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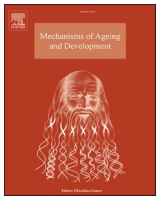

Ageing: Not only an age-related issue

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ABSTRACT

Developments in the last century have led to an unprecedented increase in life expectancy. These changes open opportunities for humans to grow and develop in healthy and adaptive ways, adding life to years as well as years to life. There are also challenges, however - as we live longer, a greater number of people will experience chronic illness and disability, often linked to lifestyle factors. The current paper advances an argument that there are fundamental biological sex differences which, sometimes directly and sometime mediated by lifestyle factors, underpin the marked differences in morbidity and mortality that we find between the sexes. Furthermore, we argue that it is necessary to consider sex as a key factor in research on healthy ageing, allowing for the possibility that different patterns exist between males and females, and that therefore different approaches and interventions are required to optimise healthy ageing in both sexes.

1. Introduction

Ageing is a very complex and not yet fully understood process in most species. Thus research in the area continues to be of great interest to various disciplines and different orientations, both basic and applied.

It is obvious that age is the crucial variable in the ageing process but, especially in humans, other variables (such as sex and gender, lifestyle, socio-economic status, etc) are also important factors. In this paper we will try to capture the relationship of sex to ageing. It is critical for the successful understanding of ageing (both healthy and pathological) that researchers become aware that the processes they are studying are often characterised by sexual dimorphism; this will improve knowledge of the ageing process in both men and women and therefore provide benefits for both. We will try to offer some insight into the sex-related (a biological construct) and gender-related (a social construct - the combination or interaction of biological sexual characteristics and factors related to behaviour, social role, lifestyle and life experience; Ostan et al., 2016) differences in ageing from a bio-psycho-social perspective. While gender and sex are different, and the frequency of transgender and gender non-binary (TGNB) self-identification seems to be rising, its overall prevalence appears to be less than 1% of the population (Nolan et al., 2019); for this reason, and in order to facilitate a mapping of sex to gender so as to allow for consideration of biological links to behaviour, the current paper treats gender as dichotomous.

As well as marked variation within the sexes, there are also important differences between the sexes in the ageing process. This is not a surprising revelation if we take into account that sexodimorphic features can be found even during the *in utero* period (Dearden et al., 2018), are expressed behaviourally just a few hours after birth (Connellan et al., 2000) and affect the whole process of growing and behaving through infancy, youth and adulthood (e.g. Duren et al., 2013; Ngun et al., 2011). Biological and non-biological factors interact continuously throughout life, modulating health and ageing (Ostan et al., 2016), and it has been observed that sex differences in ageing may be largely understood as resulting from a dialogue between brain and gonad, involving in particular the neuroendocrine (Austad, 2019) and immune systems (Ostan et al., 2016). Additionally, there is a link between gonads and both health and longevity which is manifested, for instance, in the negative and sex-related differential effects of reproductive activity (the "cost of reproduction") on life expectancy; non-reproduction (both in the sense of fewer offspring or of removing gonadal hormones) has a significant and positive impact both in humans and other species (Austad, 2019; Hoffman et al., 2018; Tabatabaie et al., 2011). Advances in neuroscience enable integration of behavioural, neuroanatomic and neurophysiologic measures (Gur and Gur, 2002), providing us with new insights into sex differences in the ageing process.

Sexual dimorphism in the context of the human lifespan has received a good deal of attention (Hodes and Epperson, 2019), but fluctuation in

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the gender gap has not received such scrutiny. The maximum difference in life expectancy between males and females was found between the 1970s and the 1990s, and the subsequent convergence can be attributed partly to the narrowing of differences in risk behaviours between males and females (Ostan et al., 2016). Consideration of the interaction of sexually dimorphic biological characteristics with environmental and cultural factors, and changes in these interactions across the lifespan, may permit a greater understanding of the processes at play in such developments (Hodes and Epperson, 2019; Maklakov and Lummaa, 2013).

2. Evolution, biology and behaviour

Ageing is a biological phenomenon, ultimately located in cellular processes. There are many domains of cellular function which contribute to cellular senescence and the ageing of an organism - for example telomere erosion, mitochondrial dysfunction, oncogene activation and persistent DNA damage (Di Micco et al., 2021; McHugh and Gil, 2018). There is evidence for sex differences in the development of these age-related changes; mutation loads are larger and appear to accumulate earlier among men (Podolskiy et al., 2016). While recognising that the drama is played out at a cellular level (Kubben and Misteli, 2017), however, the focus of this paper is on biological differences at the macro level, on differences in behavioural patterns, and on related evolutionary pressures and processes.

Biological sexual foundations are at the root of each individual's functioning, and have been over the thousands of generations of our species' evolution. Of course it is credible to argue that differential socialization plays an important role in the development of these sex differences in behaviours and attitudes (e.g. Hines, 2020; You et al., 2011). We contend that this is not an either/or matter, nor a question of mechanically estimating proportions of differences explained by biology and environment respectively; there can be brain-behaviour relationships, society-behaviour relationships, and society-brain relationships, through the impact of environment on brain through neurogenesis and neuroplasticity (Fares et al., 2019; Mishra et al., 2020), necessarily impacting behaviour.

Evolutionary pressures are a useful starting point in considering sex differences. Males and females have been under selective pressures throughout human existence, though with different demands according to sex. These differences have affected all sex-related features, physical (e.g. body size), physiological (e.g. endocrine function), and - crucially - behavioural (e.g. pain tolerance, impulsivity, aggression, harm avoidance, sensation-seeking). These sex-related behavioural differences have led to differences in social functioning, socializing styles, lifestyle preferences, leading in turn to disparities we find in epidemiology, pathophysiology, clinical manifestations, disease progression and even response to treatments (Mauvais-Jarvis et al., 2020). The health impact of these differences may be most pronounced in older age, when the distribution of health-related variables tends to broaden in line with distinctive individual trajectories of health (Rockwood et al., 2004). These dynamics are presented visually in Fig. 1.

Mortality is an area where such differences can be seen very starkly. Data show a remarkable gender difference in life expectancy and mortality, including survival to extreme age (Ostan et al., 2016). Some authors have pointed out that males may suffer from increased extrinsic mortality but not necessarily from more rapid ageing; this idea is consistent with the fact that men, but not women, retain reproductive potential until very old age (Maklakov and Lummaa, 2013) and that although women have higher life expectancy than men, among the living health status is normally better in older men than women (Graves et al., 2006).

There are evolutionary explanations of the differences in lifespan between the sexes. Sex-dependent behaviours related to the survival of family groups have favoured greater longevity of females in some species; in humans, for example, grandmothers' (but not grandfathers') presence in the family household seems to improve grandchild birth rate and survival (Lahdenperä et al., 2004). This increased birth rate and survival, of course, serve to increase the fitness of the longer-lived and engaged grandmother, contributing to increased female longevity and thus making her genes more prevalent in subsequent generations. A similar phenomenon has been found among whales and elephants (Lahdenperä et al., 2016; Nattrass et al., 2019).

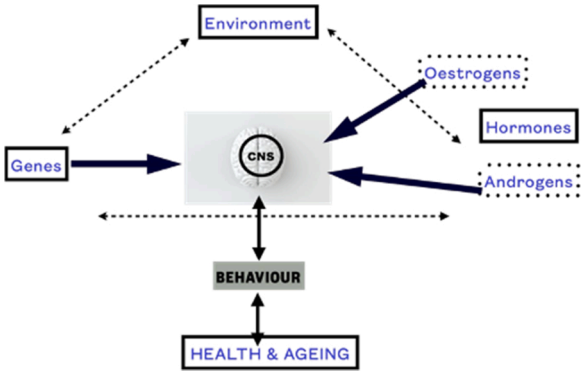

Fig. 1. Factors influencing sex differences in health and ageing.

Brain differences are also an important consideration when addressing sex differences. Considering the brain structures which have been found to be associated with the most commonly acknowledged sexodimorphic behaviours (Archer, 2019; Carlisi et al., 2020; Palmisano et al., 2020; Ritchie et al., 2018; Xin et al., 2019), males have - on average - larger volumes and higher tissue densities in the left amygdala, hippocampus, insular cortex, putamen; higher densities in the right VI lobe of the cerebellum and in the left claustrum; and larger volumes in the bilateral anterior parahippocampal gyri, posterior cingulate gyri, precuneus, temporal poles, and cerebellum, areas in the left posterior and anterior cingulate gyri, and in the right amygdala, hippocampus, and putamen. Females display higher densities in the left frontal pole, and larger volumes in the right frontal pole, inferior and middle frontal gyri, pars triangularis, planum temporale/parietal operculum, anterior cingulate gyrus, insular cortex, and Heschl's gyrus; bilateral thalami and precuneus; the left parahippocampal gyrus and the superior division of the lateral occipital cortex (Ruigrok et al., 2014). Many of the structures in which we find sex differences are within or linked to the limbic system - an early evolutionary development of the forebrain, related to emotion and memory. These findings may contribute to understanding the most salient sex-specific psychological differences, which according to Archer (2019) range from *"(i) small (object location memory; negative emotions), to (ii) medium (mental rotation; anxiety disorders; impulsivity; sex drive; interest in casual sex), to (iii) large (social interests and abilities; sociosexuality); and (iv) very large (escalated aggression; systemizing; sexual violence)"*. It has to be stated that the specific relations between structural differences and concrete behaviours are not fully understood at this time; nonetheless, there is strong evidence (including from research with people who have suffered acquired brain injury, and in antisocial behaviour - e.g. Caeyenberghs et al., 2010; Carlisi et al., 2020; Palmisano et al., 2020) of associations between specific brain structures and specific behaviours.

A key brain structure in certain sex differences in behaviour is the amygdala but evidence in relation to sex differences in the amygdala itself is inconsistent. Although it is known to play a key role in many affective behaviours and psychiatric disorders that show large differences between men and women, and although some studies have indeed reported significant sex differences (e.g. Archer, 2019), findings are conflicting and an extensive meta-analysis (Marwha et al., 2017) did not find the reported volume differences between the sexes - an outcome which the authors suggest might be due to the inconsistency in accounting for the different brain sizes in men and women across studies. A

more recent study conducted with 100 healthy participants (50 men/50 women) aged 18–69 years reports significant negative correlations between age and all subareas of the amygdala, which suggests decreases over time, but neither sex differences nor interactions between sex and age, thus suggesting that the size of the amygdala is similar in male and female brains even when properly accounting for total intracranial volume, and that the age-related decline of that crucial structure follows a similar trajectory in both sexes (Kurth et al., 2019). However, in an unusually large sample (n = 2838) ranging from 21 to 90 years of age, men displayed larger volumes than women in subcortical temporal structures such as the amygdala, hippocampus, temporal pole, fusiform gyrus, visual primary cortex, and motor areas (Lotze et al., 2019).

One of the most salient behavioural features that distinguish human males and females is aggression. Rather than just stating that males are more aggressive than females, we can point to several aggression-related features in which each sex tends to engage more frequently. Within-sex direct physical aggression, as well as risk-taking and a reduced fearfulness, are among these well-acknowledged sexo-dimorphic behaviours (Archer, 2019) and all of them can be related - although not exclusively - to the amygdala and its multiple connections (Cupaioli et al., 2020). These differences may contribute to male longevity being lower than that of females.

Lotze et al. (2019), in their large scale study, reported that greater Grey Matter Volume (GMV) was found for women in medial and lateral prefrontal areas, the superior temporal sulcus, the posterior insula, and orbitofrontal cortex. Ageing is associated with GMV decline in both sexes. Sex differences in volume loss have been noted in frontal, temporal, and parietal regions, with older men showing greater volume loss over time than older women (Armstrong et al., 2019).

Moving beyond brain structures, we can identify markers of neurohormonal influences on behaviours and outcomes. Suicides, for example, are more common among males than females across the lifespan (e.g. UK Office for National Statistics, 2020), a fact which may have a biological contribution. Recent research by Lenz and Kornhuber (2018) found that lower 2D:4D finger length ratios (a marker of in utero testosterone exposure, with male ratios typically lower than those of females), were associated with increased suicide rates in both sexes.

A further area which may help to explain several sexodimorphic outcomes is the stress response. Sex differences in stress responses can be found at all stages of life. In childhood, females have been found to have a higher cortisol reactivity than males, and males to have higher HPA-axis activity than females - but in adulthood these patterns are reversed (Hollanders et al., 2017). These differences are related to both the organizational and activational effects of gonadal hormones and to genes found on the sex chromosomes (Arnold, 2009; Bale et al., 2010; Bale, 2015; McCarthy, and Nugent, 2013; Morgan, and Bale, 2012). In animal models, effects of oestrogen on stress-induced neuroplasticity and activity changes have been demonstrated, supporting the idea that the female brain has a different innate strategy for handling stress (Navarro-Pardo et al., 2018). *In utero*, sex differences in the response to maternal stress and to environmental perturbations are well documented. Genetic sex (XX/XY) as well as the epigenetic regulation of hormones contribute to the proximate and ultimate effects of stress, across different life stages. For male offspring, maternal stress during the in utero period increases the risk for socialization-related disorders such as autism (Davis and Pfaff, 2014; Ronald et al., 2011), while females show higher resilience to the proximate effects of perinatal maternal stress (Nugent et al., 2018). Other studies with both humans and animals indicate that males are at a greater risk for short-term and long-term negative consequences, including schizophrenia in humans, following maternal adversity during pregnancy (Kim et al., 2015; O'Connor et al., 2002; Sandman et al., 2013).

3. Impact on ageing and health

While some of the sex differences identified in this paper seem to have evolutionary origins (many similar differences have been found in other mammals and especially in other primates), the complexity of human societies adds an extraordinary challenge to the analysis of sex differences and their influence on health and ageing. For instance, many diseases and pathologies (e.g. coronary heart disease, hypertension, diabetes, chronic pulmonary disease, several types of cancer, Alzheimer's disease) and their manifestations are related to sex, but lifestyle, nutritional habits, exercise, work roles, smoking and alcohol consumption, disease perception, help-seeking behaviours, use of health care, decision making, etc. are also related to sex and have clear influences on health and ageing. Thus sex influences health and longevity through both genetics and epigenetics (Mauvais-Jarvis et al., 2020). In consequence of biological sex differences, and of the impact of sex on behaviour, the gradual accumulation of damage (e.g. telomere damage arising from lifestyle factors, Shammas, 2011; oxidative DNA damage, Maynard et al., 2015) will therefore be different in men and women. Even this phenomenon is complex and apparently contradictory - for example, although much research with animal models sheds light on sex differences in lifespan, ageing and increased mortality in males (Bilde et al., 2009; Camus et al., 2012; Fox et al., 2006; Hoffman et al., 2018; Maklakov et al., 2006; Tower, 2006), *the mortality-morbidity paradox* whereby women show poorer health but higher life expectancy remains unexplained (Farrell et al., 2021).

Having said this, it is necessary to point out that pronounced advances in human longevity are a very new phenomenon; at the beginning of the 20th century, only a century ago, life expectancy at birth was less than 40 years and although sex differences in life expectancy are now accepted as normal this is actually a recent trend, with longevity of the sexes having historically been very similar (Mourits, 2017). In previous generations, the high female mortality due to pregnancy and childbirth corresponded to a higher male mortality from causes related to work, accidental injury or violence (Ostan et al., 2016), and infectious diseases similarly affected both sexes (it remains the case that victims of homicide are mostly male across the whole world, according to the Global Study on Homicide; UNODC, 2019). Advances in obstetrics led to expanding sex differences in mortality emerging in national historical populations during the late 19th century and the early part of the 20th century (Beltrán-Sánchez et al., 2015).

Mental health is also an area in which we can see important sex differences, with patterns of differences changing with age as we outline below. The stress response is a dimension which appears crucial here and may help to explain the interaction of age and sex in influencing outcomes. During adolescence and early adulthood adversity appears to differentially increase the risk for affective disorders in females, especially during their reproductive years (Bekhbat, and Neigh, 2018; Van-Tieghem and Tottenham, 2017). Women show depression at higher rates (approximately twice as much as men) from puberty until menopause (Albert, 2015; Friedrich, 2017); while perimenopause is associated with an increased risk of depression (Navarro-Pardo et al., 2018), the data subsequently become more and more similar for the sexes and the differences tend to vanish, leading to the suggestion of some effects of oestrogen on emotional brain functioning (Shanmugan and Epperson, 2014). During early and middle life, women have a higher index of sadness, rumination and coping style associated with depression (Archer, 2019), and a similar pattern can be found for anxiety-related disorders (Bale and Epperson, 2015). Postmenopausally, ovarian senescence contributes to sex differences in stress responsivity and stress-related neuropsychiatric disease risk, in part resulting from dynamic hormonal reductions in women and other ageing-related cellular processes in limbic brain regions (Bale and Epperson, 2015; Bekhbat, and Neigh, 2018; Kelly et al., 2014; Navarro-Pardo et al., 2018; Sze, and Brunton, 2020). As Hodes and Epperson (2019, p. 421) put it: "... *risk associated with developmental insults is unmasked in female offspring following periods of hormonal activation and flux, including puberty, pregnancy, and perimenopause*".

The most likely mechanisms to explain these differential age-related

sex differences are interactions of sex chromosome genes with periods of dynamic hormonal changes that happen across the lifespan. For example, in utero exposure to excessive maternal stress during key periods in development and maturation can alter the sexually dimorphic brain, leading to males having more female-typical patterns in some brain regions. This can increase disease risk through mismatch between the gonadal sex and the brain sex - where male sex hormones interact with a brain which has not developed in a male-typical fashion (Bale and Epperson, 2015).

The focus on sex differences in stress responses may help to predict disease risk and resilience and is crucial to successfully developing treatments and preventive strategies. Why these sex differences exist and continue to present across the lifespan is a key question in understanding individual health and disease, and suggests that - from an evolutionary point of view - an early adaptation made it advantageous for males and females to display different stress responses at different times in life. Studies in the area of mental health that include sex as a factor continue to be a major need across the lifespan (Bale and Epperson, 2015; Dhabhar, 2018). Considering cognitive decline in ageing, there is evidence for more pronounced age-related changes in men's brains than in women's. Sex differences are salient in the ageing process, and there is increasing evidence for the role of ovarian hormones in mediating behavior and brain function (Gur and Gur, 2002). For instance, in addition to their role in reproduction, oestrogens have effects on several organs in the body, as confirmed by the identification of oestrogen receptors in multiple tissues; its withdrawal has an impact not only in the very well-known conditions of osteoporosis or cardiovascular disease, but also on the central nervous system and therefore, on cognition and mood (Navarro-Pardo et al., 2018). Moreover, brain volume shows consistent small-to-medium correlations with cognitive performance (Gignac and Bates, 2017; Gur et al., 1999; Nave et al., 2019), and sex differences have been observed in intracranial volume (Ritchie et al., 2018), in the volume and density of language-associated cortex (Shin et al., 2021) and in the rate of age-associated changes. Age-related decline begins earlier in men than in women and the decline is most pronounced in frontotemporal regions associated with attention, inhibition, and memory (Gur and Gur, 2002).

This pattern may not be present in relation to dementia, however. Data from the Swedish Twin Registry (Beam et al., 2018) found that women had a higher incidence of dementia than men, with rates diverging in the early 80 s. While greater female longevity is an important consideration, the data show that rates of dementia are higher in females with age cohorts; Beam and colleagues considered that biological sex differences might be a factors. A possible biological explanation is seen in a recent work with Alzheimer's sufferers, in which Sundermann et al. (2020) found that higher testosterone was protective against increased phosphorylated-tau in the cerebrospinal fluid of APOEε4 carriers.

In addition, the influence of socio-economic variables cannot be ignored. It is essential to be aware that lifestyles are not simply the product of individual choice; they are influenced by economic, social, cultural and environmental factors (CSDH, 2008; Dowler, 2001). For instance, men (more so than women) living in poorer socioeconomic conditions are more likely to eat unhealthy diets, exercise less, consume alcohol, smoke, misuse drugs, or exhibit risky behaviour (European Commission, 2011).

Ageing, lifespan and longevity are complex and multifactorial traits resulting from an intriguing combination of 'nature' and 'nurture', the unique reciprocal interaction between environmental, genetic, epigenetic and stochastic factors, each contributing to the overall phenotype (Ostan et al., 2016). Thus, the ageing process is very complex and it is also quite difficult to estimate the weight/influence of each related-variable. Throughout the entire lifespan, individuals are confronted with multiple factors influencing their cognitive functions, physical and mental health and duration of life; and with advancing age, the interaction of various factors increases in its complexity (Kryspin-Exner et al., 2011). Diet, daily exercise, tobacco use and passive smoking, consumption of toxic substances, contact with contaminating agents, access to health-care, medication, socioeconomic position/social vulnerability, genetic disorders, personal and family history of disease, etc., are only some examples of heterogeneity of influences on ageing and health through the lifespan. For instance, some authors point out that greater adult male vulnerability to cardiovascular disease may also involve sex-linked biological factors that emerged during the reduction of mortality from infections (Beltrán-Sánchez et al., 2015). Moreover different human interventions may mitigate and/or exacerbate the intrinsic variability of human populations, in order to produce the observed variability of individual ageing (Farrell et al., 2021); consequently, not only should many different variables be included but also the interactions among them should be considered, in order to properly study ageing.

Of no dimension is this more true than of sex, yet it has not always been a focus of research - or even acknowledged as relevant. The earliest clinical trials focused on men (mainly young adult males), assuming that male and female cells and systems were biologically identical and to study only males was easier and cheaper; it was not until 1993 that the US National Institutes of Health (NIH) mandated the inclusion of women in NIH-funded trials (Mauvais-Jarvis et al., 2020). In this context, even in the scientific field, sex and gender were neglected as significant variables for the understanding of natural or clinical phenomena in respect of humans. However, scientific societies such as the American Endocrine Society (Bhargava et al., 2021), have recently stated the need to consider sex as an essential variable both in basic and clinical studies, and also to consider its role in diseases' pathology, treatments, and outcomes.

4. Discussion and conclusions

Evolutionary pressures have led to marked differences between the sexes, with each resolving the fundamental tradeoff between reproduction and survival differently. This has resulted in a different and sex-specific optimal adaptation throughout the lifespan. We can see considerable evidence of sex differences in brain structure, in aggression (Archer, 2019), and in stress response (Hollander et al., 2017). These differences, in turn, can be expected to be related to differences in outcomes for the sexes through three major factors - sex hormones, genes, and environment (Bhargava et al., 2021).

Recent increases in longevity, along with superior gathering of health-related data, provide us with valuable information on this question. Where, as recently as a century ago, life expectancy was considerably lower and strongly influenced by deaths resulting from work injury, childbirth and infection, people now live for longer and commonly die as a result of lifestyle-related pathologies such as cardiovascular disease and cancer (e.g. UK Office of National Statistics, 2017). The picture is a complex one, however, with the *morbidity-mortality paradox* (Farrell et al., 2021) emerging as an important factor. Biological and social processes, which tend to be complementary rather than to oppose one another, could explain this dimorphism in lifespan and health status. For example, males are more likely to smoke tobacco (Rogers et al., 2010) and consume alcohol (Erol and Karpyak, 2015) to excess, with implications for longevity - such tendencies may arise from biological differences in stress management strategies, and are reinforced by related social norms and stereotypes. Of course, such differences in health-related behaviors will lead to different accumulations of risk and pathology with increasing age, leading in turn to a divergence in outcomes for the sexes.

Biological mechanisms responsible for sex differences in ageing and longevity are quite complex and still poorly understood and their foundations must be found in the different evolutionary pressures to which males and females have been subjected, mostly as a function of their different reproductive physiologies. For instance, a very fast and aggressive response to any challenge must have better suited human

males, more likely to get involved in fight-or-flight situations - though of course other strategies could be deployed depending on circumstances. Although men report more traumatic experiences than women, the rate of posttraumatic stress disorder (PTSD) diagnosis is twice as high in women as in men (Bangasser et al., 2019) whilst the capacity to tolerate continuous pain and inconveniences derived - among other circumstances - from the long pregnancies and the continuous walking imposed by a peripatetic lifestyle is greater in women. In physiological terms this condition may have led to a more reactive HPA axis in males, which provide a more efficient response, while females have developed a more resilient HPA axis, better suited to endure chronic stress.

It is important to note that sex differences vary across the lifespan. Differences in the stress response show marked changes across the course of life, with females in the period between puberty and menopause showing greater HPA axis activity and lower cortisol reactivity than men, while in childhood this pattern is the reverse. This is likely related to patterns of psychopathology, with males experiencing greater negative outcomes from perinatal maternal stress (Hodes and Epperson, 2019), and females showing higher rates of affective disorders in adulthood - especially between puberty and menopause (e.g. Albert, 2015).

What are the implications of these sex differences? We argue that the sexes merit separate consideration in research on pathology and longevity, among many other scientific fields. The processes underlying illness and death appear different, and this must be reflected in research which seeks to improve our understanding of what influences longevity, health-related behavior, and wellbeing. Sex-blind thinking flies in the face off the evidence. We need to move to a research paradigm which analyzes data for men and women both together and separately. This will permit a better understanding of the biological and sociocultural influences at play, thus allowing for development of different approaches to health between the sexes, including in approaches to clinical assessment and treatment.

As noted previously, increased longevity is a recent phenomenon and little research has been conducted on centenarians. As heretofore the opportunities simply weren't there, it is important now to conduct studies focused on this population, characterized by a peculiar genotype plus healthy but varied lifestyles. Even controlled trials with this population are rare, with the available data pointing toward a combination of favorable genetic factors and environmental and personal traits (Ostan et al., 2016).

In conclusion, we believe there is abundant evidence that males and females develop differently, experience stress differently, behave differently, and become ill and die with different patterns. We consider there are tremendous opportunities to advance health and wellbeing through reflecting this in research agendas, with emphasis on the interaction of sex and ageing. We hope this paper is a step along this important road.

References

Albert, P.R., 2015. Why is depression more prevalent in women? J. Psychiatry Neurosci. 40 (4), 219–221.

Archer, J., 2019. The reality and evolutionary significance of human psychological sex differences. Biol. Rev. 94 (4), 1381–1415. https://doi.org/10.1111/brv.12507.

Armstrong, N.M., An, Y., Beason-Held, L., Doshi, J., Erus, G., Ferrucci, L., Davatzikos, C., Resnick, S.M., 2019. Sex differences in brain aging and predictors of neurodegeneration in cognitively healthy older adults. Neurobiol. Aging 81, 146–156. https://doi.org/10.1016/j.neurobiolaging.2019.05.020.

Arnold, A.P., 2009. The organizational-activational hypothesis as the foundation for a unified theory of sexual differentiation of all mammalian tissues. Horm. Behav. 55 (5), 570–578. https://doi.org/10.1016/j.yhbeh.2009.03.011.

Austad, S.N., 2019. Sex differences in health and aging: a dialog between the brain and gonad? GeroScience 41, 267–273. https://doi.org/10.1007/s11357-019-00081-3.

Bale, T.L., 2015. Epigenetic and transgenerational reprogramming of brain development. Nat. Rev. Neurosci. 16 (6), 332–344. https://doi.org/10.1038/nrn3818.

Bale, T.L., Epperson, C.N., 2015. Sex differences and stress across the lifespan. Nat. Neurosci. 18 (10), 1413–1420. https://doi.org/10.1038/nn.4112.

Bale, T.L., Baram, T.Z., Brown, A.S., Goldstein, J.M., Insel, T.R., McCarthy, M.M., Nemeroff, C.B., Reyes, T.M., Simerly, R.B., Susser, E.S., Nestler, E.J., 2010. Early life programming and neurodevelopmental disorders. Biol. Psychiatry 68 (4), 314–319. https://doi.org/10.1016/j.biopsych.2010.05.028.

Bangasser, D.A., Eck, S.R., Sanchez, E.O., 2019. Sex differences in stress reactivity in arousal and attention systems. Neuropsychopharmacology 44 (1), 129–139. https://doi.org/10.1038/s41386-018-0137-2.

Beam, C.R., Kaneshiro, C., Jang, J.Y., Reynolds, C.A., Pedersen, N.L., Gatz, M., 2018. Differences between women and men in incidence rates of dementia and Alzheimer's disease. J. Alzheimer Dis. 64 (4), 1077–1083. https://doi.org/10.3233/JAD-180141.

Bekhbat, M., Neigh, G.N., 2018. Sex differences in the neuro-immune consequences of stress: focus on depression and anxiety. Brain Behav. Immun. 67, 1–12. https://doi.org/10.1016/j.bbi.2017.02.006.

Beltrán-Sánchez, H., Finch, C.E., Crimmins, E.M., 2015. Twentieth century surge of excess adult male mortality. Proc. Natl. Acad. Sci. U. S. A. (PNAS) 112 (29), 8993–8998. https://doi.org/10.1073/pnas.1421942112.

Bhargava, A., Arnold, A.P., Bangasser, D.A., Denton, K.M., Gupta, A., Hilliard Krause, L. M., Mayer, E.M., McCarthy, M., Miller, W.L., Raznahan, A., Verma, R., 2021. Considering sex as a biological variable in basic dowand clinical studies: an endocrine society in basic and clinical studies: an endocrine society scientific statement. Endocr. Rev. 42 (3), 219–258. https://doi.org/10.1210/endrev/bnaa034.

Bilde, T., Maklakov, A.A., Meisner, K., la Guardia, L., Friberg, U., 2009. Sex differences in the genetic architecture of lifespan in a seed beetle: extreme inbreeding extends male lifespan. BMC Evol. Biol. 9, 33. https://doi.org/10.1186/1471-2148-9-33.

Caeyenberghs, K., Leemans, A., Geurts, M., Taymans, T., Vander Linden, C., Smits-Engelsman, B.C., Sunaert, S., Swinnen, S.P., 2010. Brain-behavior relationships in young traumatic brain injury patients: fractional anisotropy measures are highly correlated with dynamic visuomotor tracking performance. Neuropsychologia 48 (5), 1472–1482. https://doi.org/10.1016/j.neuropsychologia.2010.01.017.

Camus, M.F., Clancy, D.J., Dowling, D.K., 2012. Mitochondria, maternal inheritance, and male aging. Curr. Biol. 22 (18), 1717–1721. https://doi.org/10.1016/j.cub.2012.07.018.

Carlisi, C.O., Moffitt, T.E., Knodt, A.R., Harrington, H., Ireland, D., Melzer, T.R., Poulton, R., Ramrakha, S., Caspi, A., Hariri, A., Viding, E., 2020. Associations between life-course-persistent antisocial behaviour and brain structure in a population-representative longitudinal birth cohort. Lancet Psychiatry 7 (3), 245–253. https://doi.org/10.1016/S2215-0366(20)30002-X.

Connellan, J., Baron-Cohen, S., Wheelwright, S., Batki, A., Ahluwalia, J., 2000. Sex differences in human neonatal social perception. Infant Behav. Dev. 23 (1), 113–118. https://doi.org/10.1016/S0163-6383(00)00032-1.

CSDH, 2008. Closing the gap in a generation. Health equity through action on the social determinants of health. Final Report/Executive Summary of the Commission on the Social Determinants of Health (WHO Reference Number: WHO/IER/CSDH/08.1). WHO, Geneva (Accessed 06/01/2021). http://www.who.int/social_determinants/thecommission/finalreport/en/index.html.

Cupaioli, F.A., Zucca, F.A., Caporale, C., Lesch, K.P., Passamonti, L., Zecca, L., 2020. The neurobiology of human aggressive behavior: neuroimaging, genetic, and neurochemical aspects. Prog. Neuropsychopharmacol. Biol. Psychiatry 106, 110059. https://doi.org/10.1016/j.pnpbp.2020.110059.

Davis, E.P., Pfaff, D., 2014. Sexually dimorphic responses to early adversity: implications for affective problems and autism spectrum disorder. Psychoneuroendocrinology 49, 11–25. https://doi.org/10.1016/j.psyneuen.2014.06.014.

Dearden, L., Bouret, S.G., Ozanne, S.E., 2018. Sex and gender differences in developmental programming of metabolism. Mol. Metab. 15, 8–19. https://doi.org/10.1016/j.molmet.2018.04.007.

Dhabhar, F.S., 2018. The short-term stress response-Mother nature's mechanism for enhancing protection and performance under conditions of threat, challenge, and opportunity. Front. Neuroendocrinol. 49, 175–192. https://doi.org/10.1016/j.yfrne.2018.03.004.

Di Micco, R., Krizhanovsky, V., Baker, D., di Fagagna, F.D.A., 2021. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. Nat. Rev. Mol. Cell Biol. 22 (2), 75–95.

Dowler, E., 2001. Inequalities in diet and physical activity in Europe. Public Health Nutr. 4 (2B), 701–709. https://doi.org/10.1079/phn2001160.

Duren, D.L., Seselj, M., Froehle, A.W., Nahhas, R.W., Sherwood, R.J., 2013. Skeletal growth and the changing genetic landscape during childhood and adulthood. Am. J. Phys. Anthropol. 150 (1), 48–57. https://doi.org/10.1002/ajpa.22183.

Erol, A., Karpyak, V.M., 2015. Sex and gender-related differences in alcohol use and its consequences: contemporary knowledge and future research considerations. Drug Alcohol Depend. 156, 1–13. https://doi.org/10.1016/j.drugalcdep.2015.08.023.

European Commission, 2011. The State of Men's Health in Europe. https://ec.europa.eu/health/sites/health/files/state/docs/men_health_extended_en.pdf.

Fares, J., Bou Diab, Z., Nabha, S., Fares, Y., 2019. Neurogenesis in the adult hippocampus: history, regulation, and prospective roles. Int. J. Neurosci. 129 (6), 598–611.

Farrell, S., Stubbings, G., Rockwood, K., Mitnitski, A., Rutenberg, A., 2021. The potential for complex computational models of aging. Mech. Ageing Dev. 193, 111403 https://doi.org/10.1016/j.mad.2020.111403.

Fox, C.W., Scheibly, K.L., Wallin, W.G., Hitchcock, L.J., Stillwell, R.C., Smith, B.P., 2006. The genetic architecture of life span and mortality rates: gender and species differences in inbreeding load of two seed-feeding beetles. Genetics 174, 763–773. https://doi.org/10.1534/genetics.106.060392.

Friedrich, M.J., 2017. Depression is the leading cause of disability around the world. J. Am. Med. Assoc. 317, 1517. https://doi.org/10.1001/jama.2017.3826.

Gignac, G.E., Bates, T.C., 2017. Brain volume and intelligence: the moderating role of intelligence measurement quality. Intelligence 64 (C), 18–29. https://doi.org/10.1016/j.intell.2017.06.004.

Graves, B.M., Strand, M., Lindsay, A.R., 2006. A reassessment of sexual dimorphism in human senescence: theory, evidence, and causation. Am. J. Hum. Biol. 18 (2), 161–168. https://doi.org/10.1002/ajhb.20488.
Gur, R.E., Gur, R.C., 2002. Gender differences in aging: cognition, emotions, and neuroimaging studies. Dialogues Clin. Neurosci. 4 (2), 197–210. https://doi.org/10.31887/DCNS.2002.4.2/rgur.
Gur, R.C., Turetsky, B.I., Matsui, M., Yan, M., Bilker, W., Hughett, P., Gur, R.E., 1999. Sex differences in brain gray and white matter in healthy young adults: correlations with cognitive performance. J. Neurosci. 19 (10), 4065–4072. https://doi.org/10.1523/JNEUROSCI.19-10-04065.1999.
Hines, M., 2020. Neuroscience and sex/gender: looking back and forward. J. Neurosci. 40 (1), 37–43. https://doi.org/10.1523/JNEUROSCI.0750-19.2019.
Hodes, G.E., Epperson, C.N., 2019. Sex differences in vulnerability and resilience to stress across the life span. Biol. Psychiatry 86 (6), 421–432. https://doi.org/10.1016/j.biopsych.2019.04.028.
Hoffman, J.M., O'Neill, D.G., Creevy, K.E., Austad, S.N., 2018. Do female dogs age differently than male dogs? J. Gerontol. A Biol. Sci. Med. Sci. 73 (2), 150–156. https://doi.org/10.1093/gerona/glx061.
Hollanders, J., van der Voorn, B., Rotteveel, J., Finken, M., 2017. Is HPA axis reactivity in childhood gender-specific? A systematic review. Biol. Sex Differ. 8 (1), 23. https://doi.org/10.1186/s13293-017-0144-8.
Kelly, S.D., Harrell, C.S., Neigh, G.N., 2014. Chronic stress modulates regional cerebral glucose transporter expression in an age-specific and sexually-dimorphic manner. Physiol. Behav. 126, 39–49. https://doi.org/10.1016/j.physbeh.2013.12.002.
Kim, D.R., Bale, T.L., Epperson, C.N., 2015. Prenatal programming of mental illness: current understanding of relationship and mechanisms. Curr. Psychiatry Rep. 17, 5. https://doi.org/10.1007/s11920-014-0546-9.
Kryspin-Exner, I., Lamplmayr, E., Felnhofer, A., 2011. Geropsychology: the gender gap in human aging - a mini-review. Gerontology 57 (6), 539–548. https://doi.org/10.1159/000323154.
Kubben, N., Misteli, T., 2017. Shared molecular and cellular mechanisms of premature ageing and ageing-associated diseases. Nat. Rev. Mol. Cell Biol. 18 (10), 595–609.
Kurth, F., Cherbuin, N., Luders, E., 2019. Age but no sex effects on subareas of the amygdala. Hum. Brain Mapp. 40 (6), 1697–1770. https://doi.org/10.1002/hbm.24481.
Lahdenperä, M., Lummaa, V., Helle, S., Tremblay, M., Russell, A.F., 2004. Fitness benefits of prolonged post-reproductive lifespan in women. Nature 428 (6979), 178–181. https://doi.org/10.1038/nature02367.
Lahdenperä, M., Mar, K.U., Lummaa, V., 2016. Nearby grandmother enhances calf survival and reproduction in Asian elephants. Sci. Rep. 6 (1), 27213. https://doi.org/10.1038/srep27213.
Lenz, B., Kornhuber, J., 2018. Cross-national gender variations of digit ratio (2D:4D) correlate with life expectancy, suicide rate, and other causes of death. J. Neural Transm. 125 (2), 239–246. https://doi.org/10.1007/s00702-017-1815-7.
Lotze, M., Domin, M., Gerlach, F.H., Gaser, C., Lueders, E., Schmidt, C.O., Neumann, N., 2019. Novel findings from 2838 adult brains on sex differences in gray matter brain volume. Sci. Rep. 9, 1671. https://doi.org/10.1038/s41598-018-38239-2.
Maklakov, A.A., Lummaa, V., 2013. Evolution of sex differences in lifespan and aging: causes and constraints. Bioessays 35 (8), 717–724. https://doi.org/10.1002/bies.201300021.
Maklakov, A.A., Friberg, U., Dowling, D.K., Arnqvist, G., 2006. Within-population variation in cytoplasmic genes affects female life span and aging in Drosophila melanogaster. Evolution 60 (10), 2081–2086.
Marwha, D., Halari, M., Eliot, L., 2017. Meta-analysis reveals a lack of sexual dimorphism in human amygdala volume. Neuroimage 15 (147), 282–294. https://doi.org/10.1016/j.neuroimage.2016.12.021.
Mauvais-Jarvis, F., Bairey Merz, N., Barnes, P.J., Brinton, R.D., Carrero, J.J., DeMeo, D. L., De Vries, G.J., Epperson, C.N., Govindan, R., Klein, S.L., Lonardo, A., Maki, P.M., McCullough, L.D., Regitz-Zagrosek, V., Regensteiner, J.G., Rubin, J.B., Sandberg, K., Suzuki, A., 2020. Sex and gender: modifiers of health, disease, and medicine. Lancet 396 (10250), 565–582. https://doi.org/10.1016/S0140-6736(20)31561-0.
Maynard, S., Fang, E.F., Scheibye-Knudsen, M., Croteau, D.L., Bohr, V.A., 2015. DNA damage, DNA repair, aging, and neurodegeneration. Cold Spring Harb. Perspect. Med. 5 (10), a025130. https://doi.org/10.1101/cshperspect.a025130.
McCarthy, M.M., Nugent, B.M., 2013. Epigenetic contributions to hormonally mediated sexual differentiation of the brain. J. Neuroendocrinol. 25 (11), 1133–1140. https://doi.org/10.1111/jne.12072.
McHugh, D., Gil, J., 2018. Senescence and aging: causes, consequences, and therapeutic avenues. J. Cell Biol. 217 (1), 65–77. https://doi.org/10.1083/jcb.201708092.
Mishra, A., Patni, P., Hegde, S., Aleya, L., Tewari, D., 2020. Neuroplasticity and environment: a pharmacotherapeutic approach towards preclinical and clinical understanding. Curr. Opin. Environ. Sci. Health 19, 100210. https://doi.org/10.1016/j.coesh.2020.09.004.
Morgan, C.P., Bale, T.L., 2012. Sex differences in microRNA regulation of gene expression: no smoke, just miRs. Biol. Sex Differ. 3 (1), 22. https://doi.org/10.1186/2042-6410-3-22.
Mourits, R., 2017. Later-life mortality and longevity in late-18th and 19th-century cohorts. Where are we now, and where are we heading? Historical Life Course Stud. 4, 1–19. http://hdl.handle.net/10622/23526343-2017-0001?locatt=view:master.
Nattrass, S., Croft, D.P., Ellis, S., Cant, M.A., Weiss, M.N., Wright, B.M., Stredulinsky, E., Doniol-Valcroze, T., Ford, J.K.B., Balcomb, K.C., Franks, D.W., 2019. Postreproductive killer whale grandmothers improve the survival of their grand offspring. Proc. Natl. Acad. Sci. 116 (52), 26669–26673. https://doi.org/10.1073/pnas.1903844116.
Navarro-Pardo, E., Holland, C., Cano, A., 2018. Sex hormones and healthy psychological ageing in women. Front. Aging Neurosci. 9, 439. https://doi.org/10.3389/fnagi.2017.00439.
Nave, G., Jung, W.H., Karlsson Linnér, R., Kable, J.W., Koellinger, P.D., 2019. Are bigger brains smarter? Evidence from a large-scale preregistered study. Psychol. Sci. 30 (1), 43–54. https://doi.org/10.1177/0956797618808470.
Ngun, T.C., Ghahramani, N., Sánchez, F.J., Bocklandt, S., Vilain, E., 2011. The genetics of sex differences in brain and behavior. Front. Neuroendocrinol. 32 (2), 227–246. https://doi.org/10.1016/j.yfrne.2010.10.001.
Nolan, I.T., Kuhner, C.J., Dy, G.W., 2019. Demographic and temporal trends in transgender identities and gender confirming surgery. Transl. Androl. Urol. 8 (3), 184–190. https://doi.org/10.21037/tau.2019.04.09.
Nugent, B.M., O'Donnell, C.M., Epperson, C.N., Bale, T.L., 2018. Placental H3K27me3 establishes female resilience to prenatal insults. Nat. Commun. 9 (1), 2555. https://doi.org/10.1038/s41467-018-04992-1.
O'Connor, T.G., Heron, J., Golding, J., Beveridge, M., Glover, V., 2002. Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years. Report from the Avon Longitudinal Study of Parents and Children. Br. J. Psychiatry 180, 502–508. https://doi.org/10.1192/bjp.180.6.502.
Ostan, R., Monti, D., Gueresi, P., Bussolotto, M., Franceschi, C., Baggio, G., 2016. Gender, aging and longevity in humans: an update of an intriguing/neglected scenario paving the way to a gender-specific medicine. Clin. Sci. 130 (19), 1711–1725. https://doi.org/10.1042/CS20160004.
Palmisano, S., Fasotti, L., Bertens, D., 2020. Neurobehavioral initiation and motivation problems after acquired brain injury. Front. Neurol. 11, 23. https://doi.org/10.3389/fneur.2020.00023.
Podolskiy, D.I., Lobanov, A.V., Kryukov, G.V., Gladyshev, V.N., 2016. Analysis of cancer genomes reveals basic features of human aging and its role in cancer development. Nat. Commun. 7, 12157. https://doi.org/10.1038/ncomms12157.
Ritchie, S.J., Cox, S.R., Shen, X., Lombardo, M.V., Reus, L.M., Alloza, C., Harris, M.A., Alderson, H.L., Hunter, S., Neilson, E., Liewald, D., Auyeung, B., Whalley, H.C., Lawrie, S.M., Gale, C.R., Bastin, M.E., McIntosh, A.M., Deary, I.J., 2018. Sex differences in the adult human brain: evidence from 5216 UK biobank participants. Cereb. Cortex 28 (8), 2959–2975. https://doi.org/10.1093/cercor/bhy109.
Rockwood, K., Mogilner, A., Mitnitski, A., 2004. Changes with age in the distribution of a frailty index. Mech. Ageing Dev. 125 (7), 517–519. https://doi.org/10.1016/j.mad.2004.05.003.
Rogers, R.G., Everett, B.G., Onge, J.M., Krueger, P.M., 2010. Social, behavioral, and biological factors, and sex differences in mortality. Demography 47 (3), 555–578. https://doi.org/10.1353/dem.0.0119.
Ronald, A., Pennell, C.E., Whitehouse, A.J., 2011. Prenatal maternal stress associated with ADHD and autistic traits in early childhood. Front. Psychol. 1, 223. https://doi.org/10.3389/fpsyg.2010.00223.
Ruigrok, A.N., Salimi-Khorshidi, G., Lai, M.C., Baron-Cohen, S., Lombardo, M.V., Tait, R. J., Suckling, J., 2014. A meta-analysis of sex differences in human brain structure. Neurosci. Biobehav. Rev. 39 (100), 34–50. https://doi.org/10.1016/j.neubiorev.2013.12.004.
Sandman, C.A., Glynn, L.M., Davis, E.P., 2013. Is there a viability-vulnerability tradeoff? Sex differences in fetal programming. J. Psychosom. Res. 75 (4), 327–335. https://doi.org/10.1016/j.jpsychores.2013.07.009.
Shammas, M.A., 2011. Telomeres, lifestyle, cancer, and aging. Curr. Opin. Clin. Nutr. Metab. Care 14 (1), 28–34. https://doi.org/10.1097/MCO.0b013e32834121b1.
Shanmugan, S., Epperson, C.N., 2014. Estrogen and the prefrontal cortex: towards a new understanding of estrogen's effects on executive functions in the menopause transition. Hum. Brain Mapp. 35 (3), 847–865. https://doi.org/10.1002/hbm.22218.
Shin, S., Kim, K., Nam, H.Y., Kim, I.J., Pak, K., 2021. Sex difference in cerebral blood flow and cerebral glucose metabolism: an activation-likelihood estimation meta-analysis. Nucl. Med. Commun. 42 (4), 410–415. https://doi.org/10.1097/MNM.0000000000001343.
Sundermann, E.E., Panizzon, M.S., Chen, X., Andrews, M., Galasko, D., Banks, S.J., Alzheimer's Disease Neuroimaging Initiative, 2020. Sex differences in Alzheimer's-related Tau biomarkers and a mediating effect of testosterone. Biol. Sex Differ. 11 (1), 33. https://doi.org/10.1186/s13293-020-00310-x.
Sze, Y., Brunton, P.J., 2020. Sex, stress and steroids. Eur. J. Neurosci. 52 (1), 2487–2515. https://doi.org/10.1111/ejn.14615.
Tabatabaie, V., Atzmon, G., Rajpathak, S.N., Freeman, R., Barzilai, N., Crandall, J., 2011. Exceptional longevity is associated with decreased reproduction. Aging 3 (12), 1202–1205. https://doi.org/10.18632/aging.100415.
Tower, J., 2006. Sex-specific regulation of aging and apoptosis. Mech. Ageing Dev. 127 (9), 705–718. https://doi.org/10.1016/j.mad.2006.05.001.
UK Office for National Statistics, 2020. Suicides in England and Wales: 2019 Registrations. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/suicidesintheunitedkingdom/2019registrations#suicide-patterns-by-age.
UK Office of National Statistics, 2017. Causes of Death Over 100 Years. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/causesofdeathover100years/2017-09-18.
UNODC, 2019. Global Study on Homicide. United Nations Office on Drugs and Crime, Vienna.
VanTieghem, M.R., Tottenham, N., 2017. Neurobiological programming of early life stress: functional development of amygdala-prefrontal circuitry and vulnerability for

stress-related psychopathology. Curr. Top. Behav. Neurosci. 38, 117–136. https://doi.org/10.1007/7854_2016_42.

Xin, J., Zhang, Y., Tang, Y., Yang, Y., 2019. Brain differences between men and women: evidence from deep learning. Front. Neurosci. 13, 185. https://doi.org/10.3389/fnins.2019.00185.

You, D., Maeda, Y., Bebeau, M.J., 2011. Gender differences in moral sensitivity: a meta-analysis. Ethics Behav. 21 (4), 263–282. https://doi.org/10.1080/10508422.2011.585591.