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Clinical and environmental factors, functional status, and multimorbidity—stratifying progression and prognosis of multimorbidity, frailty, and disability: the Age-It Research Program

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Abstract

Objectives: This paper describes the methodology and activities of the third thematic challenge (Spoke 3) of the Age-It program. Spoke 3 aims to address the clinical complexity and heterogeneity of older subjects' phenotypes through an interdisciplinary biomedical approach.

Methods: Spoke 3 will investigate biomarkers related to multimorbidity and frailty, develop prognostic algorithms using novel methodological approaches, including artificial intelligence (AI) techniques to combine biological and clinical data, and identify management strategies for complex older subjects with multimorbidity and frailty. These activities will be realized by launching new prospective longitudinal studies and through new analyses of existing longitudinal cohorts.

Results: Spoke 3 is expected to generate original evidence concerning older subjects with multimorbidity and/or frailty, to support a more precise diagnostic evaluation, to improve the ability to predict the functional and cognitive trajectories, with the final aim of better managing this complex population. Spoke 3 also aims to evaluate the impact of climate change and pollution on the health status of older subjects by combining health and environmental data.

Discussion: Overcoming the traditional medical approach, focused on the diagnosis and treatment of single diseases, Spoke 3 should provide important original evidence to improve the management of older subjects with multimorbidity and frailty.

Keywords: Artificial intelligence, Health outcomes, Biomarkers of age, Functional health status

Heterogeneity at the cellular, organ, and individual levels is a hallmark of aging in humans (Nguyen et al., 2021). Starting from birth, the interplay between genetic endowment and the environment causes a progressively increasing differentiation among subjects over time, being influenced by aging, lifestyle, diseases, socioeconomic factors, and environmental factors such as climate change and pollution. Hence, older subjects cannot be fully characterized by their chronological age, as it does not capture the extreme variability of phenotypes and health in subjects of the same age. Chronic diseases and conditions are among the main elements responsible for clinical heterogeneity. Aging is considered a major risk factor for the onset of chronic diseases, since they share common pathophysiological mechanisms, as postulated by the geroscience hypothesis (Duque et al., 2023). Moreover, chronic diseases often coexist in a single individual, giving rise to multimorbidity (MM) (Skou et al., 2022). There is no universal agreement concerning the definition of MM. A recent systematic review

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(Ho et al., 2021) found that more than a third of studies did not report their definition of MM, while other definitions varied in terms of the number and types of conditions included, the way they are defined, the inclusion of functional status or other non-disease factors, and the use of different weighting systems. Despite these inconsistencies, the most common definition used in the literature is the presence in a single individual of two or more chronic conditions. The multiplicity of definitions has created uncertainties in determining the true epidemiology of MM and its consequences (The Academy of Medical Sciences, 2018). However, there is general agreement that MM prevalence increases with age, being the norm in older people, and is associated with negative outcomes such as functional limitations and disability, reduced quality of life, increased mortality, and higher healthcare costs (Skou et al., 2022).

Multimorbidity has been described as a 'challenge' for health systems (Barnett et al., 2012; Pearson-Stuttard et al., 2019). Patients with MM account for a disproportionately high share of the healthcare workload, particularly in high-income countries (The Academy of Medical Sciences, 2018). Healthcare costs and resource utilization increase when MM is present, linked to elevated rates of primary care and specialist physician visits, medication use, emergency department presentations, and hospital admissions (McPhail, 2016). A systematic literature review of studies that investigated the relationship between multiple chronic conditions and healthcare utilization and cost outcomes in older general populations identified a curvilinear relationship between multiple chronic conditions and health system costs, suggesting that the cost of care for patients with MM is more than would be predicted based on the cost of managing the individual component conditions alone, with an additional risk for insufficient care for subjects who have to sustain out-of-pocket costs (Lehnert et al., 2011), leading also to increased social inequalities. Moreover, guideline-based management for many multimorbid patients implies that they often have to see different healthcare professionals, resulting in uncoordinated and fragmented care. These issues bring associated risks such as inappropriate polypharmacy and excessive treatment burden.

Eventually, the increasing proportion of individuals with MM who will live to advanced ages has important implications for the sustainability of healthcare services, especially in resource-constrained healthcare systems (McPhail, 2016).

Besides MM, frailty has emerged as a useful construct to characterize the heterogeneity of older adults. Frailty is a condition of accelerated decline of physiological reserves that determines a high susceptibility to even minor stressors, which can induce negative clinical outcomes (Clegg et al., 2013). Frailty is a multidimensional, dynamic condition whose prevalence increases with age. While MM may contribute to the development of frailty, the two concepts are not equivalent.

This paper aims to describe the methodologies and main activities of the third thematic challenge (Spoke 3) of the Age-It program (for full details about the overall research program of Age-It, see Vignoli et al., 2025; see also https://ageit.eu/wp/en/).

This challenge will foster collaboration among renowned aging research Centers distributed throughout Italy and will promote an interdisciplinary approach that will involve clinician, biologists, medical researchers, engineers, data scientists, experts in the use of artificial intelligence (AI), with the following main aims: (1) to identify and validate biomarkers associated with MM and frailty; (2) to develop, also with the aid of AI techniques, multiparametric algorithms to support the prediction of clinical, cognitive and functional trajectories in these patients; (3) to develop effective management strategies to improve clinical outcomes in the older population with MM and/or frailty; and (4) to provide an overview of current knowledge on the impact of climate change and environment on health trajectories in older age as well as to perform original research in this field.

The identification of biomarkers of multimorbidity and frailty

In the framework of Spoke 3, a specific activity is devoted to the identification and validation of biomarkers of MM and frailty. This aspect of gerontology and geriatrics has become utterly important in recent years for a series of theoretical and practical reasons. First of all, it is known that aging is the main culprit of age-related diseases development and progression, and frailty. This is because, according to the fundamental concept of Geroscience, the molecular mechanisms underlying the aging process are widely shared with diseases and frailty. Since aging has been shown to be a malleable process, Geroscience shifted the focus away from specific diseases toward tackling the aging process as a whole, thus putting forward the idea that acting on the molecular mechanisms behind should avoid, delay or contrast not only aging but also and most importantly all the main age-associated diseases, even before they become clinically apparent (Barzilai et al., 2018; Sierra, 2016). Therefore, according to this concept, identifying biomarkers of aging, especially of biological age, should be equivalent to identifying biomarkers that can tell us about diseases and frailty. Indeed, biological age means the difference between the expected value of one or more markers at a given age and the one actually measured (a delta greater or less than 1 equates to a biological age greater or less than the chronological one). Consequently, if such biological age markers are identified and clinically validated, they should be able to effectively identify which patients are at the highest risk of developing/progressing into one or more pathological conditions (frailty, multimorbidity). Second, these biomarkers could help refine not only the diagnosis but also the prognosis of the patients, thus they could be a useful tool for better managing geriatric patients. Among biomarkers currently under study, we can distinguish those that are blood-based, composite (not necessarily based on molecular data but also imaging ones), and based on 'omic' assays. The advantage of using single blood-based markers is clear: the limited invasiveness, the relatively low cost, and the ease of execution might facilitate their diffusion and use in the clinic. On the other hand, their diagnostic/prognostic power and specificity are likely limited. Greater predictive capacity and greater specificity are attributable to composite biomarkers or those derived from 'omic' techniques, such as "signatures" based on DNA methylation patterns or transcriptome and proteome analyses. Most of these 'omic'-derived biomarkers are often referred to as "clocks" and include, among many others: pan-tissue Horvath's DNAmAge clock (DNAmAge), predictor of pace of aging (DunedinPoAm), pan-tissue DNA-methylation epigenetic clock based on deep learning (AltumAge), morbidity and mortality predictor PhenoAge, time to death predictor GrimAge (see Moqri et al., 2024 for a review [Moqri et al., 2024]), and the inflammatory clock of aging iAge (Sayed et al., 2021).

A detailed discussion of these clocks is out of the scope of this paper; however, the most important obstacle that prevents the translation from bench to bedside of these clocks and omic-derived signatures, in addition to the still high cost, is the difficulty in analyzing the results, which requires the use of sophisticated statistical tools and increasingly of appropriate AI approaches. A personalized medicine approach based on these clocks and signatures could thus result in an unsustainable level of complexity of analyses necessary for an effective diagnosis and prognosis, especially for the older patient with multiple diseases, decreased resilience, and functional capacity (to paraphrase Tolstoj, we are all healthy in the same way, everyone is sick in their own way). Moreover, in many cases, only a small part of the generated omic data is used to build the clock, while the rest remains unexploited, thus casting serious ethical doubts about the appropriateness of this type of test. Another possible issue regards privacy, as these tests yield sensitive data in a unique combination that could theoretically provide the possibility, upon adequate analysis, to unequivocally identify the owner of the biological specimen, his/her health status, and risk of death (with consequent insurance problems, healthcare system burden, etc.). To solve these problems and, at the same time, facilitate the diffusion of these methods, a simplification of the data analysis and even a minimization of the analytical methods (i.e., a reduction in the number of data points needed to obtain a trustworthy result) would be desirable. As a matter of fact, some attempts have already been carried out in this direction, such as the creation of a targeted epigenetic clock for the evaluation of biological age based on just six genomic regions (Gensous et al., 2022). It is currently debated whether such 'omic'-derived signatures, in particular DNA methylation data, are able to predict frailty and/or MM and to what extent (Mak et al., 2024). For sure, the above-mentioned shortfalls will limit their clinical use in the near future. However, the predictive power of individual markers has also been questioned. In a recent study, it has been reported that a routine frailty index based on a deficit accumulation approach is more predictive of mortality than single blood-based markers or physical performance measures (Blodgett et al., 2024). Nevertheless, there is no doubt that these biomarkers will become increasingly important in the diagnosis, monitoring, and management of the older patient as synthetic indicators that are easy to obtain and repeatable. Thus, the identification of new biomarkers (alone or more likely in combination with each other and possibly with other clinical routine parameters) that can provide useful indications to the medical team represents a very hot topic of current translational biomedical research.

Recently, in an attempt to identify promising markers to test in Spoke 3, a review was carried out on the state of the art of the study of biomarkers for MM and frailty (Salvioli et al., 2023). It was decided to focus mainly on soluble proteins that are actively secreted as part of the stress response or inflammation. Therefore, the following markers will be analyzed within the existing sample sets of the Program: Growth Differentiation Factor 15 (GDF15), Fibroblast Growth Factor 21 (FGF21), and soluble Receptor for Advanced Glycation End-products (sRAGE). Finally, neurofilament light chain (NfL) was also added to this short list as an indicator of neuronal cell damage associated with neurodegeneration (Giacomucci et al., 2022). Interestingly, these markers were originally identified for their association with a particular pathological condition, but can be related to many different age-related diseases. For example, GDF15 was initially described as a marker of mitochondrial dysfunction but has subsequently also been associated with several diseases such as diabetes, cardiovascular diseases, chronic kidney disease (CKD), sarcopenia, and tumor-associated cachexia, as well as aging itself (see Conte et al., 2022 for a review [Conte et al., 2022]). Moreover, high serum FGF21 levels are present in patients with CKD and predict renal outcomes of diabetic patients (Yong et al., 2023), as well as major cardiovascular events in patients with stable angina (Ong et al., 2019), while sRAGE levels are increased in diabetic patients and correlate with all-cause mortality (Sabbatinelli et al., 2022), and they are associated with CKD (Steenbeke et al., 2022). As a whole, these biomarkers are indicative of important biological phenomena involved in aging and frailty, such as sarcopenia (GDF15, FGF21 [Conte et al., 2022]), inflammation and anti-inflammation (GDF15, sRAGE [Conte et al., 2022]), metabolism and body composition (GDF15, FGF21 [Conte et al., 2022]), and neurodegeneration and loss of cognitive function (GDF15, NfL [Chiariello et al., 2022; Giacomucci et al., 2022]). Consistently, these phenomena are current hotspots in the field of biomarker research for physical frailty, according to a recent study (Ginevičienė et al., 2024). This study has indeed identified numerous keyword clusters related to molecular mechanisms for frailty and sarcopenia. Among these, the largest clusters (ie most occurring keywords expression) were "muscle function, signaling pathway, myokines, proteomics, biomarkers" (86 out of 640 keywords), "health care, infectious diseases, immunology" (78), "Inflammation, aging, biomarkers" (71), "Cognition" (61), "Physical performance, immunology" (51). In Figure 1, the main clusters are shown (original elaboration of the data from Table 1 of Ginevičienė et al., 2024), together with the biomarkers that will be investigated within Spoke 3. As it is possible to see, by investigating these biomarkers, we will be able to get information on the most studied domains that affect frailty; we also foresee verifying the diagnostic and prognostic power of these biomarkers concerning other biological endpoints (e.g., mortality, cognitive decline, and disability).

Spoke 3 is focusing on the current hotspots of research for frailty and sarcopenia, but also MM, as the selected biomarkers are associated with multiple pathological conditions, as mentioned, and altogether they can provide information on the older person's "diseasome". Ideally, these biomarkers should have higher levels in multimorbid patients, where more diseases are present simultaneously, compared to patients suffering from a single disease. In this SPOKE, the Age-It consortium will investigate in different cohorts of geriatric subjects whether the selected biomarkers have the power to predict frailty, MM, and mortality, and whether this power increases when these biomarkers are considered all together and not individually. The consortium will take advantage of the fact that many cohorts of geriatric patients and older community-dwelling subjects (including centenarians) with a large set of clinical records (and in some cases a longitudinal follow-up) are available within the Age-It program. In addition to these markers, others that could emerge in the framework of other studies within Spoke 3 may possibly be tested (e.g., CXCL9, amyloid peptides). An international consensus on an effective validation model for markers of biological age is still missing, even though a series of recommendations has been recently provided (Moqri et al., 2024). The Age-It Program will be able to contribute to the validation of the aforementioned biomarkers (and possibly others), as it adopts the majority of Moqri's recommendations

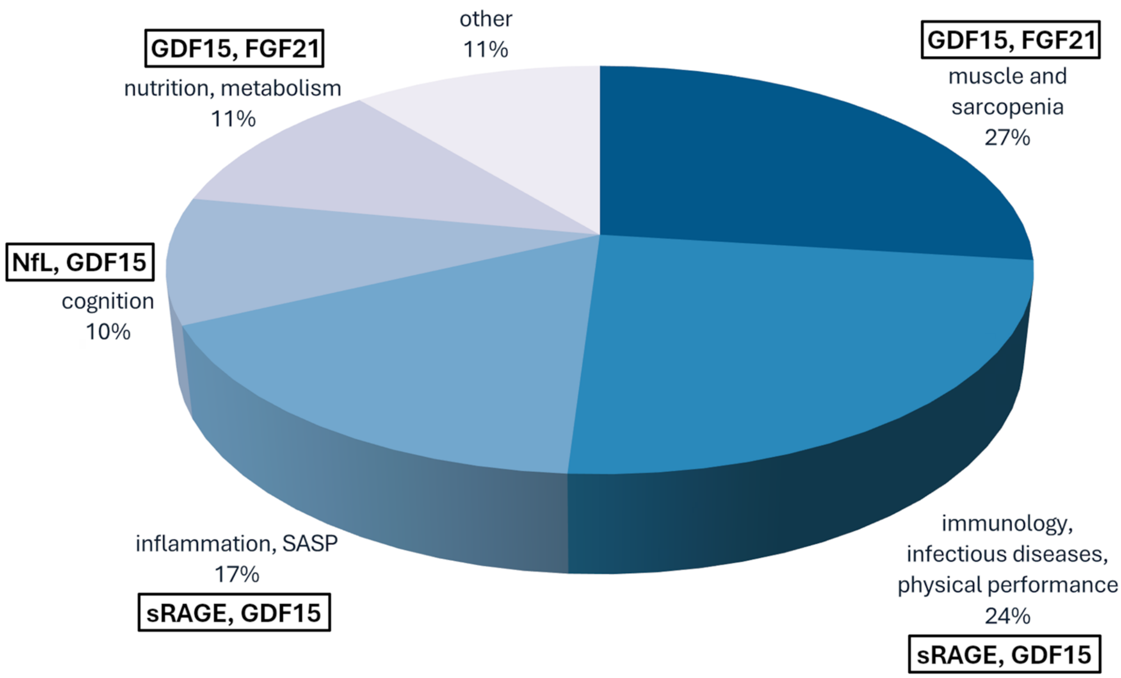

Figure 1. Main keyword clusters in Physical Frailty research (elaboration from Table 1 of Ginevičienė et al., 2024). The biomarkers considered in Age-It (in square) will cover the great majority of the domains (see text for references). FGF21 = Fibroblast Growth Factor 21; GDF15 = Growth Differentiation Factor 15; NfL = Neurofilament light chain; SASP = Senescence-Associated Secretory Phenotype; sRAGE = soluble Receptor for Advanced Glycation End-products.

(Moqri et al., 2024), in particular the aims will be: to include multiple diverse populations; to standardize and harmonize individual biomarker measurements and aging outcomes in different datasets; and to consider other important aging outcomes beyond mortality (i.e., frailty and MM).

The development of multidimensional risk stratification tools in complex older adults with multimorbidity and frailty using advanced statistical techniques and artificial intelligence

Multimorbidity and frailty pose a significant challenge for healthcare systems worldwide. The complex interplay of MM, polypharmacy, and frailty makes it difficult to predict health trajectories among older adults and to make effective and safe therapeutic choices (Zazzara et al., 2023). Risk stratification is crucial for enhancing the efficiency of care interventions targeting individuals with multimorbidity and chronic conditions, by enabling more precise allocation of resources and personalized care planning. In Italy, the Ministry of Health has emphasized the importance of risk stratification to identify population subgroups with different levels of healthcare needs and to tailor interventions accordingly (Italian Ministry of Health, Ministerial Decree n. 77/2022; Vinceti, 2023).

Risk assessment in older adults is particularly challenging because of the numerous and interacting dimensions, including physical, mental, psychosocial, economic, and environmental factors that can influence risks, especially among frail individuals with multiple chronic conditions. Traditional risk stratification methods that are based on evidence from clinical trials often fall short in adequately addressing the complexity of older adults. In fact, evidence-based medicine (EBM) traditionally relies on randomized controlled trials (RCTs) to inform clinical decision-making. However, RCTs often exclude frail older adults with MM, limiting the generalizability of their findings to this population (Crome et al., 2014). Moreover, findings from RCTs emphasize the relevance of relative risks, but these measures of effect do not capture the individual absolute risks of health outcomes that may largely differ across older adults due to their heterogeneous health profiles, diverse vulnerability to determinants of disease, and response to treatment (King et al., 2012). Alternative study designs, such as high-quality observational studies and pragmatic trials, have been recognized as valuable complements to traditional RCTs in assessing interventions for older adults. Recently, innovative analytical methods and AI are increasingly being employed for the development of risk stratification tools in older adults with complex health care needs (Choudhury et al., 2020). Such methods are applied to high-quality large datasets to provide insights into real-world effectiveness, account for the complexities of MM and frailty, and offer a sophisticated understanding of the interplay of the numerous determinants of health in this population.

The Age-It program provides an excellent ground to develop and validate multidimensional risk stratification tools by implementing innovative analytical techniques and machine learning (ML) based modelling. Indeed, large and high-quality datasets are available to researchers of the AGE-it consortium. Such sources provide information on sociodemographic, clinical, functional variables, and biological parameters that are also linked to healthcare resource utilization and mortality data. Innovative statistics such as latent class analysis (LCA), hierarchical clustering, and Bayesian networks can be applied to such multidimensional datasets to handle data with high dimensionality and heterogeneity and to identify hidden and complex patterns within the data (Becker et al., 2021).

Subgroups of older adults with similar risk profiles and propensity to develop specific outcomes can then be identified from a population of complex and heterogeneous individuals.

A further step towards the development of multidimensional risk stratification tools is the availability of AI-based methods that can be applied to the AGE-it data to develop and validate predictive algorithms. Supervised ML models, such as random forests, support vector machines, and neural networks, are particularly well-suited to analyze complex datasets, including a large variety of variables from numerous health dimensions. The value of applying AI-based methods to make predictions for multimorbid and frail older adults has been increasingly recognized. Several studies have employed ML-based methods to improve prognostication among older adults across a large spectrum of diseases or to predict the effectiveness of therapeutic interventions (Das & Dhillon, 2023; Hoogendijk et al., 2023). Machine learning algorithms have been shown to predict the probability of healthcare services utilization, including hospital care and readmissions, among older adults with frailty and complex chronic conditions (Mohanty et al., 2022). Very recently, ML models have also proven useful in predicting the onset of frailty over time (Leme & de Oliveira, 2023).

Innovative analytical methods and AI have accelerated research in the field of risk assessment and prognostication in older adults. Predictive models developed according to these methods appear to outperform traditional risk stratification tools, especially when applied to individuals with numerous biological, clinical, and social determinants of health that interact to influence the probability of a specific outcome (Liu et al., 2023). The availability of such innovative methods allows for the making of predictions from observational data, thus producing evidence that does not come from a predefined experimental ground but rather reflects the complexity of real-world experience, and it may be easily translated to clinical practice.

Moving from the need to improve risk prediction and provide effective interventions among the older population, and thanks to the availability of novel, sophisticated analytical methods, this activity of Spoke 3 aims to:

- Integrate information from multiple sources, including psychosocial, clinical, functional, and biological variables, to create comprehensive datasets for risk stratification tool development;
- Apply innovative analytical methods and AI to develop predictive algorithms and multidimensional risk stratification tools that take into account multiple determinants of health;
- Implement and validate the developed tools using available longitudinal cohorts of older adults with complex chronic conditions, frailty, and MM;
- Provide clinicians and policy makers with explainable multidimensional risk stratification tools to support decision-making and individual-centered interventions.

Strategies to manage multimorbidity in older patients

Healthcare systems are not currently designed to provide optimal management for older patients suffering from MM since the traditional medical approach is often inadequate for these patients. Indeed, Medicine, from medical education to healthcare delivery, has been increasingly dominated by the disease model, which focuses on the diagnosis and treatment of single diseases (Tinetti & Fried, 2004). Moreover, older subjects with MM have usually been excluded from clinical research as well as from clinical trials, so existing guidelines do not provide appropriate recommendations for multimorbid patients, and their implementation in patients with MM might be difficult, burdensome, and even dangerous (Tinetti et al., 2004).

On the contrary, the management of people suffering from MM might benefit from a comprehensive model of care that realizes service integration and the provision of coordinated care by multidisciplinary teams. Patient-centered care and shared decision-making have been advocated to set management goals that are acceptable to both the patient and the clinician, incorporating the priorities of patients in relation to treatments and health outcomes (Bierman et al., 2023).

The NICE guidelines (National Institute for Health and Care Excellence [NICE], 2016), the American Geriatrics Society Guiding Principles on the Care of Older Adults With Multimorbidity (Boyd et al., 2019), and the Italian guidelines on multimorbidity (Onder et al., 2022) share these principles. Furthermore, these documents suggest that it is conceivable that not all patients with MM need an approach to care that goes beyond the optimal management of their individual conditions. However, there is neither agreement nor evidence-based criteria to identify multimorbid patients who benefit from a tailored approach.

NICE guidelines identify such patients as those who find it difficult to manage their treatments or day-to-day activities, who receive care and support from multiple services and need additional services, who have both long-term physical and mental health conditions, who have frailty or falls, who frequently seek unplanned or emergency care, or who are prescribed multiple regular medicines (NICE, 2016). On the other hand, the American Geriatrics Society panel identifies older adults who need a tailored approach for MM as older adults with 2–10 years of life expectancy, an increasing number/severity of conditions, and impaired function (Boyd et al., 2019).

Strategies to improve the care of patients with MM could be provided at three different levels: the patient level, the provider level, and the organisation level (The Academy of Medical Sciences, 2018).

It is important to note that current scientific evidence provides limited support for the formulation of strong recommendations for any single strategy as an effective means to improve health outcomes in patients with MM (The Academy of Medical Sciences, 2018).

However, a recent overview of systematic reviews affirmed the possible benefit of current interventions that targeted patients directly, especially on mental, psychosocial, and general health outcomes (Zhou et al., 2023). In particular, among different interventions, exercise might play an important role in the management of patients suffering from MM (Bricca et al., 2020). A systematic review and meta-analysis of 23 RCTs showed that exercise interventions are safe, improve health-related quality of life (HRQoL), and objectively measured physical function while reducing depression and anxiety symptoms. However, a meta-regression showed that increasing age was associated with lower effect sizes of exercise for HRQoL, highlighting the need for further studies to elucidate the effectiveness of exercise in older age (Bricca et al., 2020).

Since several chronic conditions (e.g., hypertension, hyperlipidaemia, depression, diabetes mellitus, obesity, osteoarthritis, osteoporosis, and cardiovascular diseases) might benefit from physical activity programs that vary only minimally across the conditions, it has been suggested that multimorbid patients may benefit from a single standardized exercise prescription (de Souto Barreto, 2017).

Spoke 3 aims at developing optimal management strategies for multimorbid older patients. First, outcomes to be considered in interventions targeting multimorbid older patients, especially those with "complex" MM (e.g., those with frailty or disability), will be identified through a systematic literature review. Then these results will be discussed within a multidisciplinary panel, including patients and their organizations, to achieve a consensus on the preferred outcomes to consider in interventions targeting multimorbid older patients. Starting from the general recommendation made by the main national and international guidelines (Boyd et al., 2019; NICE, 2016; Onder et al., 2022), we aim at developing appropriate intervention strategies to delay progression or improve prognosis of older multimorbid patients that will be evaluated both using pre-existing available databases and implementing proof of concepts and/or pilot studies.

The impact of climate change and pollution on health in older adults

Climate change and air pollution are among the most pressing environmental challenges of our time, with profound implications for public health. Italy is on the front lines for such events, with significant health risks, especially for older adults. Average annual temperatures in Italy have risen by 1 °C in the last 100 years. In recent years, heatwaves with temperatures soaring past 40 °C (104 °F) have further exacerbated air pollution, particularly in critical areas such as the Po Valley, which is notorious for high levels of fine particulate matter (PM10 and PM2.5). The recent European Climate Risk Assessment report (No. 1/2024) highlighted the serious risks that climate change poses to human health, both at an individual level and through systemic risks to healthcare systems (European Environment Agency, 2024). The number of annual heat-related deaths in adults older than 65 years increased by 85% from 1991–2000 to 2013–2022 (Romanello et al., 2023). However, detailed considerations of disease-specific effects of climate change, particularly in older people, are sparse. Older adults are especially susceptible to the adverse effects of these phenomena due to their physiological vulnerabilities and the prevalence of chronic diseases and the related polypharmacy. Climate change can affect human health through direct effects such as changes in the normal temperature range (heatwaves or intense cold) and extreme weather events, as well as through indirect effects such as changes in air quality (air pollution, pollen, and allergens), which are themselves influenced by climate change (Gasparrini et al., 2015).

Heat-related illnesses range from mild heat exhaustion to severe heatstroke, which can be fatal. During heatwaves, older adults face an increased risk of dehydration, heat exhaustion, and heatstroke. Dehydration can lead to acute kidney injury, electrolyte imbalances, and worsened control of chronic diseases such as diabetes and heart disease (Gasparrini et al., 2015). Heatstroke, characterized by a body temperature above 40 °C (104 °F), can cause damage to the brain, heart, kidneys, and muscles. Without prompt treatment, heatstroke can result in permanent disability or death. Research shows that heatwaves significantly increase mortality rates among older adults. A study published in *The Lancet* reported that heatwaves in Europe between 2000 and 2009 were responsible for tens of thousands of excess deaths, with older adults accounting for the majority of these fatalities (Toulemon & Barbieri, 2008). Similarly, the 2003 heatwave in France caused an estimated 15,000 deaths, predominantly among older adults (Ballester et al., 2023). During the summer of 2022, the hottest season on record in Europe, 61,672 heat-related deaths (95% CI = 37,643–86,807) were observed, with the highest rates in Italy and other Mediterranean countries, particularly among the oldest individuals (Chen et al., 2024). Despite this, older persons have often been neglected in studies on the impact of climate change.

Air pollution, particularly fine particulate matter (PM2.5) and ground-level ozone, poses severe health risks (World Health Organization, 2024). Chronic exposure to air pollution has been linked to respiratory and cardiovascular diseases, which are prevalent in older populations. Emerging evidence also suggests a strong link between air pollution and neurological diseases. Fine particulate matter can penetrate the blood-brain barrier, leading to inflammation and oxidative stress in the brain. These processes are implicated in the development and progression of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. A study conducted by the University of Southern California found that older women living in areas with high levels of PM2.5 had a significantly higher risk of developing dementia, including Alzheimer's disease. Pollutants such as nitrogen dioxide (NO2) and ozone (O3) have also been associated with cognitive decline. Chronic exposure to these pollutants can impair cognitive functions and accelerate cognitive aging (Wang et al., 2023). For older adults, who may already be experiencing age-related cognitive decline, the additional burden of air pollution can significantly impact their quality of life and independence.

The combined effects of extreme temperatures and air pollution can be particularly harmful to older adults. During heatwaves, the concentration of ground-level ozone increases, exacerbating respiratory, and cardiovascular conditions. For older adults, this combination of heat and pollution poses a compounded risk. Studies have shown that mortality rates among older adults are higher on days with both high temperatures and high levels of air pollution (Zhou et al., 2023).

Understanding the interaction between the aging process, other concomitant factors such as air pollution exposure, and climate-related health risks is crucial for developing effective adaptation strategies to protect vulnerable populations and increase health resilience to changing climatic and environmental conditions. However, the number of studies focused on the influence of climate change on the risk of chronic conditions is still limited, particularly those studies attempting to identify molecular bridges between exposure and outcomes.

Spoke 3 aims to assess the impact of climate change and pollution on aging, focusing on health outcomes influenced by outdoor environmental factors. The program will involve activities to define the state of the art and collect climate and pollution data to integrate into health research. This will help understand their impact on: (1) clinical and functional trajectories, (2) clusters of age-related conditions and MM, and (3) clinical outcomes.

As a preliminary step, a systematic search of the literature on the relationship between climate change, pollution, and health in older subjects will be conducted to identify major issues, gaps, and areas requiring further research and action. Heterogeneous data sources will be integrated, and databases of aging Italian cohorts will be harmonized to analyse the combined influence of climate change, particularly heat-related stress and air pollution, on mortality, hospitalization, biological aging acceleration, frailty, and the incidence of major chronic diseases, with particular attention to MM. Fine mapping of climate and air pollution exposure will be obtained using satellite data and integrated through AI approaches.

Finally, existing literature and newly generated knowledge will be used to provide strategic recommendations for communities and policymakers to enhance resilience against climate change and pollution in the older population. These recommendations include improving urban infrastructure to reduce heat islands, increasing access to cooling centers, promoting adaptive behaviors such as staying hydrated and seeking cooler environments, training healthcare providers to recognize and treat heat-related illnesses and pollution-induced exacerbations of chronic conditions, and increasing public awareness through campaigns to educate older adults and their caregivers about the risks and preventive measures associated with extreme temperatures and pollution.

Conclusions

The health status of older adults is influenced by a variety of determinants that span from biological factors to the impact of climate change and air pollution. Delivering effective care for older adults is particularly challenging for those subjects with MM and frailty, due to the large heterogeneity of phenotypes and individual responses to treatments. Spoke 3 builds on these premises and offers the possibility to investigate determinants of health in older adults through an innovative interdisciplinary and multidimensional approach that is expected to identify relevant mechanisms of clinical and functional complexity and how they interplay. Acquiring a better understanding of MM and frailty, as well as of multidimensional determinants of health outcomes, will allow us to develop and test personalized care recommendations, ultimately enhancing the well-being and quality of life of older adults. Developing effective strategies to manage MM might increase the resilience of healthcare systems to the multiple challenges posed by the heterogeneity and complexity of older patients, eventually contributing to reducing negative outcomes, health services utilization, and healthcare-related costs.

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Conflict of interest

The authors have no commercial or financial relationships that could be construed as a potential conflict of interest to declare.

Author contributions

Licia Iacoviello, Rosa Liperoti, Patrizia Rovere Querini, Stefano Salvioli, Pasquale Abete, Massimiliano Fedecostante, Fabrizia Lattanzio, and Antonio Cherubini wrote and revised the manuscript.

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