Ital J Gender-Specific Med 2020; 6(3): 107-117

# Gender differences in cognitive decline in centenarians and the oldest old

Elisa Bientinesi, Daniela Monti

Department of Experimental and Clinical Biochemical Science "Mario Serio", University of Florence, Italy. *Received 17 July 2019; accepted 14 November 2019.*

**Summary.** The increase in human life expectancy is a worldwide phenomenon, and the oldest old and centenarians are the segment of the elderly population that is increasing the fastest. A remarkable gender difference in life expectancy and mortality, including survival to extreme age, has been demonstrated by many studies. In a population who is getting older, dementia is one of the major age-related diseases that cause disability and dependency. Thus, the study of the oldest old and centenarians might help evaluate whether cognitive impairment is an inevitable event that occurs in ageing. Indeed, although the prevalence of cognitive impairment in centenarian studies varies widely, some of them (about 20%) preserve cognitive function and, even among those who show cognitive impairment at 100 years of age, approximately 90% delay the onset of clinically evident dementia. Moreover, considering that among the oldest old and centenarians the number of women is greater than that of men, the study of gender differences regarding the cognitive status in these subjects could help identify protective and/or non-protective biological, social and behavioral factors. This review summarizes the gender differences in cognitive impairment in the oldest old and the centenarians, focusing on some of the factors involved in the onset of dementia, such as inflammaging, apolipoprotein E (APOE) genotype, and depression.

**Key words.** Centenarians, cognitive status, gender, oldest old.

***Differenze di genere nel declino cognitivo dei centenari e dei grandi anziani***

**Riassunto.** L'aumento dell'aspettativa di vita è un fenomeno mondiale, che vede soprattutto il rapido aumento del numero dei grandi anziani e dei centenari. Molti studi hanno dimostrato che c'è un'importante differenza di genere sia nella mortalità sia nell'aspettativa di vita, inclusa la sopravvivenza fino a un'età estrema. Nel contesto di una popolazione che sta invecchiando, la demenza è una delle principali malattie legate all'età che causano disabilità e dipendenza. Pertanto, lo studio dei grandi anziani e dei centenari potrebbe aiutare a valutare se il deterioramento cognitivo è un evento che si verifica inevitabilmente durante l'invecchiamento. Infatti, anche se negli studi sui centenari la prevalenza del deterioramento cognitivo varia ampiamente, si nota che alcuni di essi (circa il 20%) preservano la funzione cognitiva, e che anche tra coloro che mostrano deficit cognitivi, circa il 90% riesce a ritardare l'insorgenza di una demenza clinicamente evidente. Inoltre, considerando che il numero di donne tra i grandi anziani e i centenari è maggiore rispetto a quello degli uomini, lo studio delle differenze di genere in merito allo stato cognitivo di questi individui potrebbe portare all'identificazione di fattori biologici, sociali e comportamentali protettivi e/o non protettivi. Questa revisione riassume le differenze di genere nel deterioramento cognitivo dei grandi anziani e dei centenari, focalizzandosi su alcuni fattori coinvolti nell'insorgenza della demenza, come il genotipo dell'apolipoproteina E (APOE), l'*inflammaging* e la depressione.

**Parole chiave.** Centenari, stato cognitivo, genere, grandi anziani.

## Introduction

The increase in human life expectancy and the consequent ageing of the population are two of the main socio-economic burdens that will have to be managed over the next years. The increase in the number of elderly subjects who are potentially affected by major age-related diseases – together with the scarcity of public resources to be allocated to social security and public health – are already creating a socio-political problem. As of January 1, 2019, 13.8 million of Italians were over 65 years of age (22.8%), and 2.2 million were over 85 (3.6%). These numbers will continue to increase, and it is estimated that in twenty years the over 65s will represent 31.6% of the Italian population. In particular, the percentage of over-85 subjects has grown by 1.1 percentage points compared to 2009, and it is estimated that in the next twenty years it will increase by 147%. Furthermore, Italy – together with France – holds the European record of the largest number of centenarians alive: over 14,000 in 2019, compared to 11,100 in 2009.[1] It is also well known that, among the elderly, women are the most represented.[2,3] In Italy, men are only 32.3% of the over 85s population (the oldest old), and 17% of the centenarians[2]. A similar condition is observed in Europe,[3] as showed in Figure 1.

Women's life expectancy at 65 years of age is greater than men's (22.4 and 19.3 years, respectively),[1] although in advanced age their quality of life is worse, due to increased disability and degenerative diseases.[4] The pat-

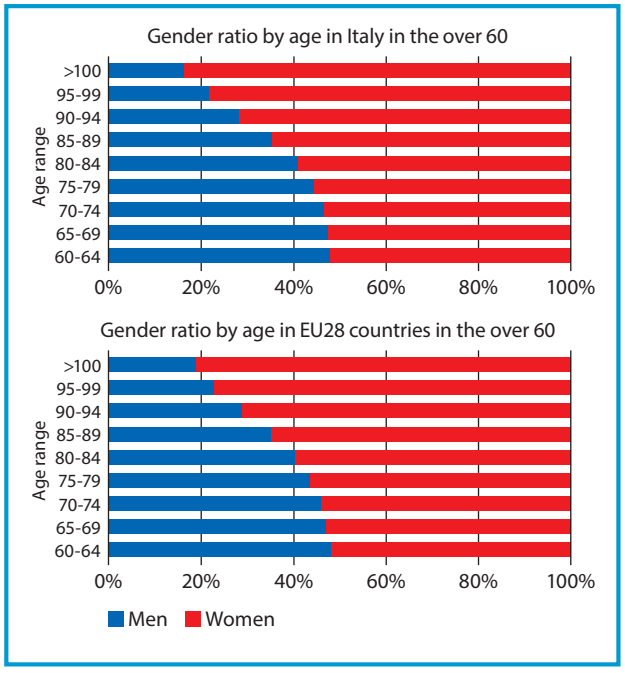


**Figure 1.** Gender ratio by age in Italian and EU28 European population over 60. The data reported for Italy is based on the age of the resident population as of January 1, 2018, according to ISTAT[2]. The data available for the EU28 countries is based on the age of the population as of January 1, 2018, according to EUROSTAT.[3]

tern observed in Italy is very similar to that found in the other European countries: women have a survival advantage, but the average life span free from disability is practically the same with respect to men (64.2 and 63.5 years, respectively).[5] This means that the longer life expectancy gained by women consists of more years of disease and disability, the so-called female-male health-survival paradox.[6] This remarkable gender difference in life expectancy and mortality, including survival to an extreme age, is a worldwide phenomenon. The basic biological mechanisms responsible for gender differences in ageing and longevity are quite complex, and still poorly understood.

In the context of a population that is getting older, one of the major age-related diseases is dementia, which causes disability and dependency, also with a strong impact on families. Dementia is a general term to indicate all the syndromes involving a progressive decline of the cognitive functions, which leads to a reduced ability to perform everyday activities. This definition includes a wide variety of diseases that primarily or secondarily affects the brain, like Alzheimer's disease (AD) or vascular dementia.[7] Globally, it has been observed that the prevalence of dementia increases from 2-3% among 70/75-year-old subjects to 20-25% among the over 85s.[8] Moreover, in 2016, dementia became the 5$^{th}$ cause of death, while in 2000 it had been the 14$^{th}$.[9] In Italy, AD or other types of dementia affect 4.7% of the elderly, and to a greater extent over-80 women (14.2% vs 7.1% of their male peers).[10]

Since advanced age is the main risk factor for dementia,[11,12] studying the oldest old – and the centenarians in particular – might help evaluate whether cognitive impairment is an inevitable event occurring with ageing. In addition, considering that among the oldest old and the centenarians the number of women is greater than that of men,[13,14] analyzing the gender difference regarding the cognitive status in these subjects can help identify the gender protective and/or non-protective biological, social and behavioral factors which may be relevant in cognitive impairment and dementia. In this context, we will analyze the gender differences in some of the most significant factors that could affect the onset of dementia in the oldest old and the centenarians, such as inflammaging, apolipoprotein E (APOE) genotype, and depression.

## Cognitive status and gender differences in the centenarians and the oldest old

The studies on human longevity show that lifespan trajectories are influenced by gender, due to a combination of sexual/biological/behavioral features, social role, and life experiences.[15] Thus, the biological mechanisms underlying gender differences in ageing are the result of a mutual interaction between genetics/epigenetics, the environment and the anthropological culture characterizing the role of men and women within society.[15,16] In Italy, the data published by ISTAT in 2018 reported a positive life expectancy trend, compared with the previous years; life expectancy reached 80.8 years for men, and 85.2 years for women.[1] Moreover, centenarians and the oldest old represent the fastest-growing segment of the older population. Since age is the major risk factor for the development of dementia,[11,12] due to the lifespan increase the number of subjects affected by cognitive impairment is growing. In addition, women are more affected by dementia (AD and vascular dementia) than men, showing a more frequent and rapid decline of their cognitive function with ageing.[15] In 2018, in the EU (28 countries) the prevalence of dementia among the over 60s increased in an age-dependent manner, always maintaining the female rate higher than the male, with the gender gap becoming wider with ageing,[17] as shown in Figure 2.

Although the age increase is the strongest indicator of the risk for cognitive decline and dementia, these conditions do not seem an inevitable consequence of ageing. The mere existence of cognitively healthy individuals over the age of 110 (mostly females)[18-21] leads to the intriguing idea that the incidence of dementia might decelerate in late life. Although the prevalence of cognitive impairment

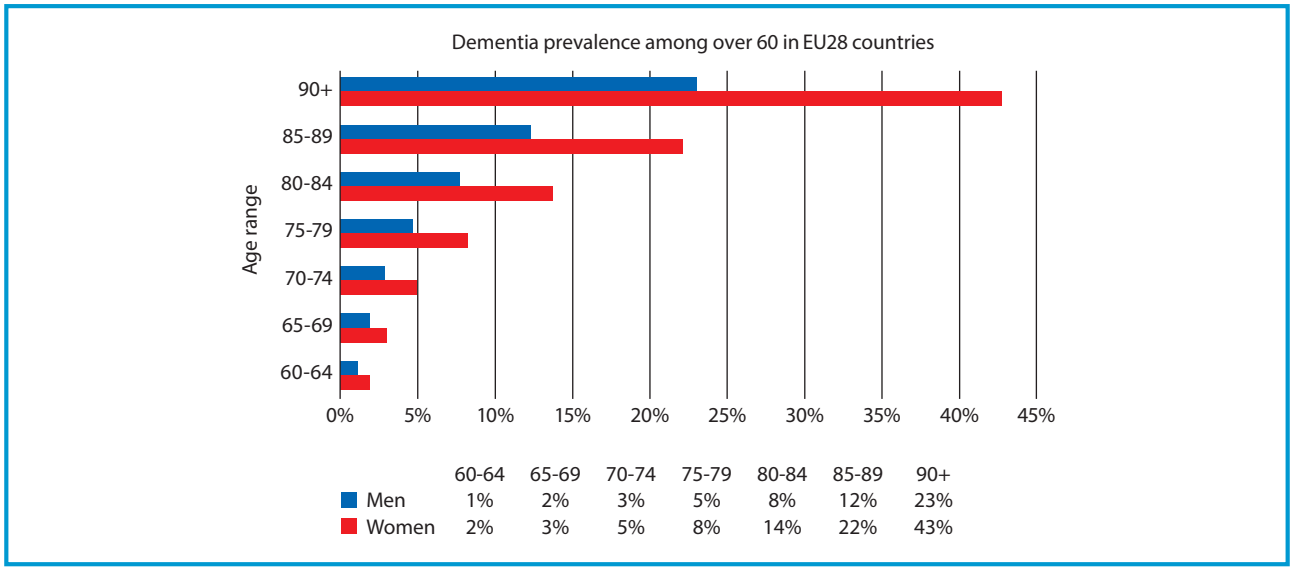


**Figure 2.** Prevalence of dementia among the over 60s and impact of gender in age groups, based on OECD 2018 data.[17]

in centenarian studies varies widely,[11] some of the subjects (15-20%) preserve their cognitive function and, even among those who show cognitive impairment at 100 years of age, in approximately 90% of the onset of clinically evident dementia is delayed until the average age of 92.[22] In addition, systematic reviews of studies with large samples of centenarians, including supercentenarians (>110), indicate that males are more likely to be cognitively unaffected than females.[11,20] It may seem a paradox that male centenarians are more mentally healthy than females, whereas females have a much greater probability of surviving to an extreme old age. A possible explanation is that women, having a major capability of remodeling, are much better equipped to survive with age-related diseases than men, and the mortality associated with these conditions is higher in men. The result is a select survivor effect by which, with respect to women, men who survive to extreme ages tend not to suffer from the diseases and the associated impairments that cause mortality at younger ages.[20]

The studies on the dementia prevalence rate in the oldest old and the centenarians are more complex, and the results are frequently conflicting. We can speculate that the reasons could depend on the reduced number and the heterogeneity of the subjects analyzed, for instance the inclusion of only healthy volunteers, and/or the exclusion of the unhealthiest, or on the difficulty in enrolling subjects who live in nursing homes.[23] Furthermore, not all the studies demand adequate proof of age, a problem particularly relevant for the researches who deal with centenarians and supercentenarians.[24] In addition, there are some methodological biases due to the lack of standardized and validated tests to assess the cognitive function of these individuals, who have reached extreme ages.[11] Furthermore, the accumulation of age-related comorbidities – such as visual deficits, hearing loss, reduced resilience and illiteracy – could make it difficult to carry out the Mini-Mental State Examination (MMSE), one of the most commonly used test for the assessment of the cognitive function, as reported in many studies.[25-27] This is a difficult topic, due to the heterogeneity of the subjects, which increases with age, as well as to the recently accepted opinion that brain ageing is characterized by a continuum between a 'normal/physiological' decline of the cognitive ability with age and severe dementia.[28] For all these reasons, the study of the cognitive status in the oldest old and the centenarians has not received all the attention this subject deserves.

However, several studies on the centenarians and the oldest old[29-34] have been conducted, and they seem to confirm the aforementioned male-female health-survival paradox, showing a prevalence of women, albeit presenting worse physical and cognitive conditions. Table 1 summarizes the main studies evaluating the gender differences in the cognitive status of the centenarians and the oldest old.

On the whole, available data has shown that women are the most represented among the oldest old and the centenarians. However, they are significantly more prone than men to have physical dysfunction and dementia, presenting a more severe cognitive impairment, and a worse quality of life.[29-31,34] An interesting cross-sectional study on 699 Chinese oldest old and centenarians showed that the prevalence of cognitive impairment in women was higher than in men (72.8% and 42.1%, respectively). Furthermore, the Authors demonstrated that the individuals with cognitive impairment were usually

**Table 1.** Main studies evaluating the prevalence of cognitive impairment by gender in the centenarians and the oldest old

| Study | Age range (years) | No. of subjects | | | Prevalence of cognitive impairment | | | Assessment method |
|---|---|---|---|---|---|---|---|---|
| | | Total | Women | Men | Total (%) | Women (%) | Men (%) | |
| Tokyo study[29] | 100-107 | 304 | 239 | 65 | 61.8 | 67.4* | 41.5 | CDR (score 1-5) MMSE |
| Mugello study[30] | 90-95 | 486 | 354 | 132 | 56.2 | 62.7* | 38.6 | MMSE |
| Leisure World Cohort Study[31] | 90-106 | 911 | 701 | 210 | 41.2 | 45.2* | 27.6 | MMSE, CASI-short, DQ, DSRS/ FAQ/ADL |
| Dujiangyan study[32] | ≥ 90 | 699 | 471 | 228 | 62.8 | 72.8%* | 42.1 | MMSE (score < 18) |
| Greece study[33] | ≥ 100 | 489 | 376 | 113 | 19 | 22%* | 10 | Unspecified questionnaire |
| The Chinese Longitudinal Healthy Longevity Survey (CLHLS)[34] | 65-79<br>80-116 | 4063<br>9523 | 1906<br>5533 | 2157<br>3990 | 2.04<br>25.7 | 2.2#<br>32.9* | 1.9<br>15.7 | CMMSE |
| Georgia study phase III[26] | 98-108 | 241 | 198 | 43 | 77.6 | 77%# | 79% | GlobDetScale |
| Rotterdam study[35] | 55-106<br>85-106 | 7528<br>709 | 4589<br>573 | 2939<br>136 | 6.3<br>34.8 | 7.9#<br>35.6# | 3.8<br>31.6 | DSM III-R |
| Northern Italy study[36] | 100-107 | 92 | 56 | 36 | 61.9 | 69.6# | 50 | DMS-IV MMSE |

* indicates a significant difference ($p < 0.01$) between women and men with regard to the prevalence of cognitive impairment.

# indicates a non-significant difference.

A review of the literature was conducted using PubMed database with the following keywords: "centenarians, oldest old, dementia and gender or sex differences". The search included articles published in the English language between January 1998 and December 2019.

Abbreviations: Clinical Dementia Rating (CDR); Mini-Mental State Examination (MMSE); Cognitive Assessment Screening Instrument-Short Version (CASI-short); Dementia Questionnaire (DQ); Informant Questionnaire that combines information from Dementia Severity Rating Scale (DSRS), Functional Activities (FAQ), and Activities of Daily Living (ADL); Chinese Mini-Mental State Examination (CMMSE); Global Deterioration Scale (GlobDetScale); Diagnostic and Statistical Manual of Mental Disorders Third Edition, Revised (DSM III-R); Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).

older, and were more likely to come from families with lower functioning scores, underlining that severe family dysfunction was an important determinant factor for cognitive impairment.[32] A study conducted on 489 Greek centenarians showed that dementia affected only 19% of participants, but the proportion of women with dementia was significantly higher than that of men (22% and 10%, respectively). Overall, Greek centenarian women showed to be less autonomous, with less social life, and only 5% of them were classified as being "in an optimal condition", vs 9% of men.[33] Finally, a population-based study on the prevalence of dementia showed that women obtained a significantly higher Global Deterioration Scale (GlobDetScale) score compared to men (4 and 3.5, respectively), which indicated a higher severity of dementia.[26] However, it is interesting to note that when men and women were divided into 3 groups by dementia severity, gender difference – where present – became marginal and non-significant.[26] Also, in other studies a gender difference in dementia prevalence did not even emerge.[35,36]

In conclusion, the majority of the studies suggest that women with increasing age present worse health conditions, which seems to be a worldwide phenomenon.

### *Inflammaging and cognitive status*

One of the main characteristics of ageing is an inflammatory response called 'inflammaging' (or *inflammageing*).

This condition progressively worsens in an age-dependent manner, and in the elderly is related to the onset of age-associated diseases and mortality.[13,37] This low-grade, chronic, sterile and persistent inflammation is supported by several processes, such as cellular senescence, immunosenescence and others,[38] and leads to slow tissue degeneration. It has also been shown that neurodegenerative diseases, as well as AD and Parkinson's disease (PD), have an inflammatory pathogenesis.[39] However, it is interesting to note that also centenarians, despite having reached the extreme limits of life avoiding – or recovering from – major age-related diseases (such as diabetes, cancer, and cardiovascular disease),[13] do not evade inflammaging, showing elevated levels of proinflammatory molecules.[40] Recently, it has been evidenced that the centenarians and the oldest old are able to induce, as an adaptive strategy, an anti-inflammatory response to compensate the damage accumulated over time, and the consequent age-related physiological decline.[41,42] Hence, they probably present a slower and more limited inflammaging compared with the general population.[13] In this context, centenarians represent a valid model to investigate the risk factors and gender differences in relation to cognitive impairment. Several pieces of evidence show that, albeit with gender differences, inflammatory biomarkers, such as IL-6 or C-reactive protein (CRP), undergo more phenotypic and genotypic alterations in older subjects compared with the younger.[15] In a context where the inflammatory status may affect the onset and development of cognitive impairment, Kravitz et al. evaluated in the oldest old (90-105) the association between the C-reactive protein (CRP) level (a nonspecific marker of inflammation) and the risk of dementia.[43] The Authors found that, in subjects with undetectable CRP levels, the MMSE score was unusually higher compared with subjects with elevated CRP levels. Moreover, a greater proportion of people with elevated CRP levels suffered from severe cognitive impairment. The association between detectable or elevated level of CRP and an increase in the odds for all-cause dementia reached the statistical significance, particularly in women.[43] A study on Danish centenarians showed that the plasma level of proinflammatory Tumour Necrosis Factor α (TNFα) was significantly higher in these subjects than in the younger ones.[44] The TNFα concentration positively correlated with plasma concentration of IL-6, Tumor Necrosis Factor Receptor 2 (TNFR2), and CRP.[44] In addition, the Authors have also shown that the increase in the plasma level of TNFα correlated with cognitive impairment. In fact, subjects with moderate or severe dementia had a significantly higher level of TNFα vs non-demented individuals.[44]

Lio et al. studied in a group of Italian centenarians, the relations between -1082 GG genotype, which is associated with and increased production of anti-inflammatory cytokine IL-10, and the genotypic frequencies of the TNF-α promoter SNPs 308G, which is associated with a low TNF-α production.[45] The Authors found that there were no differences between centenarians and younger controls with respect to the frequencies of the TNF-α promoter SNPs 308G, while the number of male centenarians homozygous for the -1082 GG genotype was significantly higher compared with the younger controls. Moreover, the study showed that in male centenarians there was a significant increase of the "anti-inflammatory" genotype combination (IL-10-1082 GG/TNF-α-308 GG) with respect to the controls, while female centenarians showed a pattern resembling their younger controls.[45] The proinflammatory cytokine IL-6 is considered the main cytokine of the central nervous system[46] related to the progression and severity of AD.[47] Adriaensen et al. evaluated in subjects aged 80 or older the serum levels of 14 inflammatory proteins considered risk factors for functional decline.[48] The study showed that only the serum level of IL-6 increased significantly with the severity of the functional decline, although no significant gender differences were found.[48]

Bonafè et al. studied the IL-6 promoter genetic variability at the -174 C/G locus and its effect on IL-6 serum levels in elderly people, including centenarians, and demonstrated that the subjects who are genetically predisposed to produce high levels of IL-6 during ageing, i.e. C- men at the IL-6 -174 C/G locus, have a reduced ability to reach the extreme limits of the human lifespan. On the other hands, the ability to produce low levels of IL-6 throughout the life span (C+ individuals) appears to be beneficial for longevity, at least in men. Compared to men, women experience high IL-6 serum levels later in life, and the age-related increase in the IL-6 serum levels in women is quite independent of the -174 C/G locus activity.[49] This gender difference could be due to the estrogen inhibitory tone on the IL-6 gene expression,[50] but an effect on so long a term is rather questionable. These data were supported by the analysis of the whole-genome peripheral blood mononuclear cell gene expression in nonagenarian men and women. The study identified 62 transcripts whose expression levels were significantly correlated with the plasma IL-6 levels in men, whereas no correlations were observed in women, suggesting that inflammaging could occur differently in nonagenarian men and women.[51]

Thus, it is intriguing that the presence of an "anti-inflammatory" genotype is significantly increased in male centenarians. However, more studies are needed to clarify and investigate the role of inflammatory gender differences – especially in the oldest subjects – in promoting or protecting through the instauration of a harmful

environment, leading to worse cognitive functions and dementia.

*Apolipoprotein E, gender, and cognitive impairment*

The apolipoprotein E gene (APOE)[52] has been recognized as the most important gene associated with longevity, and it is also widely studied in relation to the prevalence of dementia. The APOE gene presents three functional alleles, ε2, ε3, and ε4. The ε3 allele is the most common, and accounts for 60-90% of allelic variations, while ε2 and ε4 are rarer, with a frequency of 0-20% and 10-20%, respectively. In AD or in mild cognitive impairment (MCI), as well as in healthy subjects, carriers of APOEε4 display worse cognitive performance compared to non-carriers.[53,54] It is known that APOEε4 is a susceptibility factor for dementia[55], and in particular for the early and late onset of AD,[56] and its impact differs according to age.[57] A negative effect of APOEε4 is observed in the middle age,[58,59] while some evidence showed that it is not present in the young and the oldest old subjects.[60-63] The oldest old are 'selected survivors', characterized by both a lower presence of risk factors and a larger presence of protective factors, or due to the fact that other causes of impairment during ageing may mask the effect of the APOE genotype.[53] A long-lasting controversy in the literature concerns the possible antagonistic pleiotropic effects of the ε4 allele of the APOE gene, thus conferring to the individual advantages on cognitive tasks early in life, but cognitive and neural disadvantages at a more advanced age.[64,65] Recently, Ferri et al.[66] studied a large number of centenarians versus well-characterized controls and AD patients, all from the same geographical area. The results indicate that the APOE gene seems to affect the risk of developing AD, but not the chance to become a centenarian.[66] In the European project Genetics of Healthy Aging (GEHA), which includes a large group of Italian nonagenarian sibling pairs, the variants of the APOE gene locus were closely associated with longevity.[67] Conversely, the APOE gene did not show a significant association with the longevity trait in data generated by the means of a genome-wide analysis of 333 centenarians and 773 geographically-matched healthy individuals.[68] Several studies did not find any association between APOEε4 itself and the incidence of dementia in initially non-demented oldest-old women and men,[61,69-72] nor with mortality after the age of 90.[70,71,73] The study on Finnish centenarians suggested that, in the extreme limits of life, having an allele ε4 does not necessarily lead to dementia, but it could accelerate the dementia process.[72] In addition, several studies did not find any gender differences while evaluating the association between APOEε4 and the incidence of dementia.[69-71] On the contrary, it was shown that the presence of APOEε4 was significantly associated with the prevalence – and not the incidence – of dementia in women only,[70] and that female APOEε4 carriers with dementia achieved a lower MMSE score than those without the allele.[61] In Japanese centenarian women, the APOEε4 allele and a low education seem to be associated with a more severe cognitive impairment versus male centenarians, suggesting that a gender effect can also be present with regard to APOE genetics.[74]

All these studies suggest that the analysis of the genetic risk/protective factors that might influence the development of dementia and AD in the oldest old and the centenarians is quite difficult, and produces controversial results, due to the presence of confounding factors. Indeed, social status,[32,33] life experiences,[33,75,76] geographical origin,[77,78] as well as ageing itself,[12] and the biological features[79-82] – that are peculiar in these subjects – can interact with each other, thereby affecting the onset of the disease, and possibly masking or emphasizing the influence of genetic factors. The gender difference in the association between genetic risk factors and dementia need to be clarified, with the intent to identify and minimize the influence of any confounding factor.

*Depression, gender and cognitive impairment*

Over the last years, scientists have evaluated a possible association between gender and depression in relation to the incidence of dementia and AD in the oldest old. Depression symptoms and cognitive impairment are common in older adults, and often coexist within the same individual. Furthermore, late-life depression is now a recognized risk factor for cognitive decline and dementia, in particular for AD and vascular dementia.[83]

Depression is one of the major mental disorders that affect the health and quality of life of older adults, as well as of young subjects. In Italy, the prevalence of this disorder increases in an age-dependent manner, from 5.8% in subject aged 34 to 65, to 14.9% among the over 65s, and to 19.5% among the over 80s. In addition, depression – as well as dementia – also shows a higher prevalence in women than in men, especially in the over 65s (19.2% and 9.5%, respectively).[10] This gender gap is even more evident among the over 80s, where female prevalence reaches 23.5% vs 12.7% in men.[10] The relation between depression symptoms and dementia or cognitive impairment is not still clear, and needs to be further investigated. The majority of the studies indicates as a risk factor the presence of depression symptoms in older people; others consider them as part of the preclinical phase of AD.[84-86] Furthermore, gender differences are controversial in the oldest old.[87]

Studies performed by Ribeiro on Portuguese centenarians showed that subjects in an early dementia stage

had an increase in the odds of depression compared to the control. It is worth noting that no gender difference emerged.[88]

Moreover, a longitudinal study on older American subjects showed that the oldest old are more likely to suffer from persistent or worsened depression symptoms. Additionally, it is important to point out that the subjects presenting a very low risk of developing depression symptoms are mostly men with a high educational level, no social isolation, and no dementia.[89] Studies by Dal Forno et al. proved that a history of depression symptomatology is a significant risk factor for dementia, but only for men.[90] Instead, a prospective study in oldest old women indicated that only 19% of women with a Geriatric Depression Scale (GDS)[91] score of 6 or more had a normal cognitive status 5 years later, compared with 46% of those with a GDS score lower than 6.[92] In the oldest old women, the presence of elevated depression symptoms is an important risk factor for the development of cognitive impairment.

## Conclusion

The increase in human life expectancy is a worldwide phenomenon, and the number of oldest old and centenarians has been growing tremendously over the past few decades. Numerous studies have shown a remarkable gender difference in life expectancy and mortality, including survival up to an extreme age. In an ageing population, dementia is one of the major age-related diseases causing disability and dependency. In this context, we have critically reviewed the literature on the gender differences in cognitive impairment in the oldest old and centenarians, focusing on some of the factors involved in the onset of dementia, such as inflammaging, apolipoprotein E (APOE) genotype, and depression, reaching the following main conclusions:

I. the cognitive assessment of the oldest old and the centenarians is methodologically complex. Indeed, most of the data available in the literature have been obtained using tools which are not validated for such growing segment of the human populations, and which often do not take into due account their particular characteristics, as well as fatigue, a sensory impairment that could interfere with the outcomes of the cognitive tests. There is an urgent need to identify new tools for the study of this population;
II. centenarians are extremely heterogeneous with regard to their cognitive status, dementia is not inevitable in the oldest old, and cognitive capabilities show remarkable gender differences. Centenarian women outnumber centenarian men, who however usually benefit from a better physical and cognitive health. This observation is a gender paradox still difficult to explain. One of the possible explanation is that women are much better able to survive with age-related diseases than men, having a superior ability to remodel and adapt. Men have the capacity to cope with the challenges of old age up to a breaking point, whereupon they die, while women are more flexible and are able to adapt and survive. The result is a select survivor effect by which, in comparison with women, men who survive to an extreme age tend to not suffer from the diseases and the associated impairments that cause mortality at younger ages;
III. despite having reached the extreme limits of life avoiding – or recovering from – major age-related diseases,[13] centenarians do not evade inflammaging. Recently, it has been demonstrated that centenarians have also elevated levels of anti-inflammatory cytokines,[93] which counterbalance the negative effects of inflammaging. Moreover, gender differences in secreted pro- and anti-inflammatory cytokines have also been evidenced. In the oldest old, a significant association between the markers of inflammation and the risks of dementia has been demonstrated,[43] and such association reaches a significance particularly in women.[43] Male centenarians present a significant increase in the 'anti-inflammatory' genotype combination (IL-10 -1082GG/TNF-α -308GG); in addition, the capability of producing low levels of IL-6 throughout their life span (C+ individuals, at -174 C/G locus IL-6 promoter) appears to be beneficial for longevity, at least in men;[45]
IV. APOE has been recognized as the most important gene associated with longevity:[52] the analysis of its impact on successful ageing has produced controversial results, and its effects on gender-related longevity and the onset and development of dementia still have to be clarified. Nevertheless, some pieces of evidence show that, only in oldest old women, APOEε4 was significantly associated with the prevalence of dementia,[70] as well as with a worse cognitive performance versus female non-carriers.[61] However, several studies did not show any association nor any gender difference between APOEε4 and the incidence of dementia in oldest old women and men,[70-73] underlining the fact that the debate on the role of APOE in longevity and dementia is still open. The sexual dimorphism of APOEε4 in subjects over the age of 90 would also be a major problem to address, especially in a society with a high number of elderly individuals. However, it is very difficult to evaluate the effects of APOEε4 independently from other factors, such as a low education level, whose interaction with the APOEε4 gene appear to be associated with a greater cognitive impairment in centenarian women than in men. The current findings suggest that the effects of cultural and living conditions can interact

with each other, thereby affecting the onset of the disease possibly masking or emphasizing the influence of genetic factors, and should be carefully analyzed, in order to better understand the impact of the gene on the cognitive function in the centenarian and the oldest old;

V. depression is an important personality-related mental disorder, to be taken into account when evaluating the cognitive status of the oldest old, especially in relation to gender differences. Depression shows a higher prevalence in women than in men, especially in the over 80s, and the presence of elevated depression symptoms is an important risk factor for the development of cognitive impairment.

Overall, data from the literature suggest that a low education level, APOEε4, and the symptoms of depression play a key role in the cognitive decline of the oldest old women. Furthermore, a variety of evidence indicates that, with increasing age, women present a worse health status than men, and that the interaction of many factors – such as genetics/epigenetics, environment and the anthropological culture that characterize the role of men and women within society – is crucial (Figure 3).

In conclusion, it would be advisable to include gender medicine in the researches on the oldest old and centenarians, in order to complete our understanding of the main mechanisms of ageing, as well as the differences in prevention, care, treatment, evolution and outcomes of non-communicable diseases in both genders.

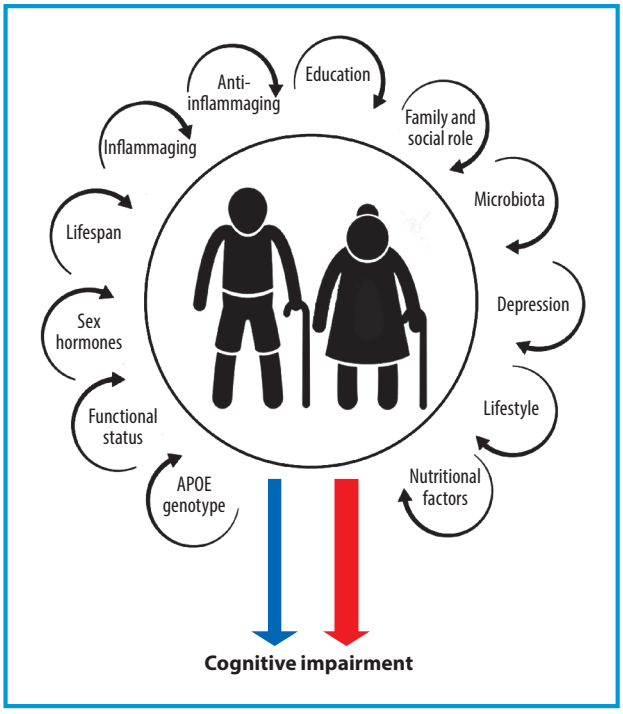


**Figure 3.** Main factors impacting cognitive decline in centenarian men and women. References: APOE genotype,[53-57,70,74] Functional status,[27,29,33] Sex hormones,[15,79] Lifespan,[11,12] Inflammaging,[37-39,43,44] Anti-inflammaging,[41,42,45] Education,[26,35,74,76] Family and social role,[32,33] Microbiota,[80-82] Depression,[83,90,92] Lifestyle,[33] Nutritional factors.[42,75]

**Key messages**

- Human life expectancy and the number of the oldest old are rapidly increasing worldwide. Several studies suggest that women present a worse health condition with increasing age.
- An advanced age is the main risk factor for dementia. Alzheimer's and other cognitive impairments are more frequent in women over 90.
- The studies on the prevalence rate of dementia in the oldest old and the centenarians are more complex, and the results are frequently conflicting. Methodological biases, in part due to the lack of standardized tests to assess the cognitive function of these individuals, have been identified.
- Low education level, gender, APOEε4 and symptoms of depression are associated with the cognitive decline in the oldest old women.
- Inflammaging could play a role in the higher susceptibility to dementia of centenarian women. An 'anti-inflammatory' profile is significantly increased in male centenarians.

## References

1. Italian National Institute of Statistics (ISTAT) [Internet]. Demographic indicators. 2019. Available from: https://www.istat.it/en/archivio/226922
2. Italian National Institute of Statistics (ISTAT) [Internet]. Resident population on 1 January. 2018. Available from: http://dati.istat.it/Index.aspx?QueryId=18460#
3. Statistical office of the European Union (EUROSTAT) [Internet]. Population on 1 January by age and sex. 2018. Available from: https://ec.europa.eu/eurostat/web/products-datasets/-/DEMO_PJAN
4. Van Oyen H, Nusselder W, Jagger C, Kolip P, Cambois E, Robine J-M. Gender differences in healthy life years within the EU: an exploration of the "health-survival" paradox. Int J Public Health. 2013;58:143-55.
5. Statistical office of the European Union (EUROSTAT) [Internet]. Healthy life years at birth. 2016. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php/Healthy_life_years_statistics
6. Oksuzyan A, Juel K, Vaupel JW, Christensen K. Men: good health and high mortality. Sex differences in health and aging. Aging Clin Exp Res. 2008;20:91-102.
7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed. Arlington. 2013.
8. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, et al. Global prevalence of dementia: a Delphi consensus study. Lancet. 2005;366:2112-7.

9. World Health organization (WHO) [Internet]. The top 10 causes of death. 2018. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
10. Italian National Institute of Statistics (ISTAT). Mental health at various stages of life years 2015-2017. 2018.
11. Arosio B, Ostan R, Damanti S, Ronchetti F, Arcudi S, Scurti M. Cognitive status in the oldest old and centenarians: a condition crucial for quality of life methodologically difficult to assess. Mech Ageing Dev. 2017;165:185-94.
12. Kravitz E, Schmeidler J, Beeri MS. Cognitive decline and dementia in the oldest-old. Rambam Maimonides Med J. 2012;3:e0026.
13. Franceschi C, Bonafè M. Centenarians as a model for healthy aging. Biochem Soc Trans. 2003;31:457-61.
14. Hagberg B, Alfredson BB, Poon LW, Homma A. Cognitive functioning in centenarians. Journals Gerontol Ser B. 2001;56:P141-51.
15. Ostan R, Monti D, Gueresi P, Bussolotto M, Franceschi C, Baggio G. Gender, aging and longevity in humans: an update of an intriguing/neglected scenario paving the way to a gender-specific medicine. Clin Sci. 2016;130:1711-25.
16. Ostan R, Monti D, Franceschi C. Gender and longevity. Ital J Gender-Specific Med. 2015;1:10-4.
17. Organisation for Economic Co-operation and Development (OECD/EU) [Internet]. Health at a glance: Europe 2018: State of health in the EU cycle. 2018. p. 108-9. Available from: https://doi.org/10.1787/health_glance_eur-2018-en
18. den Dunnen WFA, Brouwer WH, Bijlard E, Kamphuis J, van Linschoten K, Eggens-Meijer E, et al. No disease in the brain of a 115-year-old woman. Neurobiol Aging. 2008;29:1127-32.
19. Jeune B, Robine J-M, Young R, Desjardins B, Skytthe A, Vaupel JW. Jeanne Calment and her successors. Biographical notes on the longest living humans. In: Maier H et al (eds), Supercentenarians. Berlin-Heidelberg: Springer; 2010. p. 285-323.
20. Andersen SL, Sebastiani P, Dworkis DA, Feldman L, Perls TT. Health span approximates life span among many supercentenarians: compression of morbidity at the approximate limit of life span. J Gerontol A Biol Sci Med Sci. 2012;67:395-405.
21. Robine JM, Jagger C. What do we know about the cognitive status of supercentenarians? In: Finch CE, Robine JM, Christen Y (eds), Brain and longevity. Berlin-Heidelberg: Springer; 2003. p. 145-52.
22. Perls T. Dementia-free centenarians. Exp Gerontol. 2004;39:1587-93.
23. Brodaty H, Woolf C, Andersen S, Barzilai N, Brayne C, Cheung KS-L, et al. ICC-dementia (International Centenarian Consortium - dementia): an international consortium to determine the prevalence and incidence of dementia in centenarians across diverse ethnoracial and sociocultural groups. BMC Neurol. 2016;16:52.
24. Young RD, Desjardins B, McLaughlin K, Poulain M, Perls TT. Typologies of extreme longevity myths. Curr Gerontol Geriatr Res. 2010;2010:423087.
25. Engberg H, Christensen K, Andersen-Ranberg K, Jeune B. Cohort changes in cognitive function among Danish centenarians: a comparative study of 2 birth cohorts born in 1895 and 1905. Dement Geriatr Cogn Disord. 2008;26:153.
26. Poon LW, Woodard JL, Stephen Miller L, Green R, Gearing M, Davey A, et al. Understanding dementia prevalence among centenarians. J Gerontol A Biol Sci Med Sci. 2012;67:358-65.
27. Ravaglia G, Forti P, Maioli F, Boschi F, Cicognani A, Bernardi M, et al. Determinants of functional status in healthy Italian nonagenarians and centenarians: a comprehensive functional assessment by the instruments of geriatric practice. J Am Geriatr Soc. 1997;45:1196-202.
28. Ojo JO, Rezaie P, Gabbott PL, Stewart MG. Impact of age-related neuroglial cell responses on hippocampal deterioration. Front Aging Neurosci. 2015;7:57.
29. Gondo Y, Hirose N, Arai Y, Inagaki H, Masui Y, Yamamura K, et al. Functional status of centenarians in Tokyo, Japan: developing better phenotypes of exceptional longevity. Journals Gerontol Ser A Biol Sci Med Sci. 2006;61:305-10.
30. Padua L, Pasqualetti P, Coraci D, Imbimbo I, Giordani A, Loreti C, et al. Gender effect on well-being of the oldest old: a survey of nonagenarians living in Tuscany: the Mugello study. Neurol Sci. 2018;39:509-17.
31. Corrada MM, Brookmeyer R, Berlau D, Paganini-Hill A, Kawas CH. Prevalence of dementia after age 90. Neurology. 2008;71:337-43.
32. Wang B, He P, Dong B. Association between family functioning and cognitive impairment among Chinese nonagenarians/centenarians. Geriatr Gerontol Int. 2015;15:1135-42.
33. Stathakos D, Pratsinis H, Zachos I, Vlahaki I, Gianakopoulou A, Zianni D, et al. Greek centenarians: assessment of functional health status and life-style characteristics. Exp Gerontol. 2005;40:512-8.
34. Miyawaki CE, Liu M. Gender differences in cognitive impairment among the old and the oldest-old in China. Geriatr Gerontol Int. 2019;19:586-92.
35. Ott A, Breteler MMB, Harskamp F Van, Claus JJ, Cammen TJM Van Der. Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam study. BMJ. 2007;310:970-3.
36. Ravaglia G, Forti P, De Ronchi D, Maioli F, Nesi B, Cucinotta D, et al. Prevalence and severity of dementia among northern Italian centenarians. Neurology. 1999;53:416-8.
37. Franceschi C, Bonafè, Massimiliano Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G. Inflammaging: an evolutionary perspective on immunosenescence. Ann NY Acad Sci. 2006;908:244-54.
38. Salvioli S, Monti D, Lanzarini C, Conte M, Pirazzini C, Bacalini MG, et al. Immune system, cell senescence, aging and longevity-inflamm-aging reappraised. Curr Pharm Des. 2013;19:1675-9.
39. Frank-Cannon TC, Alto LT, McAlpine FE, Tansey MG. Does neuroinflammation fan the flame in neurodegenerative diseases? Mol Neurodegener. 2009;4:47.
40. Baggio G, Donazzan S, Monti D, Mari D, Martini S, Gabelli C, et al. Lipoprotein(a) and lipoprotein profile in healthy centenarians: a reappraisal of vascular risk factors. FASEB J. 1998;12:433-7.
41. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. Journals Gerontol - Ser A Biol Sci Med Sci. 2014;69:S4-9.

42. Cevenini E, Monti D, Franceschi C. Inflamm-ageing. Curr Opin Clin Nutr Metab Care. 2013;16:14-20.
43. Kravitz BA, Corrada MM, Kawas CH. Elevated C-reactive protein levels are associated with prevalent dementia in the oldest-old. Alzheimers Dement. 2009;5:318-23.
44. Bruunsgaard H. A high plasma concentration of TNF-α is associated with dementia in centenarians. Journals Gerontol - Ser A Biol Sci Med Sci. 1999;54:357-64.
45. Lio D, Scola L, Crivello A, Colonna-Romano G, Candore G, Bonafé M, et al. Inflammation, genetics, and longevity: further studies on the protective effects in men of IL-10 -1082 promoter SNP and its interaction with TNF-alpha -308 promoter SNP. J Med Genet. 2003;40:296-9.
46. Erta M, Quintana A, Hidalgo J. Interleukin-6, a major cytokine in the central nervous system. Int J Biol Sci. 2012;8:1254-66.
47. Brosseron F, Krauthausen M, Kummer M, Heneka MT. Body fluid cytokine levels in mild cognitive impairment and Alzheimer's disease: a comparative overview. Mol Neurobiol. 2014;50:534.
48. Adriaensen W, Matheï C, Vaes B, van Pottelbergh G, Wallemacq P, Degryse J-M. Interleukin-6 predicts short-term global functional decline in the oldest old: results from the BELFRAIL study. Age (Omaha). 2014;36:9723.
49. Bonafè M, Olivieri F, Cavallone L, Giovagnetti S, Mayegiani F, Cardelli M, et al. A gender-dependent genetic predisposition to produce high levels of IL-6 is detrimental for longevity. Eur J Immunol. 2001;31:2357-61.
50. Villa A, Vegeto E, Poletti A, Maggi A. Estrogens, neuroinflammation, and neurodegeneration. Endocr Rev. 2016; 37:372-402.
51. Nevalainen T, Kananen L, Marttila S, Jylhä M, Hervonen A, Hurme M, et al. Transcriptomic and epigenetic analyses reveal a gender difference in aging-associated inflammation: the Vitality 90+ study. Age (Omaha). 2015;37:76.
52. Deelen J, Beekman M, Uh H-W, Helmer Q, Kuningas M, Christiansen L, et al. Genome-wide association study identifies a single major locus contributing to survival into old age; the APOE locus revisited. Aging Cell. 2011;10:686-98.
53. Fan J, Tao W, Li X, Li H, Zhang J, Wei D, et al. The contribution of genetic factors to cognitive impairment and dementia: apolipoprotein E gene, gene interactions, and polygenic risk. Int J Mol Sci. 2019;20:1177.
54. Farlow MR, He Y, Tekin S, Xu J, Lane R, Charles HC. Impact of APOE in mild cognitive impairment. Neurology. 2004;63:1898-901.
55. Bang OY, Kwak YT, Joo IS, Huh K. Important link between dementia subtype and apolipoprotein E: a meta-analysis. Yonsei Med J. 2003;44:401-13.
56. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA. 1997;278:1349-56.
57. Kim J, Park S, Yoo H, Jang H, Kim Y, Kim KW, et al. The impact of APOE ε4 in Alzheimer's disease differs according to age. J Alzheimer's Dis. 2018;61:1377-85.
58. Lancaster C, Tabet N, Rusted J. The APOE paradox: do attentional control differences in mid-adulthood reflect risk of late-life cognitive decline. Neurobiol Aging. 2016; 48:114-21.
59. Liu F, Pardo LM, Schuur M, Sanchez-Juan P, Isaacs A, Sleegers K, et al. The apolipoprotein E gene and its age-specific effects on cognitive function. Neurobiol Aging. 2010;31:1831-3.
60. Bunce D, Ihle A, Bunce D, Kliegel M. APOE ε 4 and cognitive function in early life: a meta-analysis APOE ε 4 and cognitive function in early life: a meta-analysis. Neuropsychology. 2012;26:267-77.
61. Bathum L, Christiansen L, Jeune B, Vaupel J, McGue M, Christensen K. Apolipoprotein E genotypes: relationship to cognitive functioning, cognitive decline, and survival in nonagenarians. J Am Geriatr Soc. 2006;54:654-8.
62. Schultz MR, Lyons MJ, Franz CE, Grant MD, Boake C, Jacobson KC, et al. Apolipoprotein E genotype and memory in the sixth decade of life. Neurology. 2008;70:1771-7.
63. Welsh-Bohmer KA, Østbye T, Sanders L, Pieper CF, Hayden KM, Tschanz JT, et al. Neuropsychological performance in advanced age. Influences of demographic factors and apolipoprotein E: findings from the Cache County Memory Study. Clin Neuropsychol. 2009;23:77.
64. Han SD, Bondi MW. Revision of the apolipoprotein E compensatory mechanism recruitment hypothesis. Alzheimer's Dement. 2008;4:251-4.
65. Albin RL. Antagonistic pleiotropy, mutation accumulation, and human genetic disease. Genetica. 1993(91): 279-286.
66. Ferri E, Gussago C, Casati M, Mari D, Rossi PD, Ciccone S, et al. Apolipoprotein E gene in physiological and pathological aging. Mech Ageing Dev. 2019;178:41-5.
67. Beekman M, Blanché H, Perola M, Hervonen A, Bezrukov V, Sikora E, et al. Genome-wide linkage analysis for human longevity: genetics of healthy aging study. Aging Cell. 2013;12:184-93.
68. Giuliani C, Sazzini M, Pirazzini C, Bacalini MG, Marasco E, Ruscone GAG, et al. Impact of demography and population dynamics on the genetic architecture of human longevity. Aging (Albany NY). 2018;10:1947-63.
69. Skoog I, Hesse C, Aevarsson O, Landahl S, Wahlström J, Fredman P, et al. A population study of apoE genotype at the age of 85: relation to dementia, cerebrovascular disease, and mortality. J Neurol Neurosurg Psychiatry. 1998;64:37-43.
70. Corrada MM, Paganini-Hill A, Berlau DJ, Kawas CH. Apolipoprotein E genotype, dementia, and mortality in the oldest old: the 90+ Study. Alzheimers Dement. 2013;9:12-8.
71. Juva K, Verkkoniemi A, Viramo P, Polvikoski T, Kainulainen K, Kontula K, et al. APOE epsilon4 does not predict mortality, cognitive decline, or dementia in the oldest old. Neurology. 2000;54:412-5.
72. Sobel E, Louhija J, Sulkava R, Davanipour Z, Kontula K, Miettinen H, et al. Lack of association of apolipoprotein E allele epsilon 4 with late-onset Alzheimer's disease among Finnish centenarians. Neurology. 1995;45:903-7.
73. Skoog I, Hesse C, Aevarsson O, Landahl S, Wahlstrom J, Fredman P, et al. A population study of apoE genotype at the age of 85: relation to dementia, cerebrovascular disease, and mortality. J Neurol Neurosurg Psychiatry. 1998;64:37.
74. Ishioka YL, Gondo Y, Fuku N, Inagaki H, Masui Y, Takayama M, et al. Effects of the APOE ε4 allele and education

on cognitive function in Japanese centenarians. Age (Dordr). 2016;38:495-503.
75. Hai S, Cao L, Yang X, Wang H, Liu P, Hao Q, et al. Association between nutrition status and cognitive impairment among chinese nonagenarians and centenarians. Int J Gerontol. 2017;11:215-9.
76. Skoog J, Backman K, Ribbe M, Falk H, Gudmundsson P, Thorvaldsson V, et al. A longitudinal study of the mini-mental state examination in late nonagenarians and its relationship with dementia, mortality, and education. J Am Geriatr Soc. 2017;65:1296-300.
77. Hallman DM, Boerwinkle E, Saha N, Sandholzer C, Menzel HJ, Császár A, et al. The apolipoprotein E polymorphism: a comparison of allele frequencies and effects in nine populations. Am J Hum Genet. 1991;49:338-49.
78. Singh PP, Singh M, Mastana SS. APOE distribution in world populations with new data from India and the UK. Ann Hum Biol. 2006;33:279-308.
79. Boss L, Kang DH, Bergstrom N, Leasure JL. Endogenous sex hormones and cognitive function in the elderly. Aging Clin Exp Res. 2015;27:515-21.
80. Ticinesi A, Tana C, Nouvenne A, Prati B, Lauretani F, Meschi T. Gut microbiota, cognitive frailty and dementia in older individuals: a systematic review. Clin Interv Aging. 2018;13:1497-511.
81. Roy Sarkar S, Banerjee S. Gut microbiota in neurodegenerative disorders. J Neuroimmunol. 2019;328:98-104.
82. Santoro A, Ostan R, Candela M, Biagi E, Brigidi P, Capri M, et al. Gut microbiota changes in the extreme decades of human life: a focus on centenarians. Cell Mol Life Sci. 2018;75:129-48.
83. Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF, 3rd. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. Br J Psychiatry. 2013;202:329-35.
84. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease. Arch Gen Psychiatry. 2006;63:530.
85. Berger AK, Fratiglioni L, Forsell Y, Winblad B, Bäckman L. The occurrence of depressive symptoms in the preclinical phase of AD: a population-based study. Neurology. 1999;53:1998-2002.
86. Wilson RS, Mendes De Leon CF, Bennett DA, Bienias JL, Evans DA. Depressive symptoms and cognitive decline in a community population of older persons. J Neurol Neurosurg Psychiatry. 2004;75:126-9.
87. Bergdahl E, Gustavsson JMC, Kallin K, von Heideken Wågert P, Lundman B, Bucht G, et al. Depression among the oldest old: the Umeå 85+ study. Int Psychogeriatrics. 2005;17:557-75.
88. Ribeiro O, Duarte N, Teixeira L, Paúl C. Frailty and depression in centenarians. Int Psychogeriatrics. 2017;30:1-10.
89. Xiang X. Seven-Year trajectories of depressive symptoms and their predictors among older Americans. J Aging Health. 2019; Jun 6;898264319852835.
90. Dal Forno G, Palermo MT, Donohue JE, Karagiozis H, Zonderman AB, Kawas CH. Depressive symptoms, sex, and risk for Alzheimer's disease. Ann Neurol. 2005;57:381-7.
91. Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS) Jerome. Clin Gerontol. 1986;5:165-73.
92. Spira AP, Rebok GW, Stone KL, Kramer JH, Yaffe K. Depressive symptoms in oldest-old women: risk of mild cognitive impairment and dementia. Am J Geriatr Psychiatry. 2012;20:1006-15.
93. Franceschi C, Capri M, Monti D, Giunta S, Olivieri F, Sevini F, et al. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. Mech Ageing Dev. 2007;128:92-105.

*Funding:* this study was supported by University of Florence and CR Firenze Foundation, Grant n. 24213 (2018.1015) to DM.

*Author contribution statement:* EB wrote the manuscript and DM reviewed the draft manuscript. Both Authors read and approved the final manuscript.

*Conflict of interest statement:* the Authors declare no conflicts of interest.

*Correspondence to:*
Daniela Monti
Department of Experimental and Clinical Biochemical Science "Mario Serio"
University of Florence
Viale Morgagni 50
50134 Florence - FI, Italy
email daniela.monti@unifi.it