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Update of the Novara Cohort Study (NCS): protocol evolution of a population-based longitudinal study on ageing in Northern Italy – cohort profile

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ABSTRACT

Purpose The Novara Cohort Study (NCS) was established to investigate the biological, psychological and social factors that influence ageing in the general population. The study aims to identify early risk factors for frailty, allostatic load and cognitive decline, and to uncover molecular and functional markers of accelerated biological ageing. NCS addresses the need for detailed life-course data from Southern Europe to support personalised prevention and early diagnosis, and to promote healthy longevity.

Participants NCS is a population-based, longitudinal cohort in the Novara province (Northern Italy), originally enrolling adults aged 35 and older. The inclusion criteria were later expanded to encompass all residents aged 18 and over, facilitating the study of ageing trajectories from early adulthood onward. As of mid-2025, about 1000 participants have been enrolled, and recruitment is ongoing. The cohort's diversity in age, employment status and health conditions enhances its value for life-course analysis.

Findings to date Following a pilot phase in 2022–2023, the whole study protocol now includes detailed demographic, clinical, behavioural, cognitive and psychosocial data, along with biological samples stored in the UPO Biobank. The protocol incorporates validated tools, comprehensive physical and cognitive assessments, and over 90 laboratory biomarkers covering inflammation, metabolism, hormonal function and coagulation. Additionally, a subset of participants underwent advanced inflammatory profiling by simultaneous measurement of 92 immune-related proteins and comprehensive genomic profiling using Illumina Single Nucleotide Polymorphism (SNP) arrays, capturing common genetic variation across multiple biological domains. Preliminary results demonstrate the feasibility of integrating deep phenotyping, reveal the roles of frailty in ageing and show initial evidence of age-related changes in inflammatory proteins.

Future plans NCS plans to enrol at least 10 000 participants and will conduct long-term follow-up using both passive methods, such as linking with clinical records and administrative health databases, and active in-person reassessments. Future phases will integrate clinical, behavioural and cognitive data with large-scale omics analyses, including genomics, proteomics, metabolomics and transcriptomics. Machine learning techniques will be employed to model biological age, identify early signs of age-related decline and develop personalised prevention strategies. By combining high-resolution phenotyping with multidimensional data, NCS aims to find modifiable risk factors and molecular signatures of ageing, supporting national and European research efforts and encouraging collaborative studies through open data-sharing frameworks.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Novara Cohort Study uses a life-course approach, enrolling adults from age 18 upwards, enabling the investigation of early determinants of ageing across multiple domains.
⇒ The study combines extensive questionnaire data with standardised clinical assessments, cognitive and physical performance testing, and a comprehensive biomarker panel.
⇒ Biospecimens are collected and managed under GDPR-compliant protocols within an institutional biobank, ensuring high-quality, long-term sample preservation.
⇒ Laboratory blood analysis and advanced inflammatory profiling using multiplex proteomics support deep phenotyping and integrative ageing research.
⇒ The voluntary, community-based recruitment strategy may introduce selection bias and limit generalisability, though targeted outreach efforts are in place to improve representativeness.

INTRODUCTION

Background and purpose of the updated study

As global life expectancy increases, the focus of ageing research has shifted from lifespan to health span, referring to the years lived in good health and autonomy.[1–4] Understanding

how biological, psychological, social and environmental factors interact to shape individual ageing trajectories is essential for developing effective prevention strategies.[5–7] Such efforts, however, require high-resolution, longitudinal population data, which remain limited in several European regions, including Northern Italy.

Over the past two decades, influential European cohort studies have substantially advanced knowledge on ageing and population health. The UK Biobank, a population-based prospective cohort comprising almost 500 000 participants, has substantially advanced ageing research through its deep phenotyping, comprehensive genomic profiling and integration with national health registries.[8] The Invecchiare in Chianti (InCHIANTI) has provided seminal insights into mobility decline and physiological ageing[9]; the English Longitudinal Study of Ageing (ELSA) has offered extensive evidence on socioeconomic and psychosocial determinants of later-life health; the European Prospective Investigation into Cancer and Nutrition (EPIC) has generated large-scale data on lifestyle and chronic disease risk[10] and the Irish Longitudinal Study on Ageing (TILDA) has become exemplary for the integration of social, psychological and clinical dimensions.[11] MoLiSani, one of the major Italian cohorts, has enriched the field with detailed cardiometabolic and lifestyle information.[12] Despite their substantial contributions, these studies differ markedly in geographical coverage, age range, degree of population representativeness and, crucially, the depth of biological phenotyping. Moreover, only a minority incorporates multiomics platforms or systematic long-term biobanking.

The Novara Cohort Study (NCS) complements this European landscape by providing a deeply phenotyped, population-based sample from an underrepresented region of Southern Europe. Designed to address the scarcity of longitudinal, biologically intensive cohorts in Northern Italy, the NCS integrates standardised biospecimen collection with a comprehensive multiomics framework, including Olink proteomics, SNP genotyping, whole-genome sequencing and metabolomics, alongside harmonised clinical, behavioural, social and mental-health assessments. This multidimensional structure enables high-resolution characterisation of ageing trajectories and supports the early detection of factors associated with accelerated ageing, frailty, allostatic load and cognitive decline.[13]

The initial pilot phase, conducted between November 2022 and May 2023,[14] demonstrated the feasibility of biospecimen collection and integrated assessments within the Novara Province and identified areas for methodological refinement. These insights informed the transition to the full-scale protocol.

Objectives

Given the need for multidimensional and life-course data on ageing in Southern Europe, the NCS was designed with a set of clearly defined scientific objectives.

The primary objectives include: (1) to investigate the biological, behavioural, psychological, cognitive and social determinants of ageing trajectories across adulthood; (2) to identify early-life and midlife risk factors for frailty, allostatic load and cognitive decline, and examine how these factors interact over time through multidimensional clinical, functional and biomarker indicators; (3) to uncover molecular and functional markers of biological ageing by integrating clinical biomarkers with multiomics platforms, including proteomics, genomics and metabolomics, and with cognitive and physical assessments and (4) to develop predictive models of healthy and unhealthy ageing, including biological age estimation and early detection of accelerated ageing processes.

The secondary objectives include: (1) to examine the influence of environmental, geographical and socioeconomic exposures on health trajectories via geocoded datasets and linkage with administrative data; (2) to assess psychosocial factors, such as perceived stress, coping, social support, loneliness, personality traits and cognitive reserve, as determinants of resilience and vulnerability during ageing; (3) to investigate multimorbidity patterns, their evolution over follow-up and their associations with molecular, lifestyle and psychosocial determinants and (4) to construct an integrated research platform enabling nested studies, external collaborations and harmonised data-sharing practices within national and European biobanking infrastructures.

In addition to its scientific goals, NCS was conceived to generate direct benefits for public health and the local community. It provides updated, population-relevant health data to inform prevention strategies and planning by the local health authority and the regional administration. The study also promotes active citizen participation, valuing individual contributions as a collective resource and reinforcing trust in public research. Through direct interaction among citizens, clinicians, researchers and institutions, NCS encourages population empowerment and the adoption of healthy behaviours.

Together with the UPO Biobank, NCS is establishing a permanent territorial platform for epidemiological and biomedical data collection on ageing, with the potential to catalyse scientific collaborations, innovative projects and public–private partnerships. This groundwork positions Novara as a regional and national reference point for scientific and civic excellence. By strengthening cooperation among the University, the Local Health Authority (ASL Novara), the Maggiore della Carità University Hospital, the Municipality and citizen associations, NCS advances an integrated model of community-based research and prevention.

The project incorporates a strong social and civic-engagement dimension. Functional assessments of agility, strength and cognitive performance, together with questionnaires on diet, physical activity and daily habits, not only generate high-quality research data but also have immediate educational value. Participants gain a clearer understanding of their health status and

often share this awareness within their families and social networks, contributing to the spread of a prevention-oriented culture. Participation in NCS fosters a sense of belonging to a broader scientific enterprise that connects citizens, researchers and institutions in the shared aim of improving the health of present and future generations. This active involvement strengthens trust in public research and represents a concrete expression of scientific citizenship, in which each participant becomes an informed contributor to collective knowledge and a potential driver of positive change for the public good.

Building on this foundation, the updated protocol incorporates an expanded age range, enhanced data collection tools and increased analytical capacity. These developments reinforce the study's ability to support life-course research and to facilitate predictive modelling of ageing outcomes in the general population.

COHORT DESCRIPTION

Study design and setting: evolution and methodological updates

The NCS is a population-based, longitudinal observational cohort with continuous recruitment and repeated in-person follow-up examinations, complemented by passive follow-up through healthcare and administrative databases. The study is conducted in the Novara Province (Piedmont Region, Northern Italy), a mixed urban–rural area of approximately 370 000 residents. Recruitment, clinical assessments and biospecimen processing take place at the University of Piemonte Orientale (Ipazia Centre for Applied Research) and the Maggiore della Carità University Hospital.

The pilot phase (November 2022–May 2023) recruited 133 adults aged ≥35 years and was essential for validating data collection workflows, integrating clinical and questionnaire-based assessments, and identifying logistical challenges. During this phase, we benchmarked pilot participants against regional data from the PASSI d'Argento surveillance system,[15] confirming strong alignment with the area's older adult population. Insights from the pilot informed several methodological refinements implemented at the transition to the full-scale study, which began in March 2024 and is currently ongoing.

Participants: inclusion and exclusion criteria

The initial focus of the cohort was on adults aged ≥35 years, consistent with the study's early emphasis on mid- and late-life ageing processes. To adopt a broader life-course perspective and investigate early determinants of health, the eligibility criteria were subsequently expanded to all residents of the Novara Province aged ≥18 years. This amendment enables the study to capture exposures and risk factors emerging in early adulthood that may shape long-term ageing trajectories.

Exclusion criteria are limited to the inability to provide informed consent and acute medical instability at the time of assessment. Participants may be included if they are students or workers temporarily residing in the municipality of Novara for at least 3 years, individuals with a registered domicile for at least 3 years, or long-term residents. These requirements reflect regulatory and organisational constraints of the local health authority (ASL Novara) rather than scientific restrictions, and the long-term objective is to broaden recruitment beyond these administrative boundaries progressively.

The broadened eligibility has had a measurable impact on cohort composition. Table 1 compares pilot participants (N=133) with wave 1 participants enrolled up to September 2025 (N=961). Distributions across sex, age, education, employment status and number of self-reported chronic conditions highlight clear demographic differences between phases. While sex and educational attainment remained broadly comparable (p=0.8 and p=0.6, respectively), wave 1 participants were substantially younger (p<0.001) and more likely to be employed (p<0.001), consistent with the expanded inclusion of working-age adults. Differences in the prevalence of self-reported diseases and pathological conditions were modest and did not reach statistical significance (p=0.1).

To contextualise these changes, we compared key demographic and health-related characteristics of wave 1 participants with corresponding estimates for the Piedmont Region population using the available ISTAT demographic and health statistics, as reported in online supplemental table S1.[16] This extends the benchmarking approach adopted during the pilot phase, where PASSI d'Argento data were used to assess alignment with regional profiles.[14]

As shown in online supplemental table S1, the distribution of sex was broadly comparable between NCS wave 1 participants and the regional population, whereas age, educational attainment and chronic disease burden showed significant differences. Wave 1 included proportionally more older adults and fewer individuals aged 18–39 years, a pattern consistent with the timing of the eligibility expansion. Moreover, participants were more frequently university educated, reflecting well-documented participation gradients typical of epidemiological cohort studies.[17] The prevalence of at least one chronic condition was lower in NCS than in ISTAT estimates, suggesting a modest healthy volunteer bias. Employment status also differed significantly (p=0.01), although the absolute difference in employment rates was small.

Despite these differences, wave 1 shows greater diversity than the pilot study and brings the cohort closer to the regional population. Information on self-reported ethnicity was also collected at enrolment, and although the cohort remains mostly of White European ancestry, early participant data suggest a gradual increase in minority representation. Since foreign residents make up about 16.2% of the population in Novara,[18] this aspect will be further enhanced

Table 1 Overview of the NCS core sample: pilot and wave 1

Categories	Participants in pilot n (%) (N=133)	Participants in wave 1 n (%) (N=961)	P value*
Sex			
Males	59 (44.4)	442 (46.0)	0.7
Females	74 (55.6)	519 (54.0)	
Age			
18–29	0 (0)	57 (6.0)	<0.001
30–39	1 (0.8)	77 (8.0)	
40–49	6 (4.5)	105 (11.0)	
50–59	20 (15.0)	155 (16.1)	
60–69	60 (45.1)	286 (29.8)	
70–79	40 (30.1)	246 (25.6)	
80+	6 (4.5)	34 (3.5)	
Education			0.01
No qualifications	0 (0)	1 (0.1)	
Primary or lower secondary education	23 (17.3)	147 (15.3)	
Upper secondary or vocational education	65 (48.9)	470 (48.9)	
Higher education (degree or postgraduate)	45 (33.8)	328 (34.1)	
Missing	0 (0)	15 (1.6)	
Occupation			<0.001
Employed	34 (25.5)	442 (46.0)	
Unemployed	9 (6.8)	65 (6.8)	
Retired	90 (67.7)	448 (46.6)	
Missing	0 (0)	6 (0.6)	
Self-reported diseases/conditions			0.1
0	21 (15.8)	220 (22.9)	
1	40 (30.1)	268 (27.9)	
>1	72 (54.1)	454 (47.2)	
Missing	0 (0)	18 (2.0)	

*χ^2 test for categorical variables.
n, number; NCS, Novara Cohort Study.

through targeted recruitment efforts to better reflect the demographic makeup of the study area.

Taken together, these comparisons provide essential context for interpreting cohort characteristics and demonstrate that, although the cohort has not yet achieved full representativeness, it captures sufficient demographic and health diversity to support analyses of ageing trajectories across adulthood.

Potential sources of bias

Potential sources of bias include information bias from self-reported measures and the self-selection of individuals who are more health-engaged or health-conscious. To address these risks, the study implements mixed-mode questionnaire administration, standardised clinical procedures and linkage with electronic and clinical health records to validate outcomes during passive follow-up. Targeted recruitment strategies are used to enhance participation among underrepresented groups. Moreover, informal peer-to-peer dissemination and public engagement initiatives in less advantaged neighbourhoods have progressively widened the recruitment base, helping to reduce early selection imbalances.

Questionnaire refinements and expanded data domains

The NCS collects a wide range of variables spanning sociodemographic characteristics, lifestyle exposures, psychosocial factors, cognitive performance, physical functioning, multimorbidity and an extensive panel of biomarkers. A complete overview of these domains and their corresponding instruments is provided in table 2.

Table 2 Summary of data collected to date in the NCS cohort

Category	Data collected
Anagraphic Data	Enrolment date, tax code, name and surname, place and date of birth, age, residence and domicile addresses, postal code, phone number, email, additional contact details
Demographic Data	Country and province of birth, ethnicity, family members in the study (relationship, name and surname), years living in the province of Novara, country and province of birth of parents and grandparents (maternal and paternal)
Personal and Family Anamnesis	Basic and instrumental activities of daily living, functional limitations (Falls Efficacy Scale International), birth and breastfeeding history, menstrual and reproductive history (menopause, hormone therapy, contraception, pregnancies, breastfeeding, miscarriages), incontinence, cancer screening participation, surgical history, chronic and past illnesses (ICD-10 coded), comorbidity index (FI-40 and CCI), COVID-19 infections and long COVID, medication use (ATC coded), family medical history (parents, siblings, children—alive/deceased, conditions, cause of death), sibling and child count (biological and adopted), twin status, age of parents at birth
Physical exam and Performance	Weight and height, weight loss and gain, body mass index, waist, hip and neck circumference, waist to hip ratio, recent traumatic events or illnesses, grip strength, 6 min walk test, Timed Up and Go test, balance test, gait speed (4 m), single chair stand test, SPPB score, blood pressure, heart and respiratory rate, oxygen saturation (baseline and post 6 min walk test), lung function (PEF, FEV1, FVC), physician-assessed mobility and conditions, Clinical Frailty Scale, Mini Nutritional Assessment, FI-40, bioelectrical impedance analysis
Cognitive Function	Montreal Cognitive Assessment: visuospatial-executive, naming, attention, language, abstraction, delayed recall, orientation, subjective memory complaints, Cognitive Reserve Index
Behavioural Health	Smoking history, alcohol consumption, diet (PREDIMED, FFQ-15, Mini-Eating Assessment Tool-19), physical activity (International Physical Activity Questionnaire), level of activity at work, sleep duration/disturbance (Pittsburgh Sleep Quality Index, Stop Bang questionnaire, Epworth Sleepiness Scale)
Mental health	Psychiatric/emotional problems, anxiety and depressive disorders (Generalised Anxiety Disorder-7, Patient Health Questionnaire-9), perceived stress (Perceived Stress Scale-10)
Socioeconomic aspects	Earnings and financial assets, sources of income, pension, housing wealth
Employment	Employment situation and job details, retirement
Social and civic participation	Informal caregiving, volunteering, cultural participation, TV watching, social networks and support, loneliness (De Jong Gierveld Scale-11), social capital (Social Support Scale-17, European Social Survey-3), religiosity
Well-being and personality	Quality of Life (Short Form Health Survey-12), personality (10 item-Big Five Inventory)
Blood assays	DNA and RNA extraction, complete blood count (white/red cells, haemoglobin, haematocrit, MCH, MCHC, MCV, MPV, RDW-CV/SD, platelets, PDW, PLCR, differential counts), reticulated platelets, immature granulocytes, nucleated RBCs; coagulation profile (PT-INR, PT sec, PT ratio, APTT sec, APTT ratio, fibrinogen, D-dimer); metabolic panel (urea nitrogen, creatinine, eGFR, uric acid, albumin, electrolytes like potassium, sodium, calcium, phosphorus, cystatin C, glycated haemoglobin, glucose); iron status (serum iron, transferrin, ferritin); lipids (total cholesterol, triglycerides, HDL, LDL, ApoA1, ApoB, ApoB/ApoA1 ratio); liver function (bilirubin total/direct/indirect, AST, ALT, GGT, alkaline phosphatase); inflammatory markers (CRP, IL-6, haptoglobin, troponin T); protein electrophoresis (albumin, alpha, beta, gamma fractions, A/G, monoclonal components); thyroid panel (TSH, FT4, FT3, TPO, ATG); hormones (cortisol, prolactin, progesterone, DHEA-S, testosterone, aldosterone, insulin, somatomedin/IGF-1); vitamins (B_{12}, folate, vitamin D); other markers (homocysteine, pro-BNP, magnesium, chloride, total proteins).

A/G, albumin/globulin ratio; ALT, alanine aminotransferase; APOA1, apolipoprotein A1; APOB, apolipoprotein B; APTT ratio, activated partial thromboplastin time ratio; APTT sec, activated partial thromboplastin time seconds; AST, aspartate aminotransferase; ATC, anatomical therapeutic chemical; ATG, antithyroglobulin antibody; CCI, charlson comorbidity index; CRP, C reactive protein; DHEA-S, dehydroepiandrosterone sulfate; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in 1 second; FFQ, food frequency questionnaire; FI-40, frailty index 40 items; FT3, free triiodothyronine; FT4, free thyroxine; FVC, forced vital capacity; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; ICD-10, International Classification of Diseases-10; IL6, interleukin-6; K, potassium; LDL, low-density lipoprotein; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; NCS, Novara Cohort Study; PDW, platelet distribution width; PEF, peak expiratory flow; PLCR, platelet large cell ratio; pro-BNP, probrain natriuretic peptide; PT-INR, prothrombin time-international normalized ratio; PT ratio, prothrombin time ratio; PT sec, prothrombin time seconds; RBC, red blood cells; RDW-CV, red cell distribution width-coefficient of variation; SPPB, short physical performance battery; TPO, thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone.

The lifestyle and behavioural questionnaires were substantially extended to improve relevance and data granularity. New modules were introduced to capture employment history, occupational exposures and job complexity, as well as detailed dietary patterns (adapted from the brief version of the EPIC-Food Frequency Questionnaire and including Prevention with Mediterranean Diet),[19 20] alcohol and smoking history, social capital, support networks, civic participation and perceived stress and loneliness.

Mental health and quality of life indicators were assessed using validated tools (table 2). In particular, self-reported symptoms of depression and anxiety were investigated with the Patient Health Questionnaire-9[21] and with the Generalised Anxiety Disorder-7, respectively.[22] The ability to deal with stressful situations was measured with the Perceived Stress Scale-10,[23] while coping strategies were evaluated using the 21-item Coping Inventory for Stressful Situations, which captures task-oriented, emotion-oriented and avoidance-oriented coping styles.[24] Loneliness was assessed using the 11-item De Jong Gierveld Loneliness Scale, a widely used measure distinguishing emotional and social dimensions of perceived isolation.[25] Finally, personality traits were assessed using the 10-item Big Five Inventory.[26]

The Clinical Frailty Scale used during the pilot phase was integrated with the 40-item Rockwood Frailty Index (FI-40), a validated cumulative deficit model that offers finer resolution in quantifying frailty and vulnerability.[27 28] The FI-40 quantifies frailty as the proportion of health deficits across comorbidity, symptoms, physical and cognitive function, mobility, sensory impairments and activities of daily living, enabling sensitive detection of vulnerability.

Medical history was fully standardised using International Classification of Diseases-10 (ICD-10) diagnostic codes and Anatomical Therapeutic Chemical (ATC) medication codes, facilitating harmonisation and cross-cohort comparability. Currently, medical history is collected through a structured self-report instrument; however, consistent with the NCS longitudinal design, progressive linkage with the regional electronic health records and clinical record system (Maggiore della Carità University Hospital) is planned as part of passive follow-up. This will allow validation of self-reported conditions and incorporation of clinically confirmed diagnoses in future waves.

Questionnaire timing and administration

All questionnaires are administered during a single study morning, following a structured workflow first implemented and validated in the pilot phase.[14] Data collection is organised into sequential modules to minimise participant burden and ensure smooth transitions across assessment components.

Demographic information is obtained during the informed consent process. Trained healthcare personnel collect personal and family medical history, including parental cause of death, chronic conditions in parents, siblings and children, functional status, fear of falling, smoking history, hormonal and reproductive history, and preventive screening participation. The questionnaire further captures past and current medical conditions, surgical interventions and detailed medication use, providing a comprehensive overview of lifetime health status.

Employment history and cognitive reserve are assessed by the NCS research team, while cognitive function is evaluated using the Montreal Cognitive Assessment (MoCA) test administered by a psychologist or a trained nurse. Physical performance tests are conducted in a dedicated examination room, and anthropometric measurements are performed in the clinical area.

Lifestyle, socioeconomic, psychological and emotional questionnaires are primarily self-administered. Participants typically complete these during waiting periods within the visit, with assistance available from NCS staff when needed. For the small number of participants unable to complete the self-administered modules on-site, a secure REDCap link is provided to ensure completion at home with automatic integration into their study record. This multimodal approach has resulted in high data completeness: missing data for self-administered modules in wave 1 remained below 2%.

New clinical and functional measures

Several enhancements were introduced in the full-scale protocol. A spirometry module was added to assess pulmonary function (Forced Expiratory Volume in 1 second - FEV_1; Forced Vital Capacity - FVC; Peak Expiratory Flow - PEF), which is relevant for ageing and chronic disease. Body composition is evaluated using bioelectrical impedance analysis (BIA; Tanita), providing standardised estimates of fat mass, fat-free mass, skeletal muscle mass and total body water.[29 30] Capillary blood glucose is measured via point-of-care testing.

Physical performance assessments were expanded and standardised to include bilateral grip strength (with repeated measurements and mean values), the Timed Up and Go test, the 6 min Walk Test and the Short Physical Performance Battery, incorporating 4 m gait speed, chair stands and balance tests, in accordance with current recommendations for evaluating frailty and sarcopenia.[31 32]

Cognitive evaluations were strengthened by incorporating not only the Italian version of MoCA 7.1,[33] but also the Cognitive Reserve Index Questionnaire[34] to estimate the amount of cognitive reserve, a well-known protective factor against cognitive decline, built up through education, occupational and leisure activities across the life course. In addition, to investigate subjective memory complaints, an important marker of pre-dementia syndromes such as Motoric Cognitive Risk (MCR), participants completed three items commonly used in MCR assessments: one from the Geriatric Depression Scale and two addressing memory difficulties and perceived changes over the past decade.[35]

Table 3 Biospecimen types collected in the NCS and their intended use

Sample type	Derivatives	Applications and intended analysis
EDTA (K2)	Plasma; buffy coat mainly for genomic DNA extraction; PBMCs isolation; RNA-stabilised samples	Proteomics, metabolomics, biochemical markers, genomic DNA, transcriptomic and gene expression analyses, immunophenotyping, functional immune assays, SNP arrays, whole genome sequencing, epigenetics
Lithium heparin	Plasma aliquots	Clinical biochemistry, metabolomics
Sodium citrate	Plasma aliquots; buffy coat	Coagulation assays, inflammatory markers, cell-free DNA
Serum separator (gel)	Serum aliquots	Hormones, immunological assays, clinical chemistry
Urine	Urine aliquots	Metabolomics, endocrine and renal biomarkers
Saliva	Saliva aliquots	Metabolomics, proteomics
Future plan	Faecal and buccal swabs	Gut microbiome, metabolomics

NCS, Novara Cohort Study; PBMCs, peripheral blood mononuclear cells; SNP, single nucleotide polymorphism.

Biospecimen collection and processing

As already outlined in the pilot phase,[14] the NCS includes extensive biospecimen collection using standardised biobanking procedures (table 3). EDTA tubes support haematological analyses and provide plasma, buffy coat and peripheral blood mononuclear cells (PBMCs) for biobanking, nucleic acid extraction, proteomic and metabolomic assays. Lithium-heparin tubes yield plasma for biochemical analyses and storage, whereas sodium citrate tubes are used for coagulation testing and buffy coat preservation. Gel separator tubes enable serum collection for clinical chemistry and immunological assays, as well as long-term storage. Additionally, stabilised blood in RNA-preservation tubes allows high-quality transcriptomic analyses. Urine and saliva samples are also collected, enabling future analyses.

A subset of fresh blood samples undergoes immediate haematological and biochemical assessment, including markers of electrolyte balance, inflammation, cardiovascular risk, renal, thyroid and hepatic function (table 2). Participants receive a personalised report with these results and guidance for discussing them with their general practitioner.

Altogether, this multimodal biospecimen framework establishes a comprehensive biobank that supports large-scale molecular investigations and facilitates comparability with other national and international population cohorts.

Biomarker enhancement

Compared with the pilot study, the panel of biological markers was broadened to improve the detail and breadth of clinical profiling, allowing more comprehensive characterisation of metabolic, inflammatory and physiological processes. In the second phase of the study, beyond routine biochemical and haematological parameters, additional biomarkers were included to provide a more comprehensive overview of cardiovascular, metabolic, hormonal, inflammatory, coagulation and multiorgan functional status. The expanded panel covered markers of inflammation (eg, haptoglobin), cardiac function (eg, troponin T, proBNP), lipid metabolism (eg, apolipoprotein A1, apolipoprotein B, APOB/APOA1 ratio), iron status, stress response (eg, cortisol), coagulation (eg, Prothrombin Time–International Normalized Ratio: PT–INR; Prothrombin Time seconds and ratio: PT sec/ratio; Activated Partial Thromboplastin Time seconds and ratio: APTT sec/ratio), electrolytes and minerals (eg, chloride, magnesium) and endocrine and vitamin profiles (eg, insulin, prolactin, progesterone, DHEA-S, testosterone, aldosterone, vitamin D, somatomedin).

Follow-up strategy and study size

The full-scale study plans to enrol at least 10 000 participants. All individuals will be followed over time through a dual follow-up approach: passive follow-up, which involves periodic linkage with regional health administrative databases and clinical records, and active follow-up, consisting of repeated in-person assessments every 5 years for participants under 65 and every 3 years for those aged 65 and older. This setup aims to track the onset and progression of age-related conditions throughout life and to support predictive modelling of frailty, allostatic load, accelerated ageing and major health outcomes.

The target sample size of 10 000 participants provides adequate statistical power for stratified analyses across key demographic and clinical groups, as well as molecularly informed subgroups. It also supports machine-learning and multiomics approaches that require large training and validation sets.

Clinical diagnostic variables, multimorbidity and follow-up outcomes

Clinical diagnostic information is collected at baseline through a structured ICD-10-coded medical history questionnaire covering chronic and past diseases across major organ systems, including cardiovascular (eg, hypertension, coronary artery disease, arrhythmias), metabolic (eg, diabetes, dyslipidaemia), respiratory (eg, asthma, allergies, chronic obstructive pulmonary disease), neurological (eg, stroke, Alzheimer's disease, Parkinson's disease), psychiatric (eg, depression, anxiety), musculoskeletal

(eg, arthritis, osteoporosis), endocrine (eg, thyroid disorders), renal, gastrointestinal, autoimmune, oncological and infectious conditions. Additional information is collected on surgeries, medication use (ATC-coded), frailty indicators, functional status (activities of daily living/instrumental activities of daily living limitations), mobility impairments and falls.

Multimorbidity, an essential construct for modelling ageing and frailty trajectories, is derived from these ICD-10-coded conditions. It is operationalised both as a continuous count of chronic diseases and as categorical groups, in accordance with international standards. We also computed several established measures of multimorbidity, including (1) the deficit-accumulation model used in the Frailty Index[27]; (2) the weighted comorbidity structure of the Charlson Comorbidity Index[36] and (3) the conventional definition based on the presence of ≥2 long-term chronic conditions.[37]

During passive follow-up, linkage with regional health administrative databases and vital statistics will provide validated diagnostic information, hospital and outpatient records, pharmaceutical prescriptions and mortality data. These sources will enable the identification of incident chronic conditions, such as major cardiovascular, metabolic, respiratory, renal, neurodegenerative and oncological diseases, thereby allowing robust longitudinal tracking of health outcomes (table 4).

Active in-person follow-up visits will update clinical diagnoses, multimorbidity patterns, frailty indices, cognitive trajectories, physical performance, psychosocial and

Table 4 Health and administrative data available through passive follow-up from the Piedmont Regional Health System

Domain	Data source	Variables available	Details
Demographics and Registry Information	Regional Health Registry	Date of birth, sex, residence history and general practitioner registration	Continuous updates; enables tracking of migrations within the region
Hospital Care	Hospital Discharge Record	Admission/discharge dates, primary and secondary diagnoses, surgical/procedural codes, length of stay, discharge status	Captures public and accredited private hospitalisations
Emergency Care	ED Database	ED access dates, triage category, diagnoses, outcome (discharge, transfer, admission)	Includes all emergency department contacts
Outpatient Specialist Care	Ambulatory Care Database	Specialist visits, diagnostic tests, imaging, rehabilitation, procedure codes	Information on prescriptions of visits and services reimbursed by RHS
Pharmaceutical Prescriptions	Drug Prescription Registry	Type of medication, quantity dispensed, date of dispensing, prescriber type	Includes all reimbursed drugs dispensed in community pharmacies
Co-payment Exemptions	Co-payment exemptions	Type of exemption (chronic disease, disability, income-related), dates of validity	Useful to identify chronic conditions and socioeconomic vulnerability
Mental Health Services	CMH Registries	Contacts with mental health services, diagnosis, treatment episodes	Includes specialist mental healthcare
Laboratory and Screening Programmes	Regional Screening Registries	Participation in breast, colorectal and cervical cancer screening, test outcomes	Enables linkage to preventive service use
Mortality	Regional Mortality Registry	Date of death, cause of death	Annual updates; high completeness
Vaccinations	Regional Immunisation Registry	Type of vaccine, date of administration, dose number	Includes influenza, COVID-19 and routine vaccinations
Socioeconomic Indicators	Census-based variables, deprivation indices	Area-level socioeconomic status, deprivation index, urban/rural classification	Linked via geocoded residence
LTC	LTC/IHC Registries	Home care, residential care admission dates, assistance intensity	Tracks frailty-related health service use

CMH, Community Mental Health Services; ED, emergency department; IHC, integrated home care; LTC, long-term care; RHS, Regional Health Service.

lifestyle variables, and biomarker profiles. Together, these complementary data sources form a comprehensive clinical framework that is essential for prognostic modelling and for investigating determinants of healthy and unhealthy ageing across the life course.

Geographical and environmental data linkage

Residential address information is collected at enrolment and stored in pseudonymised form to enable future linkage with external geographic and environmental datasets. This will allow incorporation of spatially resolved indicators, including temperature, precipitation, snow events, air pollution levels, green-space availability and other neighbourhood-level characteristics, relevant to environmental and social epidemiology.

The NCS team is currently developing a dedicated geolocation application to encode residential coordinates and securely support fine-grained exposure modelling. Additional official datasets on air pollution and environmental exposures will be requested from regional authorities.[38] All procedures comply with GDPR: identifiable addresses are stored separately from research data, linkage is conducted through encrypted pseudonymised keys, and geographic variables are processed at aggregated levels to minimise reidentification risk.

Data and sample management

NCS samples are stored at the UPO Biobank. This non-profit, research-oriented biobank supports the standardised collection, processing and long-term preservation of multiple biospecimen types, including whole blood, plasma, serum, PBMCs, RNA, saliva and urine, under ethically approved protocols.[39] All samples are processed using standardised procedures and stored in −80°C freezers or liquid nitrogen tanks equipped with continuous temperature monitoring and secure access. A dedicated Laboratory Information Management System (LIMS) ensures full traceability of each biospecimen and its associated minimum dataset, including demographic variables, disease status, treatments, selected clinical biomarkers, education level, smoking and alcohol habits, and body mass index, in full compliance with GDPR (General Data Protection Regulation) and FAIR (Findable, Accessible, Interoperable, Reusable) principles.

All clinical, epidemiological and behavioural NCS data are securely stored in the REDCap platform, which serves as the study's primary data repository. All data streams are integrated through a secure, pseudonymised linkage system. Each participant receives a unique pseudonym that connects questionnaire-based information (medical history, cognitive and physical assessments, lifestyle measures) stored in REDCap with corresponding biological aliquots tracked in TDBiobank. The same pseudonym links laboratory outputs and omics data stored on dedicated servers, ensuring end-to-end traceability. This identifier also enables deterministic linkage with regional administrative health databases, clinical records of University Hospital and environmental exposure datasets, creating a unified and longitudinal data architecture while preserving strict confidentiality.

Quantitative variables and statistical methods

Continuous variables, including biomarkers and performance measures, are recorded in raw units and will be analysed both continuously and categorically when clinically meaningful cut-offs exist. Psychometric instruments follow validated scoring procedures. Omics datasets are processed using established normalisation and quality-control pipelines (eg, z-score or log transformation for biochemical markers, Olink NPX scaling for proteomics, and standardised QC pipelines for SNP genotypes).

Analyses are performed in R, STATA 18, or SPSS 23, using standardised pipelines already applied in ongoing and submitted NCS work. Baseline characteristics are summarised using mean/median and standard deviation/interquartile ranges (SD/IQR) or proportions, and between-group differences are assessed using t-tests, ANOVA (analysis of variance), Mann-Whitney or chi-square (χ^2) tests, as appropriate.

Associations between exposures (eg, lifestyle factors, psychosocial variables, biomarkers) and outcomes (eg, frailty, multimorbidity, cognitive function, age acceleration) are evaluated using correlation analyses and multivariable regression models with adjustment for relevant covariates. Moderation and interaction models assess effect modification, and mediation analyses investigate behavioural, biological and psychosocial pathways underlying ageing processes.

Predictive performance of biomarkers and composite indices is evaluated using Receiver Operating Characteristic curve (ROC) analyses and area under the curve (AUC). For multidimensional phenotyping, unsupervised clustering, principal component analysis (PCA) and penalised regression models (eg, elastic net) are used to identify latent patterns and biomarker signatures.

Longitudinal analyses will employ mixed-effects models, generalised estimating equations and survival models to characterise trajectories and incident events. High-dimensional omics datasets (SNP genotyping, whole-genome sequencing, proteomics, metabolomics) will be integrated through machine-learning and network-based approaches to estimate biological age, derive predictive models and validate molecular signatures associated with ageing pathways.

Missing data is handled using multiple imputations or full-information maximum likelihood methods, depending on the specific case. The analyses will report effect sizes, CIs and diagnostic checks of model assumptions.

Data-sharing framework and future integration of high-dimensional datasets

Access to NCS data is currently granted through scientific collaborations evaluated and approved by the Scientific Lead in accordance with study governance and GDPR regulations. Phenotypic and questionnaire data are

stored in REDCap, while biospecimens and their metadata are managed within the UPO Biobank TDBiobank platform.[40]

Within the national action 'Characterization of BBMRI.it Collections', funded through NEXTGEN EU/PNRR—Strengthening BBMRI project aimed at advancing the molecular characterisation of BBMRI.it collections,[41] UPO Biobank obtained competitive funding to characterise NCS samples, which represent its main research asset. These resources supported the Olink Reveal proteomic panel and high-throughput genotyping. Genome-wide SNP-array analyses (Illumina) provided coverage of common genetic variation across cardiometabolic, immune-inflammatory, neurocognitive and pharmacogenomic pathways. Moreover, through dedicated resources from the Ministry of University and Research, access to the Human Technopole sequencing facility[42] will enable whole-genome sequencing of 1000 participants, substantially enriching the cohort with high-resolution genomic data. Ongoing collaborations with partner universities are further expanding the molecular dataset, including targeted metabolomic panels related to oxidative stress and energy metabolism.

To accommodate the increasing volume and complexity of molecular profiling, a secure institutional server hosts an internal metadataset that integrates high-dimensional data. This meta-database operates under a tiered, controlled-access model supporting in-house analyses and, in future phases, remote controlled access. This infrastructure is being strengthened through regional and PNRR investments, which support the development of robust data storage, management and analysis capabilities. The overall data flow and linkage architecture are shown in online supplemental figure S1.

FINDINGS TO DATE AND EXPECTED RESULTS

The NCS is expected to generate one of the most comprehensive multidimensional datasets on ageing in Southern Europe. By integrating clinical, functional, cognitive, psychosocial, environmental and multiomics data, the study will support prognostic modelling of ageing trajectories, the identification of early determinants of frailty and multimorbidity, and the validation of biological ageing signatures. As follow-up waves progress, NCS will enable longitudinal analyses of health transitions and the development of predictive tools for biological age estimation and precision prevention.

The biomarker component is expanding rapidly. In addition to more than 90 routine haematological and biochemical markers, inflammatory profiling with the Olink Target Inflammation panel (92 proteins) is providing detailed insights into immune pathways. Upcoming Olink Reveal analyses will extend coverage to over 1000 proteins, supporting the identification of multiomics signatures of ageing, frailty and physiological resilience. In parallel, genomic profiling is underway: SNP genotyping has been completed for 500 participants, and whole-genome sequencing will be performed on 1000 individuals through national research programmes. Combined with clinical, lifestyle and environmental data, these layers will clarify how molecular and genetic factors contribute to ageing trajectories.

Initial findings already highlight the value of this multidomain approach. Inflammatory profiling reveals age-related shifts in cytokines and immune-regulatory proteins associated with frailty and multimorbidity, underscoring the potential of circulating inflammatory markers as indicators of biological ageing and allostatic load. Early analyses also suggest partially distinct components of frailty: clinical frailty aligns with functional performance and psychosocial vulnerability, whereas biological frailty reflects subtler physiological dysregulation that may precede overt deficits.

Several integrated research directions are underway to enhance the scientific depth of the NCS. Planned multiomics analyses will generate molecular signatures linked to inflammation, metabolism and accelerated ageing. Parallel efforts are establishing a secure, FAIR-aligned digital infrastructure to support high-quality data integration, interoperability and advanced analytical workflows. Additional research will evaluate how socioeconomic disadvantages and neighbourhood context shape ageing trajectories and incorporate biomonitoring of environmental and occupational exposures. A dedicated focus on early adulthood will investigate early biological risk markers and health-related behaviours in individuals aged 18–25.

By combining multidimensional phenotyping, omics technologies, digital innovation and community engagement, NCS will advance understanding of ageing mechanisms and provide actionable evidence for health promotion and disease prevention. The study aims to contribute to regional health planning, promote health literacy and support the development of a territorial research infrastructure that connects academia, healthcare, local authorities and communities. Ultimately, the NCS seeks to build a sustainable ecosystem for precision ageing research capable of improving population health across present and future generations.

STRENGTHS AND LIMITATIONS

NCS exhibits several notable strengths. It is a multidisciplinary, population-based study designed to capture the complex interplay between biological, behavioural, psychological and social factors across the adult life course. The combination of detailed questionnaires with clinical phenotyping, assessments of cognitive and physical functioning, and an extensive panel of biomarkers, together with long-term follow-up, provides a comprehensive framework for analysing diverse ageing trajectories.

A key infrastructural advantage is the integration with the UPO Biobank,[38] which ensures high-quality management of biospecimens across multiple biological matrices in accordance with FAIR and GDPR standards. The cohort

is supported by a stable institutional network comprising academic departments, the Maggiore della Carità University Hospital and the Local Health Authority (ASL) of Novara, ensuring sustainable clinical integration, secure data governance and robust ethical oversight.

Nevertheless, the study also faces several challenges. The current voluntary recruitment model may introduce selection bias by overrepresenting healthier or more health-conscious individuals. To address this, targeted outreach strategies are being implemented in collaboration with patient associations, immigrant communities and underserved neighbourhoods to improve diversity and representativeness. Another limitation is reliance on self-reported information for several behavioural, psychosocial and medical history variables, which may introduce recall bias and misclassification. To mitigate these issues, the study employs mixed-mode questionnaire administration, standardised clinical procedures, progressive linkage with electronic and clinical health records to validate key outcomes during passive follow-up, and targeted recruitment strategies to increase participation among underrepresented groups.

Although more than 1000 participants have been enrolled, the cohort is still under development, and the current sample size limits advanced stratified or high-resolution subgroup analyses. Continued efforts to expand recruitment will be crucial for achieving population representativeness and fully leveraging the study's analytical potential.

In summary, the updated protocol substantially enhances the scientific potential of NCS by expanding its life-course scope, deepening its biological resolution and enabling long-term linkage with administrative and environmental data. These developments strengthen the cohort's position within the European ageing research landscape and establish the foundation for future work integrating molecular, clinical, social and environmental dimensions of ageing. As the cohort matures, NCS is expected to become a central resource for precision ageing research and public health planning, supporting cross-cohort collaborations and contributing to the development of preventive strategies for healthier ageing across generations.

COLLABORATION

The cohort actively encourages collaborative studies and data-sharing agreements. It especially promotes efforts focused on ageing trajectories, frailty and life-course health determinants. Researchers are invited to submit proposals for joint analyses and nested projects that support the NCS's mission to explore the biological and societal mechanisms behind human ageing.

Researchers interested in accessing data or biospecimens from the NCS can contact the PI (daniela.capello@uniupo.it; ncs@uniupo.it) or submit a request through the UPO platform (UPO_biobank@uniupo.it). Deidentified data will be provided to qualified researchers for ethically approved studies, subject to review and approval of a research proposal, data use agreement and compliance with GDPR and institutional policies. Restrictions may apply based on the type and sensitivity of the requested data to protect participant privacy.

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Correction notice This article has been corrected since it was first published. Author Daniela Capello is listed as the last author in the author byline.

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Contributors SVC drafted the initial version of the manuscript and conducted the statistical analyses. All other coauthors contributed to the development and implementation of the Novara Cohort Study and provided critical input on the manuscript. DC and FF are the principal investigator and co-principal investigator of the study, respectively, and oversaw the study design, data collection and overall project coordination. All authors reviewed, edited and approved the final version of the manuscript. DC is the guarantor of the work. An AI tool was used to rephrase the text into correct English.

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Competing interests The following potential conflicts of interest are disclosed: DC, the study supervisor, serves as the scientific director of the UPO Biobank (Center for Autoimmune and Allergic Diseases, Novara, Italy), which supported this research and provided the biological samples. Additionally, some collaborators involved in the study hold positions within the UPO Biobank. Nonetheless, rigorous measures were implemented to maintain objectivity and ensure scientific integrity. All other authors declare no conflicts of interest.

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

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by Comitato Etico Territoriale Interaziendale AOU Maggiore della Carità di Novara, under protocol number CE137/2022 and subsequent amendment (ref. CE137/2022, 9 November 2023). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The cohort actively encourages collaborative studies and data-sharing agreements. It especially promotes efforts focused on ageing trajectories, frailty and life-course health determinants. Researchers are invited to submit proposals for joint analyses and nested projects that support the NCS's mission to explore the biological and societal mechanisms behind human ageing. Researchers interested in accessing data or biospecimens from the NCS can contact the PI (daniela.capello@uniupo.it; ncs@uniupo.it) or submit a request through the UPO platform (UPO_biobank@uniupo.it). Deidentified data will be provided to qualified researchers for ethically approved studies, subject to review and approval of a research proposal, data use agreement and compliance with GDPR and institutional policies. Restrictions may apply based on the type and sensitivity of the requested data to protect participant privacy.

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