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The heterogeneous approach to reach longevity: the experience of Italian centenarians

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People reaching old age are increasing exponentially in recent decades, and centenarians represent the fastest-growing group.
Aging is characterized by the continuous adaptation of the organism to life-long exposure to stress that leads to a relevant clinical complexity. It is reasonable to think that centenarians do not escape the physiological decline or the age-related diseases and syndromes, but the rate of such processes is slow enough to be counterbalanced by their increased capacity to respond to stresses.
Therefore, depending on the ability of each person to respond successfully or unsuccessfully to stressors, the aging process changes, leading to extremely heterogeneous phenotypes, particularly evident among centenarians.
In a cohort of Italian centenarians, the high heterogeneity in health status was well captured by means of the Frailty Index (FI) computed utilizing clinical variables. Surprisingly, in the same cohort, a FI computed utilizing biological variables showed average lower values and a narrower distribution than the clinical one. Interestingly, these centenarians showed higher blood free T4 (FT4) and thyroid-stimulating hormone (TSH) levels, and lower blood free T3 (FT3) levels and FT3/FT4 ratio than younger persons. Moreover, their endocrine profile was characterized by high adiponectin levels and insulin sensitivity, and low insulin growth factor-1 (IGF-1) and leptin levels.
Under these premises, studies on centenarians open a window to extreme longevity. Metabolic remodelling of these persons is suggestive of benefits that play a critical and positive role in shaping healthy aging.

Key words: longevity, centenarians, frailty, thyroid

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EPIDEMIOLOGY OF THE ITALIAN CENTENARIANS

The amount of people reaching old age is growing exponentially in the last decades. The last summary of the World Population Prospects indicates that the global population aged 65 years or above is projected to rise from 10 per cent in 2022 to 16 per cent in 2050. By 2050, the number of persons aged 65 years or over worldwide is projected to be more than twice the number of children under age 5 and about the same as the number of children under age 12. Because of the female advantage in life expectancy, women outnumber men at older ages in almost all populations.

Globally, women comprised 55.7 per cent of persons aged 65 or older in 2022, and their share will tend to decline slightly to 54.5 per cent by 2050 [1].
Regarding Europe, the number of very old people is projected to more than double between 2019 and 2050. In particular, the number of people aged 85 years or more will increase from 12.5 million in 2019 to 26.8 million by 2050, while the number of centenarians (people aged 100 years or more) is estimated to grow from 96,600 in 2019 to close to half a million by 2050 [2].
In Italy on January 1, 2022 there were estimated 20,159 persons 100 years old and over, of which 16,769 women (82.18%) [3]. After a steady growth until 2015, the number of centenarians has largely decreased as a result of the reduction in the birth rate during the First World War. The number has increased again starting from 2020.
Interestingly, semi-super centenarians (people aged 105 years or more) were 7,262 in the period from January 2009 to January 2021, registering a numerical increase of 135.8% during this period. Ninety per cent of these semi-super centenarians were women and those who reached 110 years of age were all female.
On the same date, the oldest person in Italy was resident in Lombardy and died in May 2022 at the age of 112 [3]. The regions with the highest centenarians' percentage respect to the total resident population are Liguria, Friuli-Venezia Giulia and Molise (0.5% in all the three regions).
Interestingly, centenarians seem to be concentrated in specific regions called "Blue Zones" [4]. These zones have been defined as "limited regions where the population shares a common lifestyle and environment and whose exceptional longevity has been accurately verified". A zone of Sardinia called "Ogliastra" is a "blue zone" showing a high concentration of centenarians compared to all the other regions of Italy.
Unlike the other groups of older persons, the centenarians and, in particular, the semi-super centenarians did not record an increase in the mortality rate during 2020, the year of the COVID-19 pandemic. Analysing the probability of death of this segment of the population from 2009 to 2020, it is noted that the number of deaths in the pandemic year is in line with that of past years [3].
These data confirmed those observed in a cohort of Japanese centenarians [5] and in a cohort of centenarians living in Belgium [6]. In the latest cohort, centenarians born before August 1, 1918, displayed a lower mortality risk than centenarians born later [6]. Two key events could justify the observed difference between centenarians born before and after second half of 1918: The World War I and the outbreak of the Spanish flu [6].

FRAILTY AND LONGEVITY

In centenarians, the physical and cognitive impairments are compressed towards the end of life, despite some of these persons had long histories of age-related diseases.
Under these premises, centenarians are persons with an extraordinary adaptive capacity and unusual functional reserve that allow them to live with debilitating (but not fatal) diseases and to delay the onset of disability for some decades [7].
In fact, aging is characterized by the continuous adaptation of the organism to life-long exposure to stress that finally leads to a relevant clinical complexity [8,9].
It is reasonable to think that centenarians do not escape the physiological decline or the age-related diseases or syndromes (i.e., frailty), but the rate of such processes is slow enough to be counterbalanced by their increased intrinsic capacity to respond to stresses of daily life (i.e., resilience) [10].
Depending on the ability of each person to respond successfully or not to stress factors, the aging process changes, thus leading to extremely heterogeneous phenotypes [11], particularly evident among persons of exceptional longevity [12,13].
Interestingly, the concept of frailty defines a condition characterized by increased vulnerability to stressors and reduced homeostatic reserves [14]. This condition is globally driven by the gradual, lifelong accumulation of molecular and cellular defects that impact on different organs and systems (e.g., skeletal muscle, brain, respiratory, cardiovascular, and endocrine systems) [14].
For all these reasons, frailty is an excellent indicator not only of the physiological decline of the individual but also of their biological age [15]. Regarding frailty, many operational approaches have been proposed over time to measure this condition [16,17]. Substantially, these approaches are constructed around two models: the frailty index (FI) [18] and the frailty phenotype [19].
In particular, the FI mirrors the biological age of the organism presenting the ratio of health deficits manifested by the individual at the end of a comprehensive geriatric assessment [15,20]. Instead, the frailty phenotype considers the physical decline of the individual as the cardinal sign of frailty [19,21].
Recent studies have demonstrated a high heterogeneity in centenarians' health status by the means of FI [12,22] confirming the categorization of these very old persons proposed some years ago by Evert and colleagues [13].
Indeed, a FI measured in a cohort of centenarians enrolled in Northern Italy and computed by the means of clinical variables that include signs, symptoms, disabilities and diseases [12], showed a relatively wide range of values, despite the narrow range of age, demonstrating

its capability to capture different degrees of frailty also in centenarians [12]. In particular, this cohort of centenarians showed a frailty prevalence of 91% (FI value > 0.25), a median FI value of 0.50 and a broad spectrum of FI values ranging from 0.13 to 0.73 [12].
A clinical FI is also able to significantly predict self-rated health and Instrumental Activities of Daily Living (IADL) dependency beyond the effect of age and gender in a cohort of Chinese centenarians [23].
Interestingly, in the Northern Italy cohort, a FI built on biological parameters showed average lower values (median value of 0.33) and a narrower distribution (from 0.11 to 0.69) than the clinical one [24].
The data observed in these centenarians are amazing, if we consider that in older persons the biological FI generally shows higher values than those of the clinical FI, since biological FI anticipates the changes in health status before the manifestation of the clinical deficits [25,26].
On the contrary, in centenarians the lowest values of biological FI suggest that their biology could be "better" than clinical manifestations and that centenarians could benefit from exceptional biological reserves that may be underestimated by the clinical appearances.

STRESS RESPONSE AND STRATEGIES FOR AGING BETTER AND LIVING LONGER

The two facets of aging are represented on one side by patients with age-associated diseases, in which inflammation plays a pathogenic role [27], and on the other side by centenarians, who delayed or avoided such diseases [11]. Moreover, the capability to respond to stress is known to play a critical role in the majority of age-related diseases.
In 2008, Mattson [28] introduced the key concept of *hormesis*, defined as 'a process in which exposure to a low dose of a chemical agent or environmental factor that is damaging at higher doses induces an adaptive beneficial effect on the cell or organism'. Consistently, many studies have shown that a mild, chronic stress can have a beneficial effect on the body's components, tissues and organs [29,30].
From this background, it is possible to identify new strategies to tailor the trajectories of aging by focusing on modifiable environmental factors, such as lifestyle. Many data on the main components of lifestyle, in particular nutrition and physical activity, are available. Recent studies showed that it is possible to improve health indicators affecting lifespan by modulating the timing of food consumption [31]. Beneficial effects of intermittent periods with no or very low energy intake involve the phenomenon of hormesis in which exposure of cells and organisms to a mild stress results in adaptive responses that protect against more severe stress [31]. Franceschi and colleagues [32] demonstrated that centenarians usually respect very regular meat timing and maintain regular circadian rhythms. A recent cross-sectional study on nonagenarians and centenarians from Abruzzo [33] highlighted the importance of an early dinner and a calorie restriction lapse of 17.5 hours between dinner and the following lunch. Moreover, the daily caloric restriction lapses in association with high consumption of vegetables and physical activity lead to a reduced nocturnal postprandial stress and an improved metabolic response in centenarians from Abruzzo [33]. Interestingly, in a cohort of centenarians born in Northern Italy from 1899 to 1908, the nutritional biological indices (i.e., albumin and total cholesterol) and anthropometric parameters (i.e., body mass index, waist circumference and hand grip strength) overlapped with those observed in adults who followed caloric restriction regimens. Therefore, although centenarians never followed a specific caloric restriction paradigm throughout their long life, a condition of caloric restriction without malnutrition was reported [34]. Furthermore, the Mediterranean diet seems to exert its healthy effects as a form of chronic hormetic stress, due to the ability of its component (i.e., vitamins, fibers, phytochemicals, lipid and carbohydrates) to maintain an optimal balance between pro- and anti-inflammaging [35].
Within the frame of NU-AGE randomized trial (NCT01754012, clinicaltrials.gov), the participants in the individually tailored dietary intervention arm showed a tendency toward global cognitive improvements after the 1-year intervention, but these changes were not significant when compared to the control group [36]. Moreover, a recent study suggested that a 1-year Mediterranean-like-nutritional intervention can promote epigenetic rejuvenation in older persons [37].
Based on the results from the EU FP7-SME Project RISTOMED (new E-services for a dietary approach to the elderly), it has been hypothesized that the adherence to the Mediterranean diet combined with a low rate of air pollution can explain the low rate of mortality and morbidity of the centenarians to COVID-19 in Southern Italy [38,39]. Indeed, centenarians have a remarkable capacity to recover after coronavirus infection, as confirmed in a group of centenarians belonging to the "Centenari a Trieste" study [40]. From this perspective, the human leukocyte antigen (HLA) locus, one of the major genetic regions associated with human longevity, seems to be crucial in influencing susceptibility and severity of COVID-19 [41].
In addition to nutrition as a possible intervention factor to promote healthy aging, it is widely accepted that also physical activity may represent a protective factor for cardiovascular and neurodegenerative diseases [42,43].

Indeed, a study conducted on Guangxi Province in China found that physical activity and cognition are associated with Activity of Daily Living (ADL) independence in centenarians [44]. Moreover, physical activity was the most significant predictor for both ADL and IADL independence [44-46].
Overall, these studies showed that nutrition and physical activity have a number of beneficial effects on mechanisms that have been selected by evolution to successfully adapt the organism to the ever-changing environment.

HETEROGENEITY OF THYROID FUNCTION IN CENTENARIANS

Among the mechanisms aimed at maintaining the body homeostasis, stress response, metabolic adaptation as well as inflammation/inflammaging seem to play a prominent role [47].
From a metabolic point of view, during aging there is a remodelling of the endocrine system that particularly involves the thyroid gland. This gland produces the well-known thyroid hormones, i.e., 3,3′,5-triiodothyronine (T3) and 3,3′,5,5′-tetraiodothyroxine (T4). Moreover, T4 is also peripherally converted to the active T3 form by 5′-deiodinases.
In the oldest old, the thyroid function is particularly complex and heterogeneous. This is probably due to the concomitant presence of several confounding variables and mild thyroid diseases occurring during aging. Under these perspectives, a population of 672 older persons (centenarians, semi-supercentenarians, centenarian's offspring and age-matched older persons) were characterized with a focus on the study of thyroid function through the dosage of blood free T3 (FT3), free T4 (FT4) and thyroid-stimulating hormone (TSH). The study showed that FT3 levels and FT3/FT4 ratio decreased, while FT4 and TSH levels increased in an age-dependent manner. Interestingly, in centenarians and semi-supercentenarians higher FT4 levels and lower FT3/FT4 ratio were associated with an impaired functional status and a shorter survival [48]. Another study described a relevant association between thyroid hormone levels and frailty in centenarians. Indeed, a negative correlation between FI and FT3, FT3/FT4 ratio and TSH, and a positive association between FI and FT4 have been observed [49]. Other studies reported a relevant decrease of FT3 or T3 levels in centenarians [50,51].
Although the progressive decline of thyroid function observed during aging could be considered as an adaptive strategy to survive longer by reducing metabolism rate and oxidative stress, this event may contribute to functional disability [52]. Indeed, thyroid hormones have several beneficial effects on cellular development, growth and metabolism. However, a preserved local T3 concentration through an efficient peripheral T4 to T3 conversion may have a beneficial effect in assuring a better functional capability and remarkable longevity [53].

OTHER BIOLOGICAL MECHANISMS IN CENTENARIANS

As reported in the previous paragraph, centenarians seem to be less prone to oxidative stress than non-long-lived persons [54,55]. Indeed, their portfolio shows a peculiar immunological, endocrinological and metabolic profile, that exerts a protection against oxidative stress and inflammaging [27,56].
Therefore, in centenarians, the functional status of thyroid gland may have adapted against an excessive catabolism determining a reduction in metabolism rate, oxidative stress and cell senescence [57].
In fact, other than a preserved local T3 concentration [53], the metabolism of centenarians is characterized by a well-maintained glucose handling and insulin sensitivity, while data concerning the growth hormone (GH)/insulin-like growth factor-1 (IGF-I) axis are controversial [58]. Indeed, a lower circulating IGF-1 bioactivity was overserved in centenarians and centenarians' offspring, and a better insulin sensitivity was found in centenarians compared to controls [59]. In addition, centenarians showed lower leptin and higher adiponectin levels than older subjects [60].
Interestingly, the endocrine profile of centenarians characterized by high adiponectin levels and insulin sensitivity, as well as low IGF-1 and leptin levels, is comparable to that of persons in caloric restriction. Hence, taking into account the ability of caloric restriction to prevent or postpone several age-related diseases and to increase lifespan in mammals, these data suggest the potential impact of the endocrine system in extending lifespan [61,62].
It should be noted that the development of omics technologies, combined with data modelling and visualization methods, has made it possible to identify other specific longevity signatures by lipidomics [63,64], glycomics [27], metagenomics [65] and metabolomics [66]. In this regard, methylome [67,68], transcriptome [69] and proteome analyses [70] have been widely used to calculate the biological age [71] of people to compare with the chronological one.
For example, different epigenetic clocks based on DNA methylation (DNAm) levels found in sets of CpG sites throughout the genome [68,72] were used to calculate biological age. In this regard, centenarians and semi-supercentenarians were epigenetically younger than

expected and showed a high variability in the predicted epigenetic age [73-75].

Surprisingly, in an Italian cohort of centenarians neither the FI nor the DNAm estimators were associated with age [76]. Once again, this result might be explained by the heterogeneous health status of these persons compressed within a narrow range of chronological age [12]. Interestingly, in this study the FI was not associated with any of the DNAm age estimators nor with the DNAm age acceleration values [76-78].

An alternative epigenetic approach consists into measurement of the miRNA levels as powerful epigenetic markers to trace successful aging [79]. The results demonstrated that centenarians seem to manifest a particular miRNA profile that differs from that of septuagenarians [80] due to a more preserved miRNA biogenic pathway [81].

CONCLUSIONS AND PERSPECTIVES

Studies on centenarians open a window to extreme longevity. Metabolic remodelling of these very old persons is suggestive of cognitive benefits, improved antioxidant capacity, and lower inflammation, all of which play a critical and positive role in shaping healthy aging. Immune and stress responses constitute an integrated and evolutionarily conserved defence network [8]. Interestingly, the progressive decline in thyroid function during aging could be considered an adaptive strategy to survive longer by reducing the metabolism rate and the oxidative stress.

In these perspectives, metabolomics in combination with metabolite analysis can bring to light the changes in the relationship between metabolites that occur during human life and how these interactions affect the phenotype and the function of individuals' aging.

However, because of the highly complex network of factors influencing individual trajectories, the development of appropriate tools and solutions that systematically model biological information related to the maturation, maintenance and degeneration of our body's functions becomes crucial.

The overall data on centenarians may suggest new strategies for tailoring aging trajectories by focusing on modifiable environmental factors, particularly nutrition and physical activity.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

AB, GV: conceptualization; BA, DM, GV: writing; EF: editing. All authors have read and agreed to the published version of the manuscript.

Ethical consideration

Not applicable.

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