Sexual dimorphism of frailty and cognitive impairment: Potential underlying mechanisms (Review)

QINGWEI RUAN[1], GRAZIA D'ONOFRIO[2], TAO WU[1], ANTONIO GRECO[2], DANIELE SANCARLO[2] and ZHUOWEI YU[1]

[1]Department of Geriatrics, Shanghai Key Laboratory of Clinical Geriatrics, Shanghai Institute of Geriatrics and Gerontology, Huadong Hospital and Research Center of Aging and Medicine, Shanghai Medical College, Fudan University, Shanghai 200040, P.R. China; [2]Department of Medical Sciences, Geriatric Unit and Laboratory of Gerontology and Geriatrics, The Scientific Institute for Research and Health Care, Home for Relief of the Suffering Hospital, San Giovanni Rotondo, Foggia I-71013, Italy

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Abstract. The aim of the present study was to assess systematically gender differences in susceptibility to frailty and cognitive performance decline, and the underlying mechanisms. A systematic assessment was performed of the identified reviews of cohort, mechanistic and epidemiological studies. The selection criteria of the present study included: i) Sexual dimorphism of frailty, ii) sexual dimorphism of subjective memory decline (impairment) and atrophy of hippocampus during early life, iii) sexual dimorphism of late-onset Alzheimer's disease and iv) sexual dimorphism mechanisms underlying frailty and cognitive impairment. Males exhibit a susceptibility to poor memory performance and a severe atrophy of the hippocampus during early life and females demonstrate a higher prevalence for frailty and late-life dementia. The different alterations within the hypothalamic-pituitary-gonadal/adrenal axis, particularly with regard to gonadal hormones, cortisol and dehydroepiandrosterone/sulfate-bound dehydroepiandrosterone prior to and following andropause in males and menopause in females, serve important roles in sexual dimorphism of frailty and cognitive impairment. These endocrine changes may accelerate immunosenescence, weaken neuroprotective and neurotrophic effects, and promote muscle catabolism. The present study suggested that these age-associated endocrine alterations interact with gender-specific genetic and epigenetic factors, together with immunosenescence and iron accumulation. Environment factors, including psychological factors, are additional potential causes of the sexual dimorphism of frailty and cognitive impairment.

Correspondence to: Dr Zhuowei Yu, Department of Geriatrics, Shanghai Key Laboratory of Clinical Geriatrics, Shanghai Institute of Geriatrics and Gerontology, Huadong Hospital and Research Center of Aging and Medicine, Shanghai Medical College, Fudan University, 221 West Yan An Road, Shanghai 200040, P.R. China
E-mail: hdyuzhuowei@163.com

Abbreviations: ABCA1, ATP-binding cassette transporter 1; AD, Alzheimer's disease; IGF-1, growth hormone insulin-like growth factor-1; DHEA(S), decreased dehydroepiandrosterone/sulfate-bound dehydroepiandrosterone; GnRH, gonadotropin-releasing hormone; HDL, high-density lipoprotein; HPA, hypothalamic-pituitary-adrenocortical axis; HPG, hypothalamic-pituitary-gonadal; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; MCI, mild cognitive impairment; THBS4, thrombospondins-4

Key words: frailty, memory performance, atrophy of hippocampus, late-onset Alzheimer's disease, gender difference

Contents

1. Introduction
2. Alterations in gonadal hormones and sexual dimorphism of frailty and cognitive impairment
3. Alterations in the hypothalamic-pituitary-adrenocortical axis (HPA) axis and sexual dimorphism of frailty and cognitive impairment
4. Iron and the sexual dimorphism of frailty and cognitive impairment
5. Conclusions

1. Introduction

Epidemiologic studies (1,2-10) have revealed that frailty and cognitive impairment appear to be correlated with the sexual dimorphism in elderly people. In communities of elderly people, the weighted average prevalence rate was 9.9% [95% confidence interval (CI) 9.6-10.2] for physical frailty and 44.2% (CI 44.2-44.7) for pre-physical frailty (1). Physical frailty rose steadily with age: 65-69 years, 4%; 70-74 years, 7%; 75-79 years, 9%; 80-84 years, 16%; and >85 years, 26%. Physical frailty was statistically more prevalent in females (9.6%, CI 9.2-10.0) than in males (5.2%; CI 4.9-5.5). Sarcopenia is the most common cause of frailty (11). The average prevalence of low skeletal muscular mass over the

age of 60 was 5-13%, over 50% in people over the age of 80 (12,13) and almost 70% in nursing home residents (14). Low lean mass was present in 33% of community-dwelling elderly females and 10% of males in an urban area of Barcelona (15). However, two epidemiologic studies of community-dwelling elderly people in Asia demonstrated that females had a reduced prevalence of sarcopenia (0.8 vs. 1.3%) (16) and low muscle mass (2.5 vs. 5.4%) compared with males (17). This difference may have been partially caused by varying screening criteria.

Alzheimer's disease (AD), the most common type of dementia, slowly and progressively develops with a preclinical stage over decades (18,19). Age and gender are the potent risk factors in late-onset AD, which affects ~10% of individuals over age 65 years (20). The prevalence of AD is ~1% between 65 and 69 years and is >60% in individuals aged 80-85 (21). A recent study (22) of 1,246 cognitively healthy individuals (age, 30-95 years) revealed sexual dimorphisms in brain aging between males and females. Males exhibited a susceptibility to poor memory performance and a severe atrophy of the hippocampus during early life (age, 40-60 years). However, there was no greater prevalence of late-onset dementia among males. Previous studies of age-associated medical temporal lobe volume decline (23-25) demonstrated that the differences between genders varied considerably. Previous studies have revealed more significant atrophy of hippocampus in males compared with females in early healthy adulthood (26,27). The speculative causes, which affect the signal intensity of Magnetic Resonance Imaging images, include inflammatory processes and the differing alterations in the iron content of the hippocampus cells between males and females (26). Certain epidemiologic studies (28-31) have suggested that there was no sexual difference in the incidence rates of AD. A previous study reported no gender differences in the incidence of dementia up to a high age (32). After 90 years of age the incidence of AD is greater in females compared with males. In addition, there are different results for the risk of vascular dementia (2,3,32). However, the majority of studies, particularly one large meta-analysis, confirmed that females were at greater risk of developing AD and deterioration of cognition (2-10). These data appear to be significant even after adjusting for well-known differences in survival rates and reciprocally for education level.

Multiple transgenic mouse models of AD have demonstrated that females are inherently more susceptible to AD pathogenesis compared with males, with earlier and greater pathology and behavioral impairment [see reviews by Li and Singh (6) and Vest and Pike (33)]. This raises the question as to the cause of early age gender differences in memory performance and brain atrophy and the subsequent risks for frailty and dementia in later life. The aging of the endocrine system is closely associated with sarcopenia, frailty and cognitive impairment (34-37). During healthy aging, endocrine pathways under hypothalamic-pituitary control show age-associated alterations. There are declines in output from the gonadal axis, the growth hormone insulin-like growth factor-1 (IGF-1) axis and decreased dehydroepiandrosterone/sulfate-bound dehydroepiandrosterone [DHEA(S)] output from the adrenal axis; however, there is an increased output of cortisol (6,7). One potential cause may be endocrinologically different alterations within the hypothalamic-pituitary-gonadal (HPG)/adrenal axis, particularly with regard to gonadal hormones, cortisol and DHEA(S) prior to and following andropause in males and menopause in females. In addition, the complex interactions between endocrine and neurophysiological, immune, genetic and epigenetic factors in aging may serve important roles.

The present study conducted literature searches on the PubMed database (https://www.ncbi.nlm.nih.gov/pubmed) to identify relevant papers published between January 1990 and June 2015. The database was searched with the following key words: Frailty, sarcopenia, prevalence, gender difference, memory performance, subjective memory decline (impairment), late-onset AD, endocrine system, aging, gonadal hormones, androgens, estrogens, immunosenescence, brain aging, genetics, cortisol, DHEA(S), iron overload and hippocampal atrophy. The searches were limited to English language articles. In addition, the pertinent references mentioned in the previously identified papers were analyzed.

2. Alterations in gonadal hormones and sexual dimorphism of frailty and cognitive impairment

Decline in sex hormones from the gonadal axis. Sex hormones have been considered as the cause of sexual dimorphisms in various pathophysiological alterations. In humans, aging leads to a decline in estrogen and testosterone, with an increase in luteinizing hormone, follicle-stimulating hormone and sex hormone-binding globulin in humans (38,39). Estrogen is produced primarily by developing follicles in the ovaries, and by the corpus luteum and placenta. The secondary sources of estrogen, including the liver and adrenal glands, produce smaller quantities; however, these are important sources of endogenous estrogen that alter little in postmenopausal females. The most significant difference between males and females >55 years is the menopause, which results in a rapid decrease in circulating baseline levels of estrogens and androgens (40-43). On average, 80% of estrogens is lost in females during the first year of menopause with little alterations following the menopause (40). Serum testosterone concentrations in postmenopausal females are ~15% of premenopausal levels (44). In addition, brain levels of estrogens and androgens exhibit a similar pattern in postmenopausal females (45). The circulating levels of estrogens and androgens in healthy aging males decrease gradually, beginning in the fourth decade (46). Due to the increase in age-associated sex hormone-binding globulin, the decrease of free testosterone is greater compared with total testosterone (46,47). The circulating bioavailable testosterone concentrations decrease ~20% in males >60 years and 50% in those >80 years, compared with young males (46,47). Almost 5% of males aged 70-79 years demonstrated andropause (48). Testosterone may be converted to estradiol, an active metabolite of estrone, by the aromatase enzyme, which is located peripherally and throughout the male brain. Although the conversion rate of testosterone to estrogen is low, at ~0.2%, it is the primary source of plasma estradiol in males. In contrast to circulating testosterone, the levels of testosterone in male brains exhibit a strong decline and are at their lowest at ~80 years old (45). Healthy aged males possess a 10-25-fold greater circulating concentration of androgens

and a 2-4-fold greater quantity of estrogens compared with females (41-43).

Frailty and decline in gonadal hormones. Of the gonadal hormones of the HPG axis, the age-associated decline in testosterone may serve a primary role in decreased muscle mass and strength (49). Mohr *et al* (50) identified that total and free testosterone levels were not associated with frailty in males. In the Women's Health and Aging Studies, Coppola *et al* (51) identified that relative deficiency in a number of anabolic hormones, including IGF-1, DHEA(S) and free testosterone, was an independent predictor of frailty, although deficiency of a single hormone was not significantly associated with frailty. However, other studies (49,52-54) have demonstrated that low testosterone levels are associated with sarcopenia and frailty in elderly males. Furthermore, IGF-1, DHEA(S) and free testosterone were each associated with age-related cognitive and physical events (52). In a cohort study (55) of community-dwelling males ≥70 years (n=1645), individuals in the lowest testosterone quintile had 2.2-fold greater odds of demonstrating physical frailty compared with the highest testosterone quintile. Furthermore, a decline in testosterone, calculated free testosterone or luteinizing hormone was associated with 1.2 to 1.3-fold increase in the severity of frailty at a 2-year follow-up. The relevance of serum free testosterone and frailty is gender-specific. In one cross-sectional study (n=2,488), a U-shaped association between serum free testosterone and frailty, which appeared to be modulated by body mass index, was reported in elderly females (56). The gender-specific association between testosterone and frailty may involve different underlying biological mechanisms.

Cognitive impairment and decline in gonadal hormones. During critical periods of neural development, sex steroid signaling may contribute to the increased vulnerability of females to AD pathology [see review by Vest and Pike (33)]. The levels of circulating gonadal hormones influence cognitive functions. Healthy people also exhibit aging-associated gender differences in cognition. Older males performed worse in mental rotations tasks compared with younger males and older females (57). During brain developmental maturation in puberty, hippocampal volume negatively correlates with the circulating testosterone levels, which cause gender-specific differences in hippocampal volume (58). Thus, male susceptibility to poor memory performance and severe atrophy of the hippocampus during adulthood may be a normal aging process. Estrogens and progesterone possess numerous brain-protective effects against various aspects of AD pathogenesis [see review by Li and Singh (6)]. Females with AD exhibit reduced circulating (59) and brain levels of estrogens compared with age-matched controls (45,60). The circulating and brain estrogens were of gonadal and extra-gonadal sources, which may explain why ovariectomy in wild-type rodents and certain AD mouse models resulted in increased amyloid (A)β accumulation, but not in other AD models (33,60). The cognitive function of aged ovariectomized rhesus monkeys may be significantly improved by estrogen replacement (61). The deficiency of estrogens may cause a decrease in hippocampal volume. The partial or complete loss of an X-chromosome in young females results in disproportionately reduced hippocampal volumes compared with age-matched individuals (62). Exogenous estrogen only demonstrated neuroprotective effects in cognitively intact females prior to menopause and accelerated the progression of neurodegeneration once that neurodegeneration process was present at menopause (63). Therefore, the abrupt decline of gonadal hormones at menopause may be a potential reason for the greater prevalence of late-onset AD in females compared with males. The influences of testosterone levels on cognitive functions are controversial. Certain studies (45,64-66) have identified that decreased circulating and brain levels of testosterone in old age were associated with cognitive decline and increased risk of AD in males. In male 3xTg-AD mice, depletion of endogenous androgens by orchiectomy significantly accelerates AD-like pathology, including Ab accumulation and cognitive impairment (67). However, another study (68) demonstrated that greater levels of testosterone failed to improve cognitive function. Therefore, certain studies (33,69) have speculated that an optimal level of testosterone is beneficial to cognition. The gender-specific differences of risks for frailty and late-onset AD involve the underlying mechanisms described below.

Regulation of immunosenescence by gonadal hormones. Estrogens enhance immunity, particularly humoral immunity, and menopause transition with decreased estradiol promotes female immunosenescence. Androgens and progesterone function as an immunosuppressors (70). In chronic inflammatory diseases where monocytes, macrophages, dendritic cells, T cells, fibroblasts and neutrophils serve a dominant role, estrogens demonstrate anti-inflammatory effects by inhibiting numerous pro-inflammatory pathways involved in innate immunity, adaptive immunity and inflammatory tissue responses (71). However, when B cells are dominant in an inflammatory disease, as in the case of systemic lupus erythematosus, estrogens may stimulate the disease process. In addition, estrogens reduce low-density lipoprotein (LDL) and increase high-density lipoprotein (HDL) cholesterol; HDL is a powerful anti-inflammatory agent. Furthermore, estrogens exhibit antioxidant properties by upregulating the expression of genes that encode antioxidant enzymes, which results in a decrease in mitochondrial free-radical production. Thus, compared with males, females are more susceptible to autoimmune diseases and associated infections, and exhibit greater efficacy from vaccinations (72). Females also demonstrate reduced susceptibility to age-associated disorders, including cardiovascular disease and AD, and numerous infectious diseases when compared with males of the same age (70). Due to the age-associated alterations in the levels of sex hormones and corresponding atherogenic lipid serum concentrations, including increases in LDL and total cholesterol and decreases in HDL in menopausal females, the risk of age-associated disorders increases and is similar to males of equivalent age. The improved response to vaccination and the reduced predisposition to infections in females are eliminated following the menopause, when their inflammatory status is characterized by the increased expression of pro-inflammatory cytokines including tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-8, IL-13, interferon-γ and monocyte chemoattractant protein 1 (71). Inflammatory and stress responses may activate nuclear factor (NF)-κB in the hypothalamus and induce a

signaling pathway that results in a reduction in the neuronal production of gonadotropin-releasing hormone (GnRH) (73). This decline in GnRH may contribute to an age-associated reduction in neurogenesis. Therefore, there is a bi-directional connection between the HPG axis and the immune system, which leads to age-associated disorders. The pro-inflammatory status that results from innate immunity senescence is toxic to neurons and affects the metabolism of the amyloid precursor protein. An imbalance between the production of Aβ by neuronal cells and astrocytes, and its degradation, may trigger chronic inflammatory processes in microglial cells and astrocytes and initiate a vicious cycle that ultimately results in AD (74).

In addition, chronic low grade systemic inflammation is a primary contributor to sarcopenia, frailty and age-associated diseases (75-77). Inflammatory cytokines, including IL-6 and TNF-α, activate catabolism of skeletal muscle and cause an imbalance between new muscle cell formation, hypertrophy and protein loss, resulting in the loss of muscle mass and strength (75). Compared with elderly males, menopausal females are more susceptible to certain age-associated diseases, including atherosclerosis, obesity and diabetes, depression, and osteoporosis (6,78). These comorbidities increase the risk of sarcopenia and frailty (76,79,80). The advantages that mitochondria from young females exhibit, including protection against Aβ toxicity, reduced generation of reactive oxygen species and reduced release of apoptogenic signals compared with males, are lost in mitochondria from older females (81). Thus, the critical mechanisms include low grade inflammation, oxidative stress and decline of anabolic hormones due to vascular perfusion decrease, hypoxaemia and increased insulin resistance. A population-based cohort study of a total of 2,719 participants with a median follow-up of 4 years (82), identified cardiac disease as an independent risk factor for nonamnestic mild cognitive impairment (MCI) in females, which would progress to vascular and other non-AD dementias. Another population-based cohort study (83) demonstrated that type 2 diabetes was associated with a higher risk of amnestic MCI in males and a strong association with single-domain nonamnestic MCI in females. Baseline depression of elderly community-dwelling individuals promotes the conversion of MCI to dementia (84). Apart from comorbidities, sarcopenia in older females is associated with cognitive impairment (85). Physical frailty may predict future cognitive decline (86). Lean mass loss is associated with brain atrophy and cognitive performance and AD patients exhibit an accelerated lean mass loss (87). The connection between frailty and cognitive impairment suggests they share a common pathogenesis (34-36,76,88,89).

Neuroprotective and neurotrophic effects of gonadal hormones. Androgens and estrogens are neuroprotective in males and females, respectively. Estrogens demonstrate neuroprotective (memory preserving) and neurotrophic (memory enhancing) actions in rodents and rhesus monkeys, through nuclear and extranuclear hippocampal estrogen receptors that function to increase spine density and synapse formation (90,91), improve brain structural and functional plasticity by neurotrophin expression and neurogenesis (92-94), regulate brain metabolism (95), effect connectivity within prefrontal-hippocampal circuitry (96), affect the synaptic distribution of estrogen receptor (97), neuronal excitability (94), brain Aβ levels (95,98,99) and hyperphosphorylated t levels (100), and decrease the toxic effects of amyloid (101). In addition, progesterone demonstrates neuroprotective effects against AD by modulating γ secretase and Aβ production (102), and increasing Aβ clearance (103). A GnRH agonist that suppresses ovarian function in young adult females causes deficits in verbal memory and task-associated neural activity patterns that may be corrected by the administration of exogenous ovarian hormones (104). The rapid decline of ovarian estrogens and progestogens at menopause has been considered as a reason for increased female susceptibility to AD. Furthermore, animal and human studies have suggested that brain estrogen, rather than circulating estradiol, deficiency is more significantly associated with the risk of AD and induced AD-associated neuropathological changes (60).

The associations between sex steroid hormones and AD risk are gender-specific. Although androgens may be converted to estradiol by aromatase enzyme, there is no association between brain estrogens levels and AD risk in males (33). Age-associated reduced levels of available testosterone have been associated with an increased risk of AD. Males with AD demonstrate decreased circulating and brain levels of testosterone compared with age-matched controls (6,45). An optimal level of testosterone exhibits neuroprotective effects by a high density of androgen receptors in the hippocampus and its associated cortical areas (105,106). Testosterone may promote synaptic plasticity (107,108), protect against apoptosis in hippocampal neurons (109) and attenuate Ab toxicity (110). The age-associated decline in androgen levels appears earlier compared with the neuropathological diagnosis of AD and the decline in androgen levels may be a cause of AD.

Genetics may also be a cause of sexual dimorphism of frailty and cognitive impairment. Polymorphisms of the aromatase gene intron 1 (CYP19A1, rs1062033), which codes for a rate-limiting enzyme in the synthesis of estrogens, result in epistatic interactions with IL10-1082 polymorphisms (rs1800896) that are restricted to females >75 years old (adjusted synergy factor=2.29; 95% CI, 1.24-4.21; P=0.008) compared with females <75 years old (1.00; 95% CI, 0.28-3.51; P=1.00). Each genotype (CYP19A1 interaction 1 CC+CG and IL10-1028 AA+ AG) is associated with an increased risk of AD in the presence of the other genotype, which could result from the reduction of IL-10 production and estrogen synthesis (111). These age-associated differences are consistent with the epidemiological evidence that demonstrate a greater susceptibility to AD of females compared with males only in the very elderly, for example, >80 years old (7-10).

The effect of apolipoprotein Eε4 (APOEε4) on the hippocampus and memory performance appears to be more directly associated with co-occurrences of β-amyloidosis in later life (>70 years of age) on a background of pre-existing structural and cognitive decline that is associated with aging (112). In cognitively healthy elderly individuals, an increased cerebral amyloid burden, which is highly associated with the APOEε4 genotype (113), is associated with subtle declines in cognitive performance and an increased risk of future dementia (114,115). In addition, in elderly individuals with MCI, the APOEε4 genotype appears to exhibit a more deleterious effect in females

compared with males on gross hippocampal pathology and memory performance. The presence of one or more ApoEε4 alleles confers a substantially greater risk of AD in females compared with males (116). Females with ApoEε4 demonstrated greater rates of decline in cognitive function compared with male ApoEε4 carriers (112). Furthermore, compared with male ApoEε4 carriers, female ApoEε4 carriers with MCI possess a greater risk of cardiovascular mortality (117). In late-onset familial AD, ApoEε4 heterozygous females demonstrated a significant 2-fold increased risk of developing AD compared with ApoEε4 heterozygous males (118). In cognitively healthy, late-middle-aged individuals (49 to 67 years old), individuals with different copies of ApoEε4 allele exhibit similar hippocampal volume; therefore, the gender differences in ApoEε4-associated cognitive impairment are not associated with volume alterations of the hippocampus (119). Estrogen has been revealed to improve synaptic sprouting through an APOE-dependent mechanism (120). Therefore, the combined influence of estrogen loss and the presence of the APOEε4 genotype may, in part, account for the reports of an increased risk of late-onset AD in females (2-10). The LDL receptor (LDLR) is a primary ApoE receptor. The rs688T/T genotype that modulates the splicing efficiency of LDLR exon 12 was associated with increased risk of AD in males but not in females (121).

The thrombospondin-4 (THBS4) gene encodes a glycoprotein involved in inflammatory responses and synaptogenesis. In humans, THBS4 possesses two haplotypes and interacts with gender in influencing THBS4 expression. AD females with haplotype 1 homozygous demonstrate the lowest expression of THBS4 and reduced gray matter volumes (122). Single-nucleotide polymorphism variants of sortilin receptor 1 exhibit gender-specific effects on late-onset AD. Those homozygous males with rs2070045 risk allele demonstrated improved cognitive performance prior to the age of 75, while females demonstrated overall detrimental effects on cognitive performance (123). ATP-binding cassette transporter 1 (ABCA1) mediates cellular cholesterol efflux. Female carriers of ABCA1 polymorphism rs2230806 demonstrated a 1.75-fold increased risk of late-onset AD compared with non-carrier females (124). In addition, gonadal hormone-induced DNA methylation and histone modifications at specific gene regulatory regions may increase or decrease this susceptibility to AD (125).

3. Alterations in the hypothalamic-pituitary-adrenocortical axis (HPA) axis and sexual dimorphism of frailty and cognitive impairment

Alterations in the HPA axis during aging. A remarkable sexual dimorphism in adrenal hormone regulation, including the HPA and adrenal androgen DHEA(S) axis, may be an important factor in the sexual dimorphism observed in frailty and cognitive impairment. Cortisol, a lipophilic steroid hormone, is released from the cortex of the adrenal glands into circulation by the HPA axis in response to stress; 90% of cortisol binds to cortisol binding globulin and 8% to albumin. The cortisol level and rhythm demonstrate age-associated alterations. The mean cortisol levels increase progressively with age (126,127) and the majority of studies indicate that the typical age-associated decline in cortisol across the course of the day is attenuated (128,129). A meta-analysis of 45 studies (130) reported that pharmacological and psychosocial challenge resulted in a significantly greater cortisol stress response in older compared with younger subjects. DHEA(S) is the most abundant steroid hormone and the circulating level of DHEA, the majority of which is present in the sulfate-bound form DHEA(S), peaks at ~20 years old and declines rapidly and markedly from 25 years old (131). By 80 years old, individuals possess DHEA levels only 10-20% of those of younger counterparts due to an aging-associated reduction of the zona reticularis within the adrenal cortex (132,133).

Healthy older females have reduced levels of DHEA(S) and greater cortisol levels compared with older males and these disparities persist into advanced age (38,39). The differences in cortisol levels in males and females exhibit a progressive increase with aging. Compared with pre-menopausal females and older males, the HPA responses to psychosocial stress in post-menopausal females are increased. This effect of aging on the cortisol response is approximately three times greater in females compared with males (69). The sexual dimorphism in adrenal hormones may serve important roles in the susceptibility to age-associated alterations involved in cardiovascular disease and brain function (126).

Alterations in the HPA axis influence frailty. Regulating the response to stressors by negative feedback at the level of the hippocampus and associated structures is an important function of glucocorticoid. Cortisol serves an important role in the development of vulnerability to stressors in frail subjects. Greater circulating levels and blunted diurnal variation of cortisol are associated with frail community-dwelling elderly females (134). In elderly residents of long-stay institutions, frailty was positively correlated with salivary cortisol level (135). Sarcopenic individuals demonstrated elevated salivary cortisol levels compared with normal lean, sarcopenic-obese or obese subjects (136). Glucocorticoids inhibit protein synthesis and promote protein degradation, increase myostatin and decrease IGF-1 expression (137). Persistently high levels of cortisol, as in Cushing's syndrome, are associated with increased catabolism, contributing to the loss of muscle mass, muscle atrophy, reduced energy expenditure and sarcopenia (138,139). In addition, DHEA(S) levels have been identified to be significantly decreased in frail compared with robust individuals in a small case-control study (140). Furthermore, frail subjects possess decreased levels of serum IGF-1 and increased levels of IL-6 compared with robust, age-matched individuals (140). However, Puts *et al* (141) reported that low IGF-1 and high IL-6 levels were not consistently associated with frailty, in another longitudinal study.

Dysfunction of the HPA axis may contribute to aging-associated diseases including neuro-cognitive dysfunction (depression, cognitive deficits and AD), and frailty possibly due to sarcopenia. Inflammaging, the coexistence of inflammation and immunodeficiency referred to as immunosenescence, is one of the pathophysiological mechanisms underlying frailty. The aging-associated activation of the HPA axis by numerous non-specific stressors results in an increase in cortisol levels due to decreased glucocorticoid negative feedback at the level of the paraventricular nucleus of the hypothalamus, hippocampus

and prefrontal cortex, and the levelling of the diurnal pattern of cortisol release (142). Persistent anti-inflammaging, mainly exerted by cortisol, leads to a marked decline of immunological functions and its coexistence with the increased levels of pro-inflammatory cytokines of inflammaging, ultimately exerts negative effects on metabolism, bone density, strength, exercise tolerance, the vascular system, cognitive function and mood. This in turn results in frailty (143). As an abundant circulating adrenal androgen, DHEA(S) is positively correlated with successful aging and acts directly as a neurosteroid that may possess cardioprotective, antidiabetic, antiobesity and immunoenhancing properties (128). Low serum levels of DHEA(S) predict all-cause and cardiovascular mortality in elderly males (144). Disabled older females with increased DHEA(S) levels are at greater risk of 5-year cancer mortality, whereas these with decreased DHEA(S) are at greater risk of 5-year cardiovascular mortality (145). In older males and females, frailty is associated with DHEA and gender does not affect the association between increased DHEA levels and reduced frailty status (146); however, obesity attenuated the association. In another cohort of the oldest subjects, investigators reported (147) that female-specific DHEA(S) decline, not baseline level, is associated with functional performance decline, including gait speed and cognition. Due to a deficient feedback regulation of the HPA axis, serum cortisol suppression is less effective in frail individuals following adrenocorticotropic hormone stimulation and causes an increased cortisol DHEA(S) ratio (148).

Alterations in the HPA axis influence the sexual dimorphism of cognitive impairment. Apart from frailty, the increased cortisol and persistent activation of the biological stress system has additional negative effects on age-associated cognitive decline. Age-associated elevations in endogenous cortisol levels contribute to hippocampal atrophy and cognitive impairments, including a decline in memory performance and executive function in patients with Cushing syndrome, depression and AD (69,149,150). Dysfunction of HPA axis activity and psychosocial factors, include chronic feelings of loneliness, low social status and negative age stereotypes, as stressors increase the risk of progressive cognitive impairments, dementia and depression in older people (69).

Cortisol has gender-specific effects on cognitive impairment. Although cortisol is associated with the decline in hippocampal volume for older males but not older females (26,27), older females and young males appear to be the most susceptible to the effect of cortisol on cognitive and socioemotional domains due to increasing levels of HPA axis activity (151-153). The hippocampus and its associated cortical areas serve important roles in declarative memory, which includes the recall of personal experiences and the acquisition of semantic or factual knowledge (154). The hippocampus has a marked structural plasticity. The atrophy of the hippocampus resulting from atrophy of pyramidal cell dendrites and the loss of synapse, but not from death of neurons, is reversible (80). Increased stress responses in older females compared with older males may be associated with a sharp decline of estrogens in post-menopausal females. Excessive levels of cortisol in post-menopausal females may compromise the structural plasticity of the hippocampus by increasing the atrophy of pyramidal cell dendrites, the loss of synapses and inhibiting neurogenesis, and inhibiting the formation of new synapses (80).

4. Iron and the sexual dimorphism of frailty and cognitive impairment

Alterations in iron levels during aging. Circulating iron overload is also considered to be a factor in the sexual dimorphism of brain aging. Increased iron levels are observed in males during adolescence (age, 18-30 years) (155). Of 30- to 70-year-old males, 9.4% had ample iron stores, whereas 1.4% had exhausted iron stores and 0.24% had iron deficiency anaemia. In females, serum ferritin levels remained low from adolescence until the menopause. Of 30- to 50-year-old premenopausal females, 0.49% had ample iron stores, whereas 18% had depleted iron reserves and 2.6% had iron deficiency anaemia (156). The loss of iron in menstrual blood has been postulated to be a uterine function to contribute to a decrease in the risk of cardiovascular disease risk in young females (157,158). During menopausal transition, levels of serum ferritin increase 2- to 3-fold (159,160). The corresponding body iron storage from 4.8 mg/kg bodyweight at the beginning of perimenopause at age 45 years increases to 12 mg/kg bodyweight following menopause at age 60 years. Serum ferritin increased from baseline to 24-month follow-up during the menopause transition: 37 (CI 20-79) to 67 (CI 36-97) ng/ml ($P<0.01$), but remained lower compared with males: 111 ng/ml (CI 45-220; $P<0.01$) (161). Following menopause, serum ferritin gradually increased and approached levels in males. Of 60- to 70-year-old postmenopausal females, 3.0% had ample iron stores, 2.3% had depleted stores and none had iron deficiency anaemia (156). Brain iron levels increase with age and males exhibit greater levels of stored iron in brain compared with females across their lifespan (162).

Iron influences the sexual dimorphism of frailty. Iron deficiency and excess cause deleterious clinical outcomes. Among older adults, anemia prevalence is increased as it is associated with iron deficiency. Anemia or mildly reduced hemoglobin may accelerate the development of frailty and increase the risk of dependence, physical decline, falls and fractures, frailty, cognitive decline and even mortality (163,164). Iron, recognized as a potent pro-oxidant and a catalyst for the formation of reactive oxygen species in biological systems, is essential for oxygen transport, DNA synthesis and energy production (165). Aging-associated iron accumulation may contribute to the decline in muscle function due to increasing oxidative damage. A study of a rat model of sarcopenia (166) demonstrated that the non-heme iron concentration in gastrocnemius muscle increased by ~2-fold and the levels of oxidized RNA were significantly increased between 29 and 37 months of age. Although the role of iron in frailty has yet to be elucidated, the greater levels of stored iron in males and in postmenopausal females is responsible for the pathogenesis of numerous diseases, including ischemic heart disease, cancer, diabetes, infections and neurodegenerative disorders (159,165,167). Gender-specific alterations in the endocrine system and iron level may contribute to the sexual dimorphism of frailty.

Oxidative and informatory damage serve critical roles in frailty resulting from iron accumulation.

Iron influences the sexual dimorphism of cognitive impairment. Iron deficiency, which affects the differentiation of oligodendrocytes and the continual process of myelin repair or replacement, has adverse consequences on cognition (168). Abnormally high levels of iron in the brain promote oxidative and inflammatory damage to vulnerable brain tissue, which is observed in age-associated neurodegenerative diseases including preclinical AD, MCI, AD and dementia with Lewy bodies (169,170). In healthy older males, declarative memory function is adversely affected by increased hippocampal levels of ferritin iron (168). These results support the hypothesis of an early-age-onset of poor memory function in males. However, iron overload in males occurs during later life in conjunction with a slow decline of male sex hormones, which may provide protection against the harmful effects of the increased iron levels. The increase in iron levels in females occurs at the same time as the rapid decrease in female sex hormones levels, which may be the cause of increased susceptibility to late-onset AD (40). Elevated brain iron levels may be a mechanism for the susceptibility of AD from ApoEε4 (171). Therefore, the combined effects of iron overload, deficiency of gonadal hormones and the ApoE genotype may exert significant effects on the health of females and increase the risk of late-onset dementia.

Estrogen and iron homeostasis. Serum iron accumulation is conversely associated with the estrogen level in females and ferritin is significantly increased in postmenopausal compared with in premenopausal females (40,172). Estrogen deficiency and a concurrent increased iron retention are risk factors affecting the health of postmenopausal females, including cardiovascular disease (172-174), osteoporosis and late-onset AD (40). Estrogen regulates iron metabolism through hepcidin-ferroportin signaling via an estrogen response element (175-177). Iron homeostasis is closely regulated by the hepcidin-ferroportin axis. Hepcidin is the master regulator of the hepcidin-ferroportin axis and the promoter region of the hepcidin gene has an estrogen response element. In ovariectomized mice, the transcription of hepatic hepcidin was elevated compared with the control (176). An *in vitro* study (177) demonstrated that the transcription of hepcidin was suppressed by 17β-estradiol (E2) treatment in human liver HuH7 and HepG2 cells and this downregulation was blocked by E2 antagonist ICI 182780. Ferroportin, the only known iron exporter in the majority of mammalian cells, regulates the level of intracellular iron and maintains iron homeostasis. Estrogen regulates iron metabolism by inhibiting hepatic ferroportin expression via a functional estrogen response element within the ferroportin promoter. Estrogen receptor antagonist tamoxifen attenuates the inhibitory effect of estrogen (175). Thus, estrogen deficiency results in increases in hepcidin and ferroportin and the overload of iron.

5. Conclusions

The male prevalence of poor memory performance and severe atrophy of the hippocampus in early life may result from reduced circulating estrogens and greater circulating iron overload compared with females. The increased risk for late-life frailty and dementia in postmenopausal females compared with males may involve brain iron elevation, in combination with multiple hormonal derangement, including a sharp decline of circulating estrogens and androgens, and persistent greater cortisol and reduced DHEA(S) levels. The aging endocrine system, particularly sexual dimorphism alterations within the HPG/adrenal axis, interacts with neurophysiological, psychological, immune, genetic and epigenetic factors, and iron aggregation may contribute to the sexual dimorphism of brain aging; however, their exact roles remain to be elucidated. A systematic assessment of the above interdependent factors may further the understanding of the underlying mechanisms of the sexual dimorphisms of frailty and cognitive impairment, and provide gender-specific interventions, including iron chelators, anti-oxidant, anti-inflammatory and multiple anabolic hormone-replacement therapy for frailty and cognitive impairment.

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