory cytokines, and oral microbiome.

Expected results The CGA-based PPP might reduce unplanned hospitalization rates and potentially institutionalization rates, emergency department (ED) and unplanned GP visits, and mortality. Further outcomes explored in the IG will be the adherence to PPP, resilience, health-related quality of life, and multidimensional frailty as assessed by the Brief-MPI.

Conclusions Results will suggest whether the CGA-based multicomponent PPP is able to improve specific outcomes in a primary care setting.

Trial registration ClinicalTrials.gov; identifier: NCT06224556; Registered January 25, 2024.

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Keywords Primary care setting, Non-communicable chronic diseases, Personalized prevention program, Multicomponent interventions, Comprehensive geriatric assessment, Older people

Introduction

The prevention of noncommunicable chronic diseases (NCDs) has progressively gained relevance when considering the global population aging and thus the importance of a healthy aging [1]. Recent data estimated that people aged 75 years or older in Italy are around 7 million (11.7% of population), and almost half of them are affected by three NCDs [2]. Evidence suggests that the NCDs may share common pathophysiological mechanisms as for example chronic inflammation and imbalance of redox status that may be related to an accelerated aging process and an increase of frailty condition [3].

In this context, comprehensive geriatric assessment (CGA) can be considered a gold standard in clinical practice for assessing frailty in older people, though its association with biological markers is still underexplored [4]. The main features of CGA are (a) early identification of changing needs in older adults, (b) development of personalized multicomponent interventions based on detected impaired domains, and (c) monitoring changes in the individual multidimensional health status [5]. The multidimensional clinical approach may help identifying older people at a higher risk of frailty who could benefit from a personalized preventive program (PPP) based on a CGA [6]. Multicomponent interventions dealing with different domains of health status, including mobility, cognitive, nutrition [7, 8], and self-management of chronic disease [9, 10], may be effective in the management of older people with chronic diseases.

However, evidence on the efficacy of CGA-based multicomponent interventions in a primary care setting [11] and specifically in older people with NCDs are still scarce and conflicting in the European context [9, 10, 12].

The PrimaCare_P3 project, a cluster-randomized controlled trial conducted in Italy, aims to evaluate in a primary care setting the effectiveness of a CGA-based PPP on 12-month rate of unplanned hospital admission among older people with NCDs.

Materials and methods

Study design and inclusion criteria

PrimaCare_P3 is a project funded by the European Union (NextGenerationEU, project code n. PNRR-MAD-2022–12376781), and it includes 4 partners: (i) Galliera Hospital (EOG), Genoa, Italy, which is the coordinating center; (ii) the Italian National Institute of Health (Istituto Superiore di Sanità (ISS)), Rome, Italy; (iii) Paolo Giaccone University Hospital (AOUP), Palermo, Italy; (iv) "Aldo Moro" University of Bari (UNIBA), Bari, Italy.

The study is a cluster-randomized controlled trial, with 33 general practitioners (GPs) as clusters. GPs selected by voluntary participation among four GPs cooperatives, i.e., Desenzano del Garda (Brescia), Florence, Naples, and Putignano (Bari), will identify a list of potentially eligible subjects from their electronic records based on an age 65 years and older and the presence of at least one NCD. GPs were randomly allocated to either the intervention group (IG) or the control group (CG). A centrally generated random list of 1216 participants (in 1:1 ratio) will be selected by the Italian National Institute of Health and encouraged by their own GPs to take part of the project. Participants will be required to meet the following inclusion criteria: (1) any gender, (2) age 65 years or older, (3) at least one NCD, (4) willing to participate in the study, and (5) provide signed informed consent. Participants will be excluded based on the following criteria: (1) age lower than 65 years; (2) the absence of at least one NCD; (3) unwilling to participate and provide signed informed consent.

The IG ($n=608$) will receive a PPP, and at baseline saliva samples will be collected in this group. The CG ($n=608$) will receive usual care. Both groups will be followed up to 12 months after enrolment by research staff including physicians, nurses, and health educators.

In both IG and CG participants, the rate of unplanned hospitalizations during 1-year of follow-up will be collected (main aim of the study). Moreover, the rates of institutionalizations, the number of admissions to emergency department (ED), number of visits to GP clinics (except those planned by GPs), and death rate will be collected at 6- and 12-month follow-ups (secondary aims of the study). Figures 1(a, b) and 2 show the study design. The process for auditing trial will be conducted by the four principal investigators which belonged to the four involved project's partners; it will be independent from investigators and the sponsor, and it will last for the entire project period. No data monitoring committee (DMC) is foreseen by the NPRR (National Plan of Recovery and Resilience) call, investment 2.1 Enhancement and strengthening of biomedical research in the National Health System (NHS).

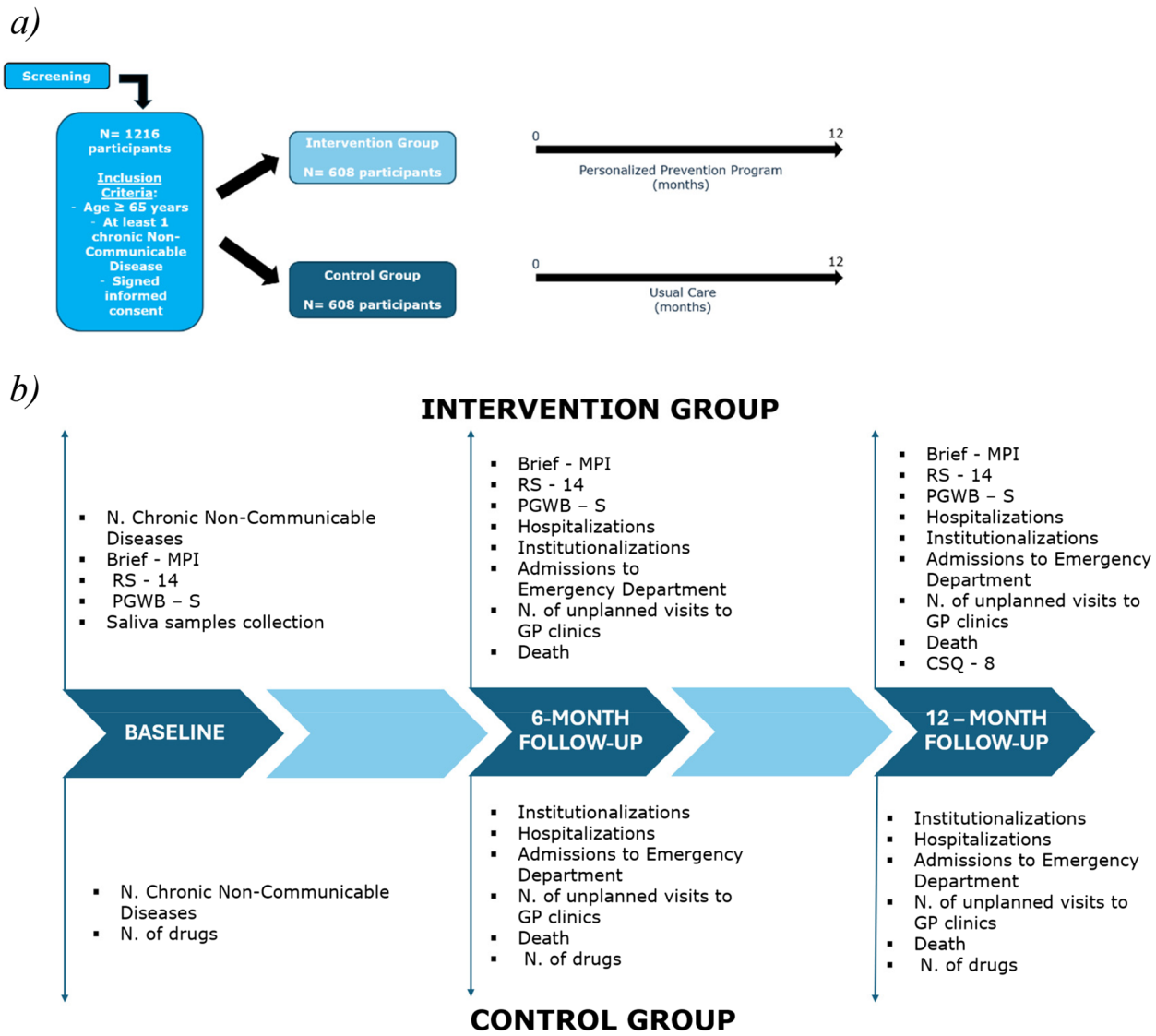

Fig. 1 **a** Study design and inclusion criteria. **b** Timeline of the PrimaCare_P3 project related to the Intervention Group and the Control Group. Abbreviations: Brief-MPI, Brief- Multidimensional Prognostic Index; RS-14, Resilience Scale—14 Items; PGWB-S, Psychological General Wellbeing index—Short version; CSQ-8, Client Satisfaction Questionnaire—8 items; GP, General Practitioner

Intervention group

Clinical evaluation

Participants included in the IG will undergo at baseline and after 6 and 12 months a CGA-based Brief-MPI (Multidimensional Prognostic Index) assessment [13] that is the abbreviated version of the standard version of the MPI (Multidimensional Prognostic Index) [14], a well-known and validated prognostic tool of several negative outcomes, including institutionalization, hospitalization, and mortality. As the MPI standard version, the Brief-MPI explores eight domains: (1) basal, (2) instrumental activities of daily living, (3) mobility, (4) cognition, (5) nutrition, (6) comorbidity, (7) number of medications, and (8) cohabitation status. The Brief-MPI evaluates the level of risk related to each domain (0 = no problems; 0.5 = minor problems; 1 = major problems) and, through a specific algorithm, provides a global score ranging from 0.0 (lowest risk) to 1.0 (highest risk of multidimensional frailty). According to a pre-defined algorithm, the Brief-MPI identifies three classes of risk multidimensional frailty, i.e., MPI 1 class (score between 0.00 and 0.33 = low risk of frailty); MPI 2 class (score between 0.34 and 0.66 = moderate risk of frailty; and MPI 3 class (score ≥ 0.67 = high risk of frailty). Further details on MPI and the Brief MPI calculation and clinical significance have been reported elsewhere (13, 17).

	STUDY PERIOD			
	Pre-admission	***At admission (baseline)***	***6-months follow-up***	***12-months follow-up***
GPs allocation	*X*			
Eligibility screen	*X*			
Participants randomization	*X*			
Informed consent		*X*		
Intervention Group:				
PPP		◆—	—	—◆
Brief-MPI		*X*	*X*	*X*
RS-14		*X*	*X*	*X*
PGWB-S		*X*	*X*	*X*
Saliva sample collection		*X*		
Control Group:				
N. of drugs		*X*	*X*	*X*
All participants:				
N. chronic non-communicable diseases		*X*		
Hospitalizations			*X*	*X*
Institutionalizations			*X*	*X*
Admissions to Emergency Departments			*X*	*X*
N. of unplanned visits to GP clinics			*X*	*X*
Death			*X*	*X*

Fig. 2 SPIRIT figure. Schedule of enrolment, interventions, and assessments

Moreover, at baseline and after 6 and 12 months, the IG participants will undergo the following:

- The Resilience Scale—14 items (RS-14) [15], a 14-statement questionnaire based on a 7-point scale assessing the level of resilience. Resilience scores range from 14 to 98, and scores lower than 56 are considered as very low;
- The Psychological General Wellbeing Index—Short (PGWB-S) [16], a self-administered 6-item questionnaire for health-related quality of life, including assessment on a scale from 0 to 5 (with 0 as the minimum score) of the following domains: anxiety, vitality, depressive mood, self-control, general health, and positive well-being.

After 6 and 12 months follow-up visit, the IG participants will report the grade of adherence to the PPP, and at the end of the study, they will fill the Client Satisfaction Questionnaire—8 items (CSQ-8) [17], a tool that evaluates the general satisfaction about the intervention through a scale from 1 to 4, with a possible score ranging from 8 to 32, with higher scores indicating higher satisfaction.

Participants who will show a cognitive impairment at the Brief-MPI (see the paragraph 2.2.3 on PPP) will undergo the General Practitioner Assessment of Cognition—Italian (GPCOG-It) test [18], the validated Italian version of GP assessment of cognition. It is a tool used by GPs to screen patients for cognitive decline or dementia. The GPCOG is structured in two sections: one for the patient ("Section A") which includes a 6-item cognitive test with possible total scores between 0 (indicating severe impairment) and 9 (indicating no impairment) and one for the relative/caregiver ("Section B") including 6 questions on patient history with possible total scores between 0 (indicating severe impairment) and 6 (indicating no impairment). The GPCOG will be conducted in two stages; if Section A scores between 5 and 8, Section B is not required.

Participants who will show a nutritional deficit at the Brief-MPI (see the paragraph 2.2.3 on PPP) will undergo the Malnutrition Universal Screening Tool (MUST) [19], a screening tool developed and validated by the British Association for Parenteral and Enteral Nutrition (BAPEN) to assess for potential nutritional risks in community-dwelling people. It includes assessment of 3 items: body mass index (BMI), weight loss over time, and acute diseases on a scale from 0 to 2. The total MUST score indicates the overall risk of malnutrition, with 0 indicating a low risk, 1 a moderate risk, and ≥ 2 a high risk.

Laboratory data

Saliva samples will be collected to assess selected biomarkers of oxidative stress and inflammatory status. Specifically, unstimulated whole saliva (UWS) samples will be collected in two plastic sterile tubes. Samples will be stored in the GP clinic at − 20° C until delivery, through dry ice (− 80 °C), to the central laboratories (University of Bari Aldo Moro and ISS) for the analysis. One tube will serve for the analysis of biomarkers of oxidative stress, including (1) lactate (Cell biolabs, MET-5012), (2) NAD/NADH (nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide hydrogen) ratio (Abcam, ab65348), and (3) products of lipo-peroxidation using ThioBarbituric Acid Reactive Substance analyses (TBARS) Assay Kit (Zeptometrix, 0801192). The second tube will be used for the analysis of levels of salivary inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-8 measured by specific Enzyme-Linked ImmunoSorbent Assay Kits—ELISA Kits (Salimetrics, L.L.C).

In a subsample of 210 participants, stratified across the three risk classes of risk (low, moderate, and high risk) of the Brief-MPI scale, the oral microbiome composition will also be analyzed. In this case, the samples will be stored at room temperature and sent to the central laboratory (ISS) by refrigerated transport. Bacterial genomic DNA will be extracted and 16S rRNA gene amplicons amplified using the special fusion primer set specific for V3-V5 hypervariable regions.

Personalized prevention program (PPP)

Participants in the IG group will receive a multicomponent PPP based on results of the CGA-based Brief-MPI (see Table 1). PPP is structured as a series of interventions: (i) to improve functional, physical, cognitive, and nutritional status; (ii) to better manage NCDs; (iii) to improve vaccinations adherence; and (iv) to prevent the social isolation.

For the physical status, a set of standardized exercises have been made available online to be performed at home by participants.

As for cognitive and nutritional status, decision-making algorithms were created based on the domain score of the Brief-MPI to guide physicians in assigning specific interventions to each participant.

In detail, if at least one question is wrong at the cognition section of the Brief-MPI, the GPCOG-It will be administered [18]. According to its results, four clinical categories of subjects will be identified: (a) participants with a "Section A" score of 9 points will receive a list of suggestions for cognitive health and scheduled to repeat the GPCOG-It after 1 year; (b) participants with a "Section A" score between 5 and 8 and a "Section B" score between 4 and 6 will receive instructions on life-style and a follow-up re-assessment after 6 months; (c) participants with a "Section A" score between 5 and 8 and a "Section B" score ≤ 3 will be recommended to the specialist center, i.e., the Cognitive Disorders and Dementia Centre (CDCD); (d) participants with a "Section A" ≤ 4 will be referred to a specialist center, i.e., CDCD.

For nutritional status, in case of at least one error in the nutrition questions of the Brief-MPI, participants will be stratified according to their BMI. Participants with BMI less than 30 kg/m^2, we will perform the MUST [19], and they will be categorized into three risk classes: (a) malnutrition low risk class (MUST score = 0): participants will be reassessed after 12 months; (b) malnutrition medium-risk class (MUST score = 1): participants will be monitored for food intake during the following three days and then they will be reassessed after 3 months or, in case of low food intake, will receive an intervention to improve the overall nutritional intake; (c) malnutrition

Table 1 The personalized prevention program interventions based on the CGA impaired domains

Impaired domain	Personalized prevention program interventions
Physical	Participants will receive practical suggestions for an active daily routine and will perform standardized exercises at home available through a QR code
Cognitive	Participants will receive practical suggestions to prevent cognitive impairments
Nutritional	Participants will receive practical suggestions for a healthy nutrition based on the Mediterranean diet
Comorbidity	Participants will receive vaccinal recommendations based of the Italian National Plan of Vaccination Prevention for older adults available through a QR code
N. of drugs	Participants will receive instructions on the prevention rules of the NCDs and GPs will use the STOPP/START criteria (3rd version) for potentially inappropriate prescribing
Functional	GPs will organize assistance by formal or informal caregivers, activate integrated home care programs, suggest specialist consults
Instrumental	GPs will organize assistance by formal or informal caregivers, activate integrated home care programs, suggest specialist consults
Co-habitation	GPs will suggest opportunities for socialization through the frequency of community centers and the use of technology (i.e., videocall, and online meetings)

high-risk class (MUST score ≥ 2): participants will be referred to a specialist in nutrition. On the other hand, participants with BMI score between 30 and 34.9 kg/m^2 (class I obesity) will receive dietary suggestions based on the principles of Mediterranean diet, while participants with BMI ≥ 35 kg/m^2 (class II obesity) will be referred to a specialist in nutrition.

As regards the management of NCDs, subjects will receive instructions on the prevention rules of the NCDs and instruction on appropriate drugs use according to the STOPP/START criteria (3rd version) for potentially inappropriate prescribing [20]. Similarly, depending on the vaccination profile of each participant, indications will be provided based on the recommendation of the Italian National Plan of Vaccination Prevention (Piano Nazionale Prevenzione Vaccinale (PNPV)) for older adults [21].

For the prevention of the social isolation and loneliness, opportunities for socialization will be suggested through the frequency of community centers and the use of technology (i.e., videocall, and online meetings).

For the functional status, in case of impairment in basic and instrumental autonomy, we will intervene organizing assistance by formal or informal caregivers or activating integrated home care programs or if needed suggesting specialist consults.

Control group

Participants in the control group will receive standard usual care by their GP. At baseline, data will be collected on chronic diseases (number and category), number of visits to GP clinics (except those planned by GPs), and number of drug prescriptions. At 6- and 12-month follow-ups, data on rates of institutionalization, hospitalization, admission to ED, unplanned visits to GP clinics, on number of drugs, and mortality will be collected.

Training of GPs

All GPs included in the study will be involved in a general training on the project about the following: (i) study objectives, (ii) timeline, (iii) electronic case report form (eCRF), (iv) data entry into the eCRF. GPs assigned to the IG will also receive an additional specific training on study procedures for the following: (1) multidimensional assessment using the Brief-MPI and other clinical scales, (2) administration of the PPP, (3) methods for collecting salivary samples and their storage and delivery to the laboratories for analysis,

Sample size

A recent Cochrane systematic review [22] reported a significantly lower risk of unplanned hospitalizations in community-dwelling older people treated with CGA compared to standard clinical practice (relative risk (RR) = 0.83; confidence interval (CI) 95%: 0.70–0.99), with a proportion of unplanned hospitalizations at 12 months of 47.7%.

Based on a comparison of proportions between two samples, with a pre-determined number of clusters consisting of 33 general practitioners, assuming an intra-cluster correlation coefficient of 0.004 [23], 28 patients per cluster will be necessary to detect an improvement in the proportion of unplanned hospitalizations at 12 months of approximately 9% in the intervention group, assuming a power of 80% and a type I error of 5%. Taking into account a drop-out rate of 20% over the 1-year of follow-up period, a total of 1216 participants, 608 in IG and 608 in CG, will be enrolled, corresponding to 34 patients per cluster.

Statistical analysis plan

Baseline characteristics of participants in the IG and the CG will be described and compared. Continuous variables will be compared using Student's *t*-test; categorical data will be analyzed using the chi-square test.

We will use generalized estimating equations (GEE) analysis with exchangeable correlation matrix to estimate the association between the primary outcome (secondary outcomes) and the study group; this method takes account of the correlations between observations within the same cluster. The estimates will be adjusted for baseline characteristics that significantly correlated with the primary outcome (secondary outcomes) by including these variables as covariates in the model. Moreover, we will use both intention-to-treat (IIT) and per-protocol (PP) analyses to avoid potential biases related to missing data.

The incidence rate ratios of hospitalization, institutionalization, admissions to ED, and mortality will be estimated using Poisson regression random effects model.

The scores of clinical scales (Brief-MPI, RS-14, PGWB-S) will be compared between baseline and follow-up using Student's *t*-test for paired samples. The linear mixed-model analyses will be used to assess if the baseline characteristics and biomarkers will be associated with different trajectories of clinical scales, accounting for the clustering of participants.

Expected results

The PrimaCare_P3 study is designed to investigate the effectiveness of a standardized PPP based on CGA approach among older people with NCDs in a primary care setting. As primary outcome, we expected to observe a significant lower rate of unplanned hospitalizations over 12 months among subjects undergoing PPP intervention compared to those in the CG. Secondary outcomes will be the rates of the following: (1) a composite

outcome including admissions to ED, hospitalizations, and institutionalizations; (2) unplanned visits to the GP; (3) mortality (see Table 2). The following outcomes will also be considered in the IG: (1) adherence to the PPP, (2) health-related quality of life, (3) levels of resilience, (4) personal satisfaction with the program.

Moreover, the study will also explore the association between selected salivary biomarkers and multidimensional frailty at baseline, assessing markers of oxidative stress (i.e., lactate, NAD/NADH, products of lipid peroxidation), inflammatory cytokines (i.e., TNF-α, IL-1β, IL-6, IL-8), and oral microbiome composition. The results will be showed and communicated to the funder through reports and to the community through scientific publications with a specific statement about the funder, as reported in the Funding section.

Discussion

The PrimaCare_P3 study includes the development and implementation of a PPP targeted to older people with NCDs in a primary care setting. Multicomponent interventions providing older people with information about a healthy lifestyle have been proven effective in the management of chronic diseases [9, 10, 12, 24]. Both CGA and some psychological components have been reported to be important in caring for older people. Previous literature already highlighted the benefit of CGA-based interventions carried out in community-dwelling older adults in particular on reduction of hospitalizations, but most of the positive evidence derived from very outdated studies. In a country like Italy undergoing rapid changes of population structure and of healthcare resources offered to older adults, it is of primary importance to verify these findings. Moreover, previously published studies showed that the training of GPs on a validated CGA-based tool can be feasible and easily implemented in a primary care practice [10, 24, 25]. In particular, the MPI and its derived tools, as the Brief-MPI, have been reported to be effective in identifying older people prognosis in different settings and in guiding clinical decision-making to offer more tailored interventions [26].

Therefore, the PrimaCare_P3 project will test the effectiveness of PPP in reducing rate of unplanned hospitalizations and of other negative outcomes (institutionalization, ED admission, unplanned visits to the GP, mortality) in a large population of community-dwelling older adults with NCDs without any specific exclusion criteria (e.g., levels of frailty condition, disability, terminal illnesses). The study will also test the effect of PPP on more qualitative outcomes such as the level of multidimensional frailty, the psychological wellbeing, and the resilience, in order to demonstrate the importance of a CGA-based personalized management of older people with NCDs [27] performed directly by GP in a primary care setting.

Moreover, through the analysis in a non-invasive and practical way of biological samples (i.e., saliva), the project could shed light on some potential biomarkers associated with different evolutions of NCDs and multidimensional frailty [28]. Chronic low-grade inflammation may contribute to exacerbate damage at a macromolecular level, leading to an increased frailty condition. Research showed that inflammation could be the common soil of NCDs leading to accelerated aging [29]. Thus, levels of inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6, IL-8), imbalance of redox status with modifications in the cellular bioenergetic marked by lactate, NAD/NADH ratio, and products of lipo-peroxidation including might be closely related to multidimensional frailty and the evolution of chronic diseases [3, 30, 31]. Changes in the composition of the oral microbiome might be pathogenetically linked to inflammatory status and could represent an early biomarker of multidimensional frailty [32–34].

Despite its strengths, the study has potential limitations. CGA is not commonly used by GPs to assess older adults in a primary care setting. For this reason, GPs participating in the study will be provided a specific training program. Moreover, because changes in the lifestyle require a high level of compliance to the proposed recommendations, the effectiveness of the PPP will depend also by adherence that could be challenging to reach in the older population. However, the active involvement of

Table 2 Primary and secondary outcomes of PrimaCare_P3 study related to the intervention group and control group

	Primary outcomes at 12 months	Secondary outcomes at 12 months	Exploratory outcomes
Intervention group	• Unplanned hospitalization rate • Adherence to the PPP • PGWB-S • RS-14	• ED, hospital ward, long-term care facilities admission rate • Unplanned GPs visits • Mortality rate	• Lactate, NAD/NADH, products of lipo-peroxidation, TNF-α, IL-1β, IL-6, IL-8 • Oral microbiome changes
Control group	• Unplanned hospitalization rate	• ED, hospital ward, long-term care facilities admission rate • Unplanned GPs visits • Mortality rate	

the GP, the motivation of the patients, and the provision of simple and feasible recommendations might warrant a successful maintenance of the PPP.

Conclusions

Results will suggest whether a CGA-based multicomponent PPP in older people with NCDs is able to reduce negative outcomes and help promoting active aging and an appropriate management of NCDs in a primary care setting. Moreover, the analysis of saliva sample might allow to identify biomarkers associated with multidimensional frailty condition and better responsiveness to the intervention.

Trial status

Protocol version n.01, date of submission 7 August 2023. Estimated start date of recruitment: by the end of April 2024. Approximate date of completed recruitment: after 5 months from the beginning of the recruitment (end of September 2024).

Abbreviations

AOUP	Giaccone Hospital of Palermo
BAPEN	British Association for Parenteral and Enteral Nutrition
BMI	Body mass index
Brief-MPI	Brief Multidimensional Prognostic Index
CDCDC	Cognitive Disorders and Dementia Centre
CG	Control group
CGA	Comprehensive geriatric assessment
CI	Confidence interval
CSQ-8	Client Satisfaction Questionnaire—8 items
DMC	Data monitoring committee
eCRF	Electronic case report form
ED	Emergency department
ELISA Kits	Enzyme-Linked ImmunoSorbent Assay (ELISA) Kits
EOG	Galliera Hospital
GEE	Generalized estimating equations
GP	General practitioners
GPCOG-It	General Practitioner assessment of Cognition -Italian
IG	Intervention group
IIT	Intention-to-treat
ISS	Italian National Institute of Health (Istituto Superiore di Sanità)
MPI	Multidimensional Prognostic Index
MUST	Malnutrition Universal Screening Tool
NAD/NADH	Nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide hydrogen
NCD	Noncommunicable chronic diseases
NHS	National Health System
NPRR	National Plan of Recovery and Resilience
PGWB-S	Psychological General Wellbeing Index—Short
PNPV	National Plan of Vaccination Prevention (Piano Nazionale Prevenzione Vaccinale)
PP	Per-protocol
PPP	Personalized preventive program
RCT	Randomized clinical trial
RR	Relative risk
RS-14	Resilience Scale -14 items
TBARS	ThioBarbituric Acid Reactive Substance analyses
UNIBA	University of Bari Aldo Moro
UWS	Unstimulated whole saliva

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Authors' contributions

Conceptualization and Methodology: AP, CC, Nicola Veronese, Nicola Vanacore, Mario Barbagallo. Funding: AP, EL, VS, Mario Barbagallo. Supervision: EL, EF, EC, PLA, VS. Writing – original draft: AP, CC, Marina Barbagelata, VM, WM, ES. Writing – review & editing: AP, CC, Nicola Veronese, Nicola Vanacore, Mario Barbagallo, EL, EF, EC, PLA, VS. All authors have read and approved the final manuscript.

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Sponsor contact. E.O. Galliera Hospital, Mura delle Cappuccine 14, 16128 Genoa, Italy. Principal Investigator: Alberto Pilotto. Email address: alberto.pilotto@galliera.it.
Role of study sponsor. This is an investigator-initiated and investigator-led trial.
Role of the coordinating centre. EO Galliera Hospital is the coordinating centre and it is responsible of coordinating: the other three partners; the cooperatives who are in charge of recruiting the GPs and patients; and the purchases among the partners. EO Galliera was in charge also of developing the protocol, the eCRF through a digital website, and of training the GPs involved both in the Control Group and the Intervention Group. Finally, data will be collected and managed according to Good Clinical Practice (D.Lgs. 211/2003) and to the current legislation on the management of personal data (Regulation (EU) 2016/679 and D.Lgs. 196/2003 as modified by D.Lgs. 101/2018). Data will be managed centrally by the coordinator centre as the only centre responsible for processing and storing personal data. All data will be collected in the digital platform hosted on the Hospital's servers and available on its web domain.
Trial Steering Committee and Stakeholder and Public Involvement Group (SPIG). The trial is not supported by an external steering committee nor a formal stakeholder and public involvement group (SPIG).

Availability of data and materials

Future analyzed data will be available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol (version n.01, 7 August 2023) was approved by the Ethics Committee of the Region Liguria (n. 678/2022, 15 November 2023) and was registered in the Clinical Trials.gov database (identification number: NCT06224556). Any amendments in the study protocol will be submitted to the local ethics committee and communicated to the involved partners and GPs through official email communication. The consent form is signed after the anonymized randomization process, as described in the 2.1 paragraph. Data will be collected and managed according to Good Clinical Practice (D.Lgs. 211/2003) and to the current legislation on the management of personal data (Regulation (EU) 2016/679 and D.Lgs. 196/2003 as modified by D.Lgs. 101/2018). To ensure the confidentiality of collected data, each participant will be assigned an anonymized code, and their identification will be allowed only to the GP and the principal investigator. Data will be managed centrally by the coordinator center (Galliera Hospital, Genoa, Italy) as the only center responsible for processing and storing personal data. All data will be collected in a digital platform hosted on the hospital's servers and available on its web domain. The coordinating center will monitor the data entry process.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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