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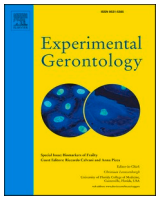

Review article

The biological roots of the sex-frailty paradox

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ABSTRACT

Aging is a dynamic process that requires a continuous response and adaptation to internal and external stimuli over the life course. This eventually results in people aging differently and women aging differently than men. The "gender paradox" describes how women experience greater longevity than men, although linked with higher rates of disability and poor health status.

Recently, the concept of frailty has been incorporated into this paradox giving rise to the "sex-frailty paradox" which describes how women are frailer because they manifest worse health status but, at the same time, appear less susceptible to death than men of the same age. However, very little is known about the biological roots of this sex-related difference in frailty.

Inflamm-aging, the chronic low-grade inflammatory state associated with age, plays a key pathophysiological role in several age-related diseases/conditions, including Alzheimer's disease (AD), for which women have a higher lifetime risk than men. Interestingly, inflamm-aging develops at a different rate in women compared to men, with features that could play a critical role in the development of AD in women.

According to this view, a continuum between aging and age-related diseases that probably lacks clear boundaries can be envisioned in which several shared biological mechanisms that progress at different pace may lead to different aging trajectories in women than in men. It, therefore, becomes urgent to consider a holistic approach in the study of aging, and decline it from a gender medicine perspective also considering the biological roots of the sex-frailty paradox.

1. Introduction

In the recent decades a dramatic demographic transition has been witnessed worldwide (Bongaarts, 2009). This is mostly due to the extension of the individuals' average life expectancy and lead to a growth in the number of old and very old persons. This has posed an unprecedented demand on the healthcare system and has ignited special attention on aging research (Jones and Dolsten, 2024).

Aging is a dynamic process that requires continuous response and adaptation to internal and external stimuli over the life course (Lissek, 2024). As a result of inter-individual heterogeneity, people age differently, which is also likely the reason why the health status of persons of the same chronological age can differ drastically. Indeed, in a same person, chronological age, the time expressed in terms of years lived, can show substantial discrepancies with biological age, the set of characteristics in terms of physiological evidence defining the age of cells and tissues (Graham et al., 1999). Aging can also have different effects in women and men, resulting in sex-dependent aging trajectories with women surviving longer than men (Austad, 2006; Barford et al., 2006; Glei and Horiuchi, 2007) despite a worse health status indicating a gender paradox in the aging continuum (Oksuzyan et al., 2008).

The concept of frailty, a condition characterized by an increased vulnerability to stressors due to a reduction in homeostatic reserves, may offer an opportunity to capture the individual's physiological decline and biological aging (Cesari et al., 2017; Gordon and Hubbard, 2018).

Among the biological roots of frailty, inflamm-aging, the age-associated chronic low-grade inflammatory state (Franceschi et al., 2000a), has been attributed a key pathophysiological role in several age-associated conditions (Gale et al., 2013) and indicated as a *trait d'union* between aging and onset of age-related diseases (Franceschi et al., 2018b; Fulop et al., 2018). The phenomenon of inflamm-aging is characterized by a different rate of decline in immune and inflammatory functions in women compared to men (Goetzl et al., 2010; Hewagama

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et al., 2009), and these different traits play a prominent role in women's frailty (Gale et al., 2013).

Among all age-associated conditions, inflamm-aging has been well declined in the brain and indicated as a contributor to neuro-inflammation (Wyss-Coray, 2006), the inflammatory reactions that underlie most neurodegenerative diseases, including Alzheimer's Disease (AD). Two thirds of AD patients are women (Rajan et al., 2021) and women have a greater life time risk of developing AD compared with men ("2021 Alzheimer's disease facts and figures", 2021), even after adjusting for survival (Bachman et al., 1992).

According to such a view, a continuum likely void of clear boundaries may exist between aging and age-related disease/conditions (Franceschi et al., 2018a), in which a set of shared biological mechanisms progressing at different rates may lead to different aging trajectories in women compared to men (Franceschi et al., 2018a).

Herein, we provide an overview of the concepts that led to the formulation of the sex-frailty paradox and an initial appraisal of the molecular pathways that are involved and that can be further exploited to understand its biological roots. Within this framework, we discuss inflamm-aging and neuro-inflammation as mechanisms underlying both biological differences in the gender paradox and susceptibility to dementia. We also highlight the need of implementing a holistic approach in the study of aging and associated diseases/conditions as proposed by the geroscience paradigm. A geroscience perspective may provide great support in framing gender medicine by untangling the biological roots of the sex-frailty paradox.

2. The trajectories of aging in women and men: The Italian experience

The World Population Prospects published in 2022 indicated that the world's population over the age of 65 was about 10 % and that this segment of people is set to reach nearly 12 % in 2030 and 16 % in 2050 (United Nations, 2024). In 2022, Europe and North America had the highest proportion of older adults, with nearly 19 % aged 65 or older. Projections indicate that by 2050 one out of four people in both countries could be 65 or older (United Nations, 2024).

In Italy, as of January 1, 2024, the estimated resident population was about 58 million 990 thousand, and deaths showed a decrease of 54 thousand compared with the previous year. The decrease in the total number of adverse events mainly affected people aged 80 years and older, the segment of the population mainly affected during the pandemic years.

The decline in mortality translates into a conspicuous increment in life expectancy at birth, which rises to 83.1 years in 2023, gaining six months over 2022 (ISTAT, 2024). Therefore, the number of the so-called very old people (80 years and older) is increasing, with 4 million 554 thousand individuals (50 thousand more than in the previous 12 months). The life expectancy at birth in men reaches 81.1 years recovering the pre-pandemic levels, while in women reaches 85.2 years with a slightly lower gain than that of men. This means that women still have some room of recovery for the life expectancy at birth exhibited, for example, in 2019 (85.4 years).

Interestingly, as of January 1, 2024, a total of 844 semi-super centenarians (people 105 years and older) were alive and residing in Italy. Semi-super centenarian women far outnumbered men (738 women vs. 106 men).

The greater longevity of women compared to men has been experienced since the 18th century. However, this survival advantage in women is counterbalanced by a worse health status in older age correlated with higher burden of disability and diseases, indicating the existence of a gender-paradox in the aging continuum (Oksuzyan et al., 2008). According to this paradox, human aging is influenced by the combination of biological characteristics (e.g., anatomy, reproductive functions, sex hormones, expression of genes on the X or Y chromosome) and factors related to lifestyle and subjective and personal experiences (Park and Ko, 2021; Regitz-Zagrosek, 2012).

In the 1980s, Verbrugge (Verbrugge and Wingard, 1987) hypothesized that women had chronic diseases with high morbidity but low mortality. In fact, this study described how women experienced not only more acute illnesses (e.g., infectious diseases) per year than men, but also more chronic disease conditions and greater medication use throughout their lifetimes. In contrast, men showed a higher prevalence of heart disease even at younger ages, and a higher likelihood of injury at all ages (Verbrugge and Wingard, 1987). Gradually, over the years, this theory has been revised and reconsidered according with the role of biological, behavioral, and social factors that could strongly contribute to this sex gap (Gordon and Hubbard, 2020).

3. Frailty: Add-in to the sex-frailty paradox

Among the multiple definitions of aging the one referring to a collapse of resilience in favour of damage accumulation has gained support over time (Ferrucci et al., 2020). According to this view, towards the end-of-life new stresses can cause a rapid accrual of damage due to overwhelmed resilience which predisposes to a phenotype identified as frailty (Ferrucci et al., 2020). Due to the different effects of aging in women and men, the "male-female health-survival paradox" also known as the "gender paradox," has been formulated.

Recently, the concept of frailty has been incorporated in this paradigm and allowed to frame a "sex-frailty paradox". The "sex-frailty paradox" is based on the fact that women are more frail because they manifest worse health status but, at the same time, appear less vulnerable to death than men of the same age. Therefore, women and men have a diverse chance to attain longevity and, at the same time, the aging process is qualitatively different between the two sexes.

In general, it has been reported that mortality rates are lower in community-dwelling older women than men, regardless of age or severity of frailty (Gordon et al., 2017) and that men experience life-threatening chronic conditions (e.g., stroke and ischemic heart disease), while women experience greater morbidity (e.g., fractures, depression, constipation, headache, and dementia) (Case and Paxson, 2005; Gordon and Hubbard, 2019).

Interestingly, in an Italian cohort of centenarians, frailty measured by the frailty index (FI) using both clinical (clinical FI) and biochemical (biological FI) variables, confirmed that women had worse health status than men, but surprisingly women showed values of biological FI similar to that observed in centenarian men (Arosio et al., 2019, 2022). These data indicated that centenarian women likely had a better biology compared to clinical manifestations, suggesting that their biological reserve may be underestimated by the clinical phenotypes (Arosio et al., 2019, 2022).

Under these premises, the different perception of stress between women and men may underlie women's greater sensitivity to physical discomfort, which, for instance, leads women to seek medical attention more frequently (Boerma et al., 2016; Hibbard and Pope, 1986; Park and Ko, 2021; Verbrugge, 1985). However, women generally cope better with their vulnerability due to a greater support network, whereas men seem to experience higher mortality due to a relative lack of coping mechanisms (Park and Ko, 2021).

4. Biological roots of aging: The geroscience paradigm

The magnitude of age as a risk factor for age-related conditions becomes clear when considering epidemiological evidence (Meirelles et al., 2024). These latter, indeed, while outlining factors (e.g., high cholesterol, high blood pressure, diabetes, and smoking habits) that increase the risk for the development of age-related conditions (e.g., cardiovascular disease) clearly show that individual's age is the risk factor that impacts the development of age-associated conditions for a much larger extent (Niccoli and Partridge, 2012).

What is encouraging in this analysis is that such aging effect has a

biology, and likely this biology of aging is the factor that drives age-related diseases (Niccoli and Partridge, 2012). Already in the 44 b.C. Cicero in *De Senectute* postulated that *"pugnandum, tamquam contra morbum sic contra senectute"* and is likely this aging, and most probably this biology of aging, that should be targeted. Bringing this old concept to our days, geroscience was born to address chronic diseases by targeting biological processes (Kennedy et al., 2014). The geroscience paradigm, indeed, identifies biological age as the driver of these diseases (Kennedy et al., 2014).

Biological age is an attempt to identify individual's age based on a set of characteristics, including circulating biomarkers, and/or tissular mediators that help defining the so-called biological clocks. Individuals can show a biological age that is older than the chronological one or can have a biological age similar to chronological age based on individual genetics and epigenetics characteristics, and health-related behaviours (Jylhävä et al., 2017). The concept of the markers of biological age, also referred to as "biological age predictors," is that of a biomarker related to chronological age that brings additional information in assessing the risk of age-related conditions other than chronological age (Jylhävä et al., 2017). Therefore, adult individuals with the same chronological age might have different risks for age-associated diseases as judged by their biological ages. Usually, the positive predictive value of a biological age predictor decreases starting from middle age, due to a greater biological heterogeneity when approaching older ages (Jylhävä et al., 2017).

The hallmarks of aging include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis (López-Otín et al., 2023). The most important aspect of these hallmarks is that they are all interconnected. According to the geroscience hypothesis, failure of this network of homeostatic mechanisms affects the rate of aging and, in turn, causes increasing susceptibility to disease. There is not a unified theory of aging but the one describing aging as the constant duel between cell damage accumulation and resilience potential in the face of this latter (Ferrucci et al., 2020) clearly highlights the role of preserving these mechanisms to ultimately preserve health.

The study of age-related conditions in the light of the geroscience paradigm has been implemented in some instance. In this view, while intermittent increases in inflammation have been recognized as crucial events for the promotion of survival during physical injury and infection, a set of social, environmental, and lifestyle factors have been indicated to promote systemic chronic low-grade inflammation for which several consequences have been identified (Furman et al., 2019). The most common triggers of systemic chronic low-grade inflammation include chronic infections, physical inactivity, (visceral) obesity, intestinal dysbiosis, diet, social isolation, psychological stress, disturbed sleep and disrupted circadian rhythm and exposure to xenobiotics (i.e., air pollutants, hazardous waste products, industrial chemicals and tobacco smoking) (Furman et al., 2019). The consequences of systemic chronic low-grade inflammation include metabolic syndrome, type 2 diabetes, non-alcoholic fatty liver disease, cardiovascular disease, cancer, depression, autoimmune diseases, neurodegenerative diseases, sarcopenia, osteoporosis, and immunosenescence (Furman et al., 2019).

Inflamm-aging, the chronic low-grade inflammatory status developing with aging (Franceschi et al., 2000a), has been increasingly recognized as a *trait d'union* between aging rate and the development of age-related disease (Franceschi et al., 2018b; Fulop et al., 2018). This age-associated inflammatory phenotype manifests as a higher secretion of pro-inflammatory mediators such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor α (TNF-α), and reduced levels of anti-inflammatory IL-10 and transforming growth factor-beta. This pro-inflammatory milieu predisposes older adults to illness and a worse prognosis for chronic diseases, increasing morbidity and mortality (Franceschi et al., 2000a; Xia et al., 2016).

Studies in large cohorts of participants (470,000 from UK BioBank) have shown that shorter mean leukocyte telomere length is associated with an increased risk of overall and disease-specific mortality (Schneider et al., 2022). Multi-marker studies, although much smaller, including mediators pertaining to as many biological domains as possible and adopting multivariate statistical approach, have tested the geroscience hypothesis to possibly obtain biological profiles of conditions and likely map the contribution of biological aging to age-associated conditions (Calvani et al., 2020a, 2020b, 2021; Marzetti et al., 2020; Picca et al., 2020). Preliminary indications on the biomarker profile of some age-related conditions have been gathered; however, there is still work to be done before this approach could be implemented in research and clinical settings and support biomarker identification (Bauer and Newman, 2022). Indeed, while a set of criteria have been outlined for the use of blood-based biomarkers in geroscience trials (Justice et al., 2018), several challenges hamper their development (Rolland et al., 2023). These include, but are not limited to, selection of ideal populations, choice of lifestyle and/or therapeutic interventions to be tested, definition of primary and secondary trial outcomes (Rolland et al., 2023). Moreover, age-related biomarkers that may be more informative on defining interventions to be selected and/or predicting/monitoring clinical responses remain to be identified (Rolland et al., 2023). To add further complication to this matter, the set of physical and mental attributes of an individual, referred to as intrinsic capacity and reporting on its resilience potential has also been included among the relevant determinants of aging that needs to be considered in light of the geroscience paradigm (de Souto Barreto et al., 2023). Indeed, greater physiological reserve in women has been hypothesized to also enable greater multi-morbidity to be acquired before death (Gordon and Hubbard, 2018). However, additional studies are needed to corroborate initial findings and a task force of experts in Geroscience has been established to work on this specific matter and their output will represent an important milestone for the field (de Souto Barreto et al., 2023; Rolland et al., 2023).

5. The contribution of inflamm-aging to the sex-frailty paradox

Chronic inflammation is a pivotal contributor to the pathophysiology of frailty in women (Gale et al., 2013). The existence of a human sexual dimorphism in immune responses has been documented with women showing lower infection rates and higher immune reactogenicity to both self and non-self-molecular patterns (Klein and Flanagan, 2016; Shepherd et al., 2020). Sex-related differences have also been described for the activation of innate immune responses (Bonafè et al., 2001; Goetzl et al., 2010; Mauvais-Jarvis et al., 2020). While genetic differences can explain the complex immune sexual dimorphism, this may also derive from differences in sex hormones altering immune cells milieu (Franceschi et al., 2000b; Ter Horst et al., 2016). To accomplish immunomodulatory activities, sex hormones bind to responsive elements of genes involved in innate immunity (e.g., myeloid differentiation primary response 88, interferon regulatory factor 7, toll-like receptors), and/or interact with DNA-binding transcription factors (i.e., nuclear factor kappa-light-chain-enhancer of activated B cells) (Jaillon et al., 2019) (Fig. 1).

The effect of sex as a source of biological variation in the levels of biomarkers of inflamm-aging has long been neglected, making them not relevant to either sex (Hägg and Jylhävä, 2021). Instead, results from a double-blinded randomized clinical trial have recently shown that sex-specific inflammatory mediators can predict anti-inflammatory responses to a pharmacological intervention (Lombardo et al., 2022).

Therefore, inflamm-aging has started to be analyzed in the light of sex-associated differences (Olivieri et al., 2023). High levels of circulating IL-6 have been found in both old men and women (Ferrucci et al., 2005). Sexual dimorphism has, instead, been found for the association of IL-6 with longevity as well as frailty (Arosio et al., 2023), showing a disadvantage (Bonafè et al., 2001) and an increased risk of developing

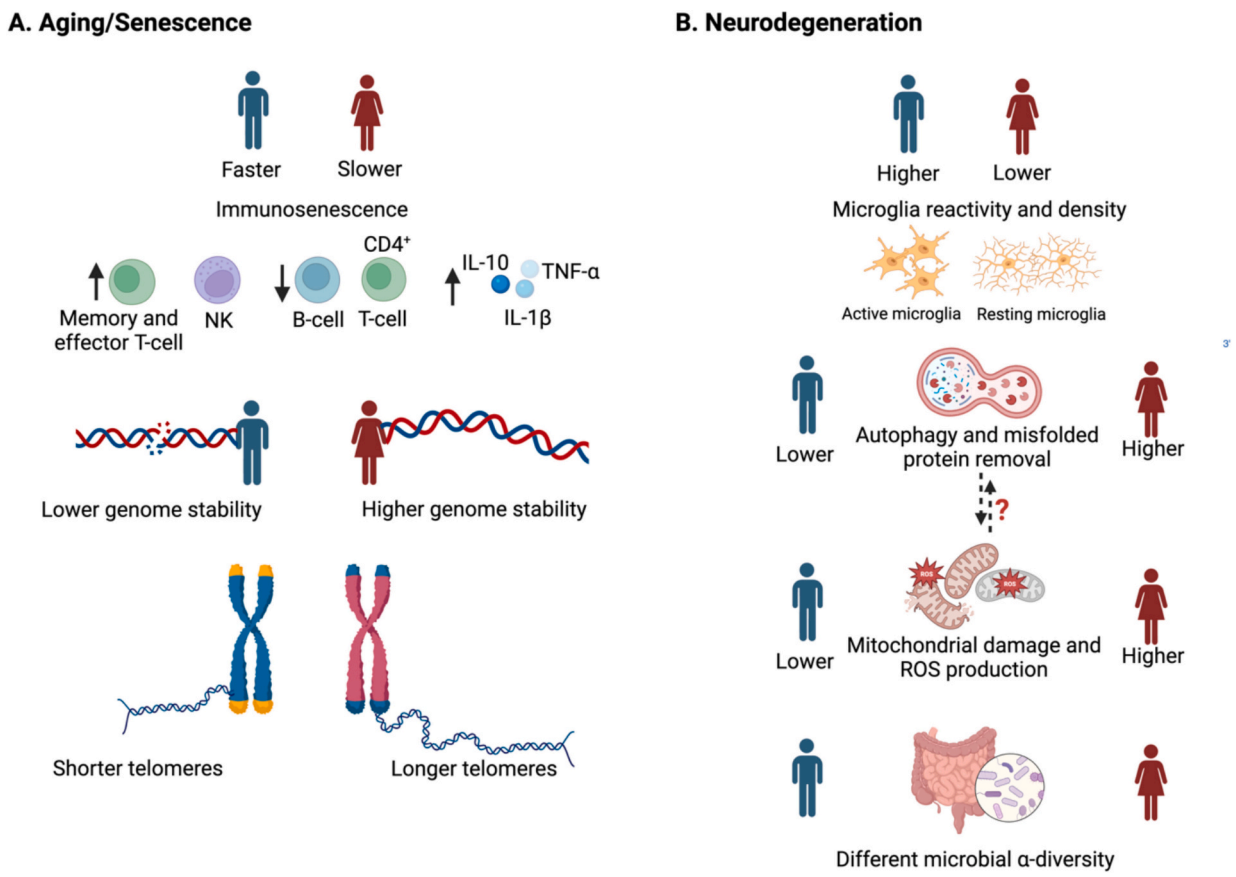

Fig. 1. Schematic representation of the main sex-related differences associated with immunesenescence and neurodegeneration. Created with BioRender.com (accessed on July 22, 2024).
Abbreviations: CD, cluster of differentiation; IL, interleukin; NK, natural killer; TNF-α, tumor necrosis factor-α; ROS, reactive oxygen species

age-related diseases for men (Bernardi et al., 2020; Ridker et al., 2000). Sexual dimorphism was also observed for the anti-inflammatory cytokine IL-10 (Islam et al., 2022). The analysis of blood leukocytes ex vivo indicated that the IL-10-mediated inhibition of TNF-α was higher in men. Notably, this sex-related difference was not paralleled by variations in the circulating levels of IL-10 and/or basal expression of IL-10 receptor in both unstimulated $CD14^+$ and $CD4^+$ T cell-monocytes and peripheral blood mononuclear cells (Islam et al., 2022). On a different note, the greater abdominal adiposity observed in women with age may also explain the critical role of chronic inflammation in the pathophysiology of frailty in women (Gale et al., 2013). Indeed, an association between body mass index and frailty has been found across different measures of frailty (i.e., frailty index scores and Fried frailty phenotype) with more frail individuals presenting higher waist circumference (Hubbard et al., 2010). Higher rates of sarcopenia have also been reported in women which can further explain higher frailty phenotype (Hwang and Park, 2022). A sex-specific profile of pro-inflammatory mediators including high levels of P-selectin, eotaxin, and lower levels of macrophage inflammatory proteins 1α and β has also been found to characterize older women with physical frailty and sarcopenia with a biological meaning that warrants investigation (Marzetti et al., 2019).

Finally, results from correlation analysis of different epigenetic clocks with chronological age in Mediterranean populations of the Blue Zones showed better correlations in women than in men (Engelbrecht et al., 2022). According to most of the DNA methylation clocks analyzed, men in these regions are biologically older than women, except for the proportion of regulatory T cells and IL-6 score (Engelbrecht et al., 2022).

6. Inflamm-aging and the sex-frailty paradox in dementia

Dementia is a major age-related and chronic degenerative disease characterized by cognitive decline, behavioral disorders, and functional impairment with loss of autonomy and self-sufficiency accompanied by varying degrees of disability (World Health Organization, 2023). In Italy, the total number of people with dementia is estimated at more than one million of which about 600,000 with Alzheimer's disease (AD) the most common form of dementia (around 60 %) (Ministero della Salute, 2024). Two thirds of people with AD are women (Rajan et al., 2021) and women have a greater lifetime risk of developing AD compared with men ("2021 Alzheimer's disease facts and figures", 2021). Although this difference may be thought to be due to the longer lifespan in women, women are reported to have higher rates of AD than men, even after adjusting for survival (Bachman et al., 1992).

The concept of resilience, the ability of the body to respond/adapt to stress, may also explain the ability to preserve cognitive function both during aging and disease (Arenaza-Urquijo and Vemuri, 2018, 2020; Montine et al., 2019; Stern et al., 2020). Interestingly, the factors that induce resilience in AD may be influenced by sex (Mayeda, 2019). For instance, genetic factors, sex hormones, X chromosome function, immune/inflammatory factors and vascular hemodynamics may determine resilience to AD pathology in a sex-different manner (Arenaza-Urquijo et al., 2024). In particular, estrogen has been shown to be protective towards AD reducing amyloid β-peptide aggregation and improving neural functions (Aenlle et al., 2009; Jaffe et al., 1994; Wang et al., 1999), thus the rapid decrease in estrogen levels after menopause may increase the incidence of AD in women (Nagakura et al., 1991) interacting with other biological mechanisms included in the hallmarks of aging (Lopez-Lee et al., 2024; Snyder et al., 2016). However, measuring

resilience at the cellular and molecular level remains a challenge for which a clear definition would help defining the pace of biological aging and the onset of chronic conditions, including AD (Beyene et al., 2024; de Souto Barreto et al., 2023).

Among the molecular routes contributing to brain aging, inflammaging is a key factor. Indeed, the development of neuro-inflammation (Wyss-Coray, 2006), a set of inflammatory reactions involving the activation of microglial cells, the brain's resident macrophages, and the subsequent production of components of the innate immune response, such as chemokines, cytokines, and complement molecules (Wyss-Coray, 2006) has been identified in most neurodegenerative diseases, including AD.

Several evidence indicate that microglia density, phenotype and phagocytic activity are different between women and men (Bonham et al., 2019; Guillot-Sestier et al., 2021; Guneykaya et al., 2018; Sala Frigerio et al., 2019) and that men with AD show significantly higher density and more amoeboid microglial morphology than women with AD (Guillot-Sestier et al., 2021).

During aging, microglia is found to be more activated in women than men (Mangold et al., 2017) making the brain more susceptible to injury and/or neurodegeneration. This sustained activation and inflammation seems to have a stronger mediation effect between amyloid β-peptide aggregation and tau burden (Casaletto et al., 2022). Finally, sex differences also occur in animal models of AD, in which amyloid deposition accelerates the transformation of microglia from resting to activated state more rapidly in female mice than in males (Sala Frigerio et al., 2019).

A deeper understanding of the pathophysiological mechanisms underlying this age- and sex-associated decline in microglia quality and function as well as of the biological mechanisms accompanying the development of age-related conditions may support the identification of novel targets for the development of therapeutic strategies.

7. Biological roots and clinical outcomes of the sex-frailty paradox

Although the pathophysiology of frailty is an area of active investigation, the underlying etiopathogenetic mechanisms remain largely unknown, and even less is clear about their sex-related differences (Table 1).

The genetic addition of an X chromosome in women as well as the presence of longer telomeres and slower telomere erosion have been indicated to confer a survival advantage in women (Öngel et al., 2021). Genes on the X chromosome include sequences coding for Toll-like receptors and receptors of various cytokines as well as genes involved in T-cell and B-cell activity. Conversely, the Y chromosome holds sequences involved in inflammatory gene pathways that are exclusively expressed in men (Charchar et al., 2012; Giefing-Kröll et al., 2015; Hirokawa et al., 2013). As a result, immunosenescence is a phenomenon that occurs more rapidly in men (Hirokawa et al., 2013), leading to greater innate and pro-inflammatory and less adaptive responsiveness than in women (Márquez et al., 2020). These changes may lead to a greater deterioration of immune system in men, causing lower survival (Gale et al., 2013; Gubbels Bupp, 2015). However, the greater age-related deterioration of the immune system experienced by men compared to women attributed to genetic differences can also be ascribed to changes in concentrations in sex hormones that alter the milieu of immune cells (Franceschi et al., 2000b; Ter Horst et al., 2016).

In particular, estrogen concentrations after menopause and testosterone concentrations after middle age decrease drastically. In this regard, testosterone by potentiating the effect of growth hormone increases the risk of some age-related diseases, such as prostate cancer and cardiac hypertrophy in men (Kloner et al., 2016), while endogenous estradiol, which is the most potent estrogen hormone, causes marked cardiovascular changes in women thereby postponing the onset of cardiovascular diseases (Eskes and Haanen, 2007). Increasing evidence

Table 1
Sex-specific association of biological pathways with frailty and related outcomes.

Population	Biological measure	Finding	Reference
Centenarians	Frailty index	No significant differences between women ($n = 46$; 0.34, IQR 0.31–0.39) and men ($n = 19$; 0.32, IQR 0.26–0.43)	Arosio et al., 2022
Older adults	Inflammatory markers	Significant differences between non-frail (IFN-γ: 0.64 pg/ml, IQR 0.44–0.95; IL-1β: 0.18 pg/ml, IQR 0.11–0.28; IL-6: 2.30 pg/ml, IQR 1.58–3.56; IL-10: 1.98 pg/ml, IQR 1.51–2.46; TNF-α: 8.83 pg/ml, IQR 7.48–10.70; TNFR1: 1.31 ng/ml, IQR 1.09–1.61; sTREM1: 0.47 ng/ml, IQR 0.39–0.59; sTREM2: 32.80 ng/ml, IQR 24.52–44.20 and frail ($n = 452$; IFN-γ: 0.85 pg/ml, IQR 0.54–1.72; IL-1β: 0.22 pg/ml, IQR 0.11–0.40; IL-6: 4.39 pg/ml, IQR 2.59–7.82; IL-10: 2.47 pg/ml, IQR 1.74–3.67; TNF-α: 11.70 pg/ml, IQR 9.58–15.95; TNFR1: 1.76 ng/ml, IQR 1.34–2.52; sTREM1: 0.67 ng/ml, IQR 0.48–0.88; sTREM2: 44.59 ng/ml, IQR 33.03–61.72. Of all markers IL-6, TNF-α, TNFR1and sTREM affected by sex, FI, and age	Arosio et al., 2023
Older women with physical frailty and sarcopenia	Inflammatory markers	In physically frail older women ($n = 75$) high levels of P-selectin (108.8 ng/ml, IQR 39.5), eotaxin (158.8 pg/ml, IQR 167.3), and lower levels of macrophage inflammatory proteins 1 α (3.3 pg/ml, IQR 10.5) and β (175.6 pg/ml, IQR 72.4)	Marzetti et al., 2019
Mediterranean populations of the Blue Zones	Epigenetic age	Positive epigenetic age acceleration in men compared to women according to all clocks, with significantly greater rates according to GrimAge ($\beta = 3.55$; $p = 1.22 \times 10–12$), Horvath ($\beta = 1.07$; $p = 0.00378$) and the Pace of Aging ($\beta = 0.0344$; $p = 1.77 \times$	Engelbrecht et al., 2022

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Table 1 (*continued*)

Population	Biological measure	Finding	Reference
UK Biobank data	Leukocyte telomere length	10–08). Men had also lower DNAm-predicted serum IL-6 scores (β = −0.00301, $p = 2.84 \times 10–12$), while women displayed higher DNAm-predicted proportions of regulatory T cells than men from the Blue Zone (p = 0.0150, 95 % CI [0.00131, 0.0117], Cohen's d = 0.517). In 472,432 English participants reduced LTL was associated with increased overall (HR, 1.08; 95 % CI, 1.07–1.09), cardiovascular (HR, 1.09; 95 % CI, 1.06–1.12), respiratory (HR, 1.40; 95 % CI, 1.34–1.45), digestive (HR, 1.26; 95 % CI, 1.19–1.33), musculoskeletal (HR, 1.51; 95 % CI, 1.35–1.92), and COVID-19 (HR, 1.15; 95 % CI, 1.07–1.23) mortality, but not cancer-related mortality.	Schneider et al., 2022
British Heart Foundation Family Heart Study (BHF-FHS), West of Scotland Coronary Prevention Study (WOSCOPS), and Cardiogenics Study	Chromosome Y haplogroup analysis	Men with haplogroup I showed inflammatory gene pathway exclusively expressed in men and 50 % higher age-adjusted risk of coronary artery disease compared with men with other Y chromosome lineages in BHF-FHS (OR 1.75, 95 % CI 1.20–2.54, p = 0.004), WOSCOPS (1.45, 1.08–1.95, p = 0.012), and joint analysis of both populations (1.56, 1.24–1.97, p = 0.0002)	Charchar et al., 2012
Healthy adult population	Peripheral blood mononuclear cells composition	Past the age of 65, men show higher monocyte and cytotoxic cell functions and low B cell proportions.	Márquez et al., 2020
English Longitudinal Study of Aging	Inflammatory markers	Analysis in 2146 participants showed sex-specific associations of CRP and fibrinogen with risk of incident frailty (In women, CRP: OR, 1.27; 95 % CI 0.96–1.69; Fibrinogen: OR 1.31, 95 % CI 1.04–1.67)	Gale et al., 2013

Abbreviations: CI, confidence interval; CRP, C-reactive protein; FI, frailty index, HR, Hazard ratio; IFN-γ, Interferon-γ; IL-10, Interleukin-10; IL-6, Interleukin-6; IL-1β, Interleukin-1β; IQR, Interquartile range; TNF-α, Tumor necrosis factor-α; TNFR1, Tumor necrosis factor receptor 1; sTREM, Soluble triggering receptor.

indicates that estradiol is not only involved in modulating the local and systemic inflammatory response but also plays a key role in preserving muscle health during aging (Kenny et al., 2003).

The onset of age-associated decline in muscle mass, strength, and power referred to as sarcopenia is, indeed, influenced by hormonal changes, altered inflammatory response, fat infiltration, altered mitochondrial signalling, and apoptosis (Walston, 2012). During the menopausal transition of women, a progressive muscle decline occurs, which is triggered by decreased proliferation of muscle satellite cells, increased levels of inflammatory markers, and altered levels of estradiol, exposing women to a higher incidence of sarcopenia (Geraci et al., 2021).

Finally, another example of the effect of sex hormones on disease pathogenesis is represented by COVID-19. Testosterone induces an up-regulation of the angiotensin-converting enzyme (ACE)-2 receptor, which serves as a cellular entry point for the virus (Wang et al., 2020). Conversely, estrogen inhibits ACE expression, thereby partly explaining the increased susceptibility to infection and mortality of men (Gadi et al., 2020). This is a further confirmation that men are more susceptible to lethal conditions compared to women (Crimmins et al., 2011). On a different note, while men may acquire different types of disabling conditions, the disabling effect of chronic diseases may still be greater among women than men (Whitson et al., 2010) and the biological roots of these differences are still underappreciated.

8. Conclusion and perspectives

Inflamm-aging, the chronic low-grade inflammatory status that characterize older people, has been attributed a key pathophysiological role and identified as a *trait d'union* between aging and onset of age-related diseases. The phenomenon of inflamm-aging develops at a different pace in women versus in men with traits that play a critical role in women's frailty.

Inflamm-aging contributes substantially also to neuro-inflammation which underlies most neurodegenerative diseases, including AD, for which women have a greater lifetime risk compared with men. While genetic factors, sex hormones, X chromosome function, immune/inflammatory factors, and vascular hemodynamic can explain, at least in part, sex-specificity of AD development, the molecular determinants that allow to differentiate gender-specific mechanisms of aging and AD are missing.

A continuum likely void of clear boundaries has been hypothesized between aging and the development of age-related conditions with sets of shared biological mechanisms progressing at different rates that may lead to different aging trajectories in women compared to men.

Therefore, studies implementing a holistic approach to untangle the biological roots of aging are in high demand. Furthermore, the analysis of these roots in the light of the sex-frailty paradox may offer an opportunity to capture sex-specific individual's physiological decline and the divergent individual's biological aging. In this regard, a composite measure of biological age and a set of geroscience-driven biomarkers that could replace self-reported functional status and integrate clinical routine evaluations with comprehensive assessment of changes in older age by including social, behavioral, and psychosocial factors are highly sought after.

CRediT authorship contribution statement

Beatrice Arosio: Writing – review & editing, Writing – original draft, Conceptualization. **Anna Picca:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare no competing interests.

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