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Review

Steroid secretion in healthy aging

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ABSTRACT

Nowadays, people spend a considerable amount of their lives as older adults, but this longer lifespan is often accompanied by an increase in chronic conditions and disease, resulting in reduced quality of life and unprecedented societal and economic burden. Healthy aging is therefore increasingly recognized as a healthcare priority. Physical and mental adaptations to changes over the life course, and the maintenance of well-being, represent pivotal challenges in healthy aging. To capture the complexity of healthy aging, we propose a specific phenotype based on body composition, cognition, mood, and sexual function as indicators of different dimensions of healthy aging. With increasing age, sex hormones as well as glucocorticoids undergo significant alterations, and different patterns emerge for women and men. This review describes age-related patterns of change for women and men, and sheds light on the underlying mechanisms. Furthermore, an overview is provided of the challenges for healthy aging resulting from these age-related steroid alterations. While clinical practice guidelines recommend hormonal treatment only in the case of consistently low hormone levels and symptoms of hormone deficiency, physical exercise and a healthy lifestyle emerge as preventive strategies which can counter age-related hormonal changes and at best prevent chronic conditions.

1. Introduction

In most countries, life expectancy is continuously increasing and the population of older individuals is growing rapidly. Currently, more than 900 million people worldwide are aged 60 and above, and this number is expected to grow by more than 50% between 2015 and 2050 (United Nations, 2015). Nowadays, people spend considerably more time as older adults as compared to previous generations. Although this represents an overall positive trend, longer life does not necessarily mean more time in good health. In fact, the rising life expectancy has led to an increase in the number of people with one or more chronic conditions such as dementia, cardiovascular disease or diabetes (Beard et al., 2016). Besides an impaired quality of life, the consequences of this demographic change include dramatically rising healthcare costs for governments and societies, posing huge financial challenges for the upcoming generations. Therefore, successful aging, which refers to the increase in time spent in good health with higher age, has become a global healthcare priority (Hung et al., 2010).

Aging is caused by an accumulation of flaws in molecules and cells, with effects on their integrity and function often resulting in functional and morphological frailty. The study of aging is complex due to the great interindividual variability in the manifestation of its biological effects. As a consequence, each person ages differently (Masoro and Austad, 2010). It is therefore important to identify markers which provide insights into the age-related changes in body functions and the underlying morphology. Lengths of telomeres, epigenetic patterns, or hormones represent markers of aging. Longevity studies show clear differences in life expectancy between men and women, which stem particularly from endocrine factors (Gems, 2014). Regarding endocrine alterations with age, the hypothalamic-pituitary-gonadal (HPG) and the hypothalamic-pituitary-adrenal (HPA) axes (steroids), as well as the interplay between the axes, have an impact on central and peripheral tissues with implications for physical and mental functioning. Healthy aging markers and geroprotective interventions have been derived from endocrine studies in healthy older individuals. However, most studies examined steroid hormones with regard to pathological aging and clinical states such as depression, anxiety, dementia and sexual dysfunction (Amanatkar and Chibnall, 2014; Lupien et al., 1999; Pluchino et al., 2015). Only a small number of studies have addressed steroid hormones in healthy older men and women, providing first evidence of an association between specific hormone constellations and healthy aging (e.g. Walther et al., 2017). Such studies are highly relevant for interventions aiming to prolong healthy years in aging people.

In the following, we propose dimensions of healthy aging derived

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from the literature. Along these dimensions, we provide an overview of age-related steroid changes and their underlying biological mechanisms, and summarize consequences in important areas of life for older women and men. Moreover, we outline potential intervention and prevention strategies to counter age-related steroid hormone alterations.

2. Healthy aging

The concept of healthy aging reaches beyond the avoidance of disease and disability (Rowe and Kahn, 1987). Rather, healthy aging is defined by the feeling and experience of physical and mental functioning (Kuh et al., 2013). Physical and mental adaptations to changes over the life course, and the maintenance of well-being, represent pivotal challenges in healthy aging (Karlamangla et al., 2002; Kuh et al., 2013; Martin and Martin, 2002; Scholz et al., 2015). The physical, mental and well-being domains interchangeably influence one another, which affects the power to adjust within each particular domain (e.g. Flicker et al., 2006; Zaslavsky et al., 2014). Thus, the achievement and maintenance of high abilities within these domains might delay the onset and rate of age-related functional decline. To capture the complexity of healthy aging, we propose a specific phenotype based on indicators of different dimensions of healthy aging (see Fig. 1). Derived from the literature, we describe physical health according to the two indicators body composition and sexual function (Iannuzzi-Sucich et al., 2002; Morton, 2017; Wannamethee and Atkins, 2015). As indicators of subjective well-being, we draw on sexual function and mood (DeLamater and Moorman, 2007; Kalmbach and Pillai, 2014; Oberzaucher and Grammer, 2009). Mental health is described according to the two indicators mood and cognition (Bauermeister and Bunce, 2015; Flicker et al., 2006).

2.1. Dimensions of healthy aging

Healthy aging is a highly ambitious goal, and a huge number of studies have depicted the difficulty of achieving it: First, the onset of physical changes such as an increase in fat mass, a decrease in muscle mass, and a loss of bone mineral density (BMD) typically occurs around the age of 40, ultimately leading to frailty and an increased risk of falls (Lippuner et al., 2009). Second, a reduction in cognitive skills such as speed of processing, working memory, and long-term memory occurs with age, culminating in more than 40 million dementia patients worldwide (Park and Bischof, 2013). Third, an 11% increase in mild depressive symptoms has been reported from the age of 50–64 years to the age of over 65 years (Baer et al., 2013). Fourth, the prevalence of sexual dysfunction is as high as 77% in men over the age of 70, with similar prevalence rates reported for women (Wagle et al., 2012).

To adequately describe healthy aging, it is important to define the upper end of the functional outcomes. The composition of body tissues can be defined as healthy if the balance in muscle mass, total and visceral body fat, and BMD allows an active and independent life, encompassing a lower risk of developing obesity, sarcopenia or frailty (Baumgartner, 2000). Cognitive function includes domains such as working memory, executive functions and verbal episodic memory (Lezak, 1984). Healthy cognition in age is seen as the continued ability to think, plan and remember, which are all important contributors to an independent life (Murman, 2015). Being in a good mood mostly means the absence of depression and anxiety. In relation to healthy aging, this means achieving and stabilizing psychological well-being, since a depressive state in particular is associated with a higher risk of morbidity, disability, and mortality (Waraich et al., 2004). Having a healthy, satisfying sex life with pleasurable and safe sexual experiences is an important contributor to subjective well-being (Lusti-Narasimhan and Beard, 2013) and studies clearly show that sexuality remains an important aspect throughout the entire lifespan (Foley, 2015).

3. Age-related steroid hormone alterations and their underlying biological mechanisms

Over the last 30 years, research on successful aging has increasingly focused on age-related hormonal changes and their consequences for physical health, mental health, and subjective well-being. Different age-related patterns of sex steroid changes emerge in women and men, whereas glucocorticoids show more comparable aged-related changes in men and women.

3.1. Sex steroids in women

Women experience marked curvilinear changes in estradiol and progesterone with respect to the final menstrual period (FMP) (Dennerstein et al., 2007). Testosterone (Burger et al., 2000) and dehydroepiandrosterone (DHEA) (Davison et al., 2005), on the other hand, show a relatively linear age-related decrease and cortisol shows an increase (Van Cauter et al., 1996), as demonstrated in Fig. 2.

With age, the number of oocytes decreases from around 6 to 7 million during fetal development to less than 1000 in each ovary at the age of 40. As a consequence of ovarian changes, women in the early perimenopause experience more frequent anovulatory cycles and a follicular phase deficiency (Prior, 1998). Moreover, there are fewer granulosa cells and less estradiol and inhibin production per growing follicle, leading to a reduced negative feedback regulation of the follicle-stimulating hormone (FSH) release. Through this FSH

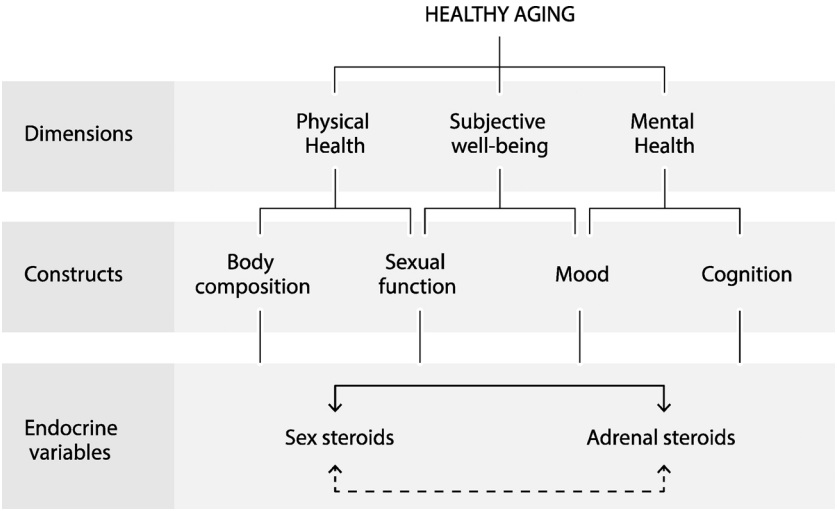

Fig. 1. Dimensions of healthy aging.
Healthy aging is defined by the domains physical health, subjective well-being, and mental health. A specific healthy aging phenotype is described based on the indicators body composition, sexual function, mood, and cognition. Sex steroids and adrenal steroids influence each of the dimensions (solid arrows) and mutually interact (dotted arrows).

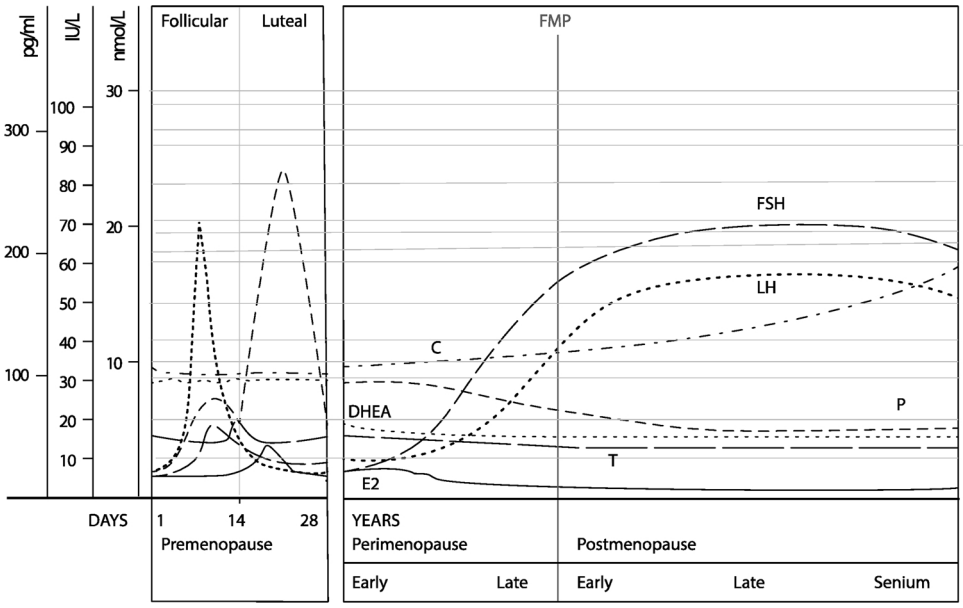

Fig. 2. Steroid alterations in women.
Left: Hormonal alterations during the follicular and luteal phase of a regular menstrual cycle. Right: Hormonal alterations as a functioning of age and menopausal status in middle aged to older women with reference to the final menstrual period (FMP).
Estradiol (E2), progesterone (P), testosterone (T), and dehydroepiandrosterone (DHEA) indicated in pg/ml (prototypical salivary levels); follicle-stimulating hormone (FSH) and luteinizing hormone (LH) indicated in IU/L (prototypical blood levels; cortisol (C) indicated in nmol/L (prototypical salivary levels).

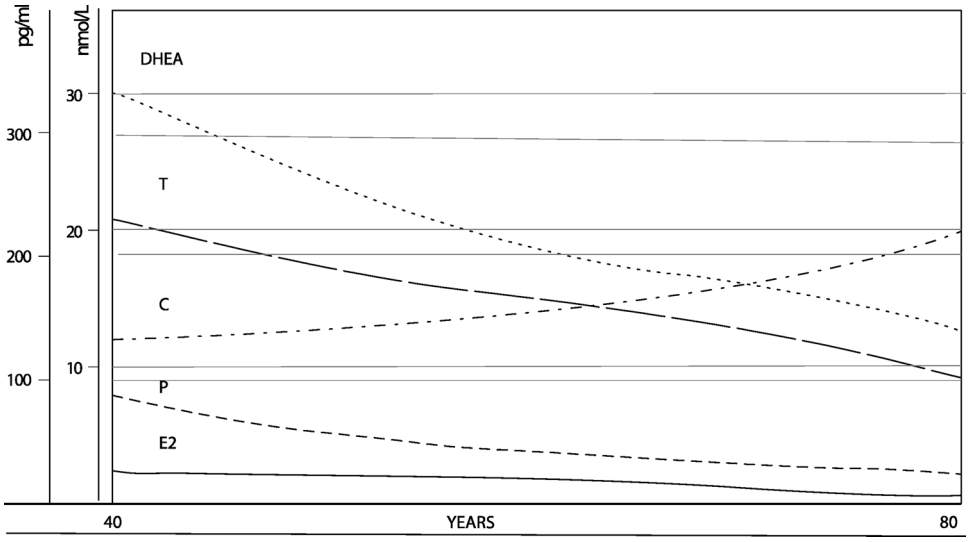

Fig. 3. Age-related steroid alterations in men.
Estradiol (E2) progesterone (P), testosterone (T), and dehydroepiandrosterone (DHEA) indicated in pg/ml (prototypical salivary levels); and cortisol (C) indicated in nmol/L (prototypical salivary levels).

overproduction, more follicles are recruited throughout each cycle, leading to transiently high serum estradiol levels and continuing menstrual bleedings (Burger et al., 2007; Harlow et al., 2012).

Estradiol levels, but also progesterone levels, fluctuate in the perimenopause (Prior, 1998). The late stages of the perimenopause are associated with significantly increased FSH and luteinizing hormone (LH) levels and a progressively increasing estradiol variability (Burger et al., 2007). In the absence of an ovulation, progesterone levels are relatively low and progesterone is reduced to its adrenal production. FSH and LH levels continue to rise in the early postmenopause, stabilize thereafter, and possibly decrease again in the senium (Randolph et al., 2015). Estradiol and progesterone levels continue to decrease in the early postmenopausal stages and remain at a low level in the following years (Hall, 2004).

The zona reticularis is the innermost layer of the adrenal cortex and the production site of DHEA and its sulfate (DHEA-S) (Parker et al., 1997). An age-related morphological diminishment of the entire zona reticularis in relation to the other layers (zona fasciculata and glomerulosa) leads to a diminished production of DHEA-S and a subsequent steady decline in DHEA (Luu-The et al., 2001). While Burger et al. (2000) found no changes in total testosterone across the menopausal transition, Fabbri et al. (2016) reported a progressive decline before menopause and a slight increase in total testosterone afterwards. After menopause, the ovaries still produce testosterone and androstenedione, and a large proportion of the circulating estradiol results from the peripheral conversion of androstenedione (Davison et al., 2005).

For females, estradiol and progesterone show a curvilinear decrease with respect to the FMP and stabilization at a low level in the late postmenopause and senium. DHEA shows a relatively linear decrease with age and testosterone a progressive decrease or slight increase after the FMP. DHEA and testosterone remain at a constantly low level in the late postmenopause and senium.

3.2. Sex steroids in men

In contrast to the marked changes in primary sex hormones in

women, in men, an annual reduction in testosterone of approximately 1–3% and in DHEA of up to 4% occurs starting around the age of 40 years (Feldman et al., 2002; Walther et al., 2016). Progressive impairment of testicular endocrine function with declining androgen levels is reported until the 9th decade of life (Yeap et al., 2018). Estradiol and progesterone do also decline but at a lower rate (Ferrini and Barrett-Connor, 1988; Frost et al., 2013; Nankin et al., 1981; Zitzmann et al., 2005) (see Fig. 3). However, findings regarding estradiol and progesterone are conflicting. Total vs. free concentration levels need to be considered due to an age-related increase in sex hormone-binding globulin (SHBG), with free sex hormone concentration levels declining more consistently with increasing age (Barrett-Connor et al., 1999b; Jasuja et al., 2013; Oettel and Mukhopadhyay, 2004). Good health was shown to decelerate age-related sex steroid decline in men (Feldman et al., 2002; Sartorius et al., 2012; Walther et al., 2016), while changes in androgens and estrogens are associated with all-cause and cause-specific mortality in older men (Hsu et al., 2016).

As a result of the attrition of the testosterone, progesterone and estradiol-producing testicular Leydig cells, a reduced secretion of the primary sex hormones occurs with increasing age (Neaves et al., 1985). Stimulation tests further show a decreased secretory capacity of testosterone and estradiol in elderly compared to young men (Iranmanesh et al., 2010). In addition to overall reduced testosterone levels, increased aromatase activity is reported in older men, which is responsible for the conversion of testosterone to estradiol (Vermeulen et al., 2002). Therefore, a smaller decrease in estradiol compared to testosterone in older men is observed (Frost et al., 2013). However, the bioavailability of both hormones is reduced due to an age-related increase in SHBG levels (Feldman et al., 2002; Frost et al., 2013).

In response to the reduced levels and bioavailability of the primary effectors of the HPG axis, adaptive changes in the amplitude and frequency of gonadotropin-releasing hormone (GnRH) pulses and subsequently increased levels of LH and FSH are observed both in men and women (Iranmanesh et al., 2010). In contrast, an age-related decrease in LH pulse amplitudes but an increase in pulse frequency have been reported (Iranmanesh et al., 2010). This might be caused by reduced GnRH secretion with age, which is regulated by the hypothalamic GnRH pulse generator. In support of this assumption, stimulation tests with exogenous GnRH show no difference in the subsequent LH secretion in young compared to old men, reflecting similar pituitary function (Kaufman and Vermeulen, 1997). However, it has been suggested that the paradoxical findings of an age-related decrease in LH pulse amplitudes but elevated LH levels in older men are caused by increased plasma half-life of LH and increased LH pulse frequency (Iranmanesh et al., 2010; Kaufman and Vermeulen, 1997).

With regard to the causal factors leading to a decline in DHEA, the aforementioned morphological changes in the zona reticularis cause an up to 70% reduction of circulating DHEA levels in aging men (Ferrari and Mantero, 2005; Walther and Ehlert, 2015). Thus, for males, a picture emerges of consistently reduced levels of testosterone and DHEA, and less consistently reduced levels of circulating estradiol and progesterone with increased age, while their free concentrations consistently decline.

3.3. Glucocorticoids in women and men

Aging has been suggested to be associated with a hyperactivity of the HPA axis, leading to a long-lasting exposure to stress hormones (Karlamangla et al., 2013; Nater et al., 2013). Aging studies reveal higher levels of morning and evening cortisol (Ice, 2005), higher overall daily cortisol, attenuated wake-evening slopes, and a more pronounced cortisol awakening response (CAR) in older compared to younger adults (Karlamangla et al., 2013; Nater et al., 2013). A meta-analysis on the cortisol response to challenge found a stronger response in older individuals, with a more pronounced age effect in women (Otte et al., 2005), and later studies supported a sex-specific effect of aging on cortisol (Almeida et al., 2009; Veldhuis et al., 2013). However, not all studies support the general assumption of sex differences (Wong and Shobo, 2017). Moreover, studies on aging should consider the mediating effect of the female`s menopausal state on the association between sex and cortisol due to its interaction with gonadal steroids (Edwards and Mills, 2008).

The age-related increase in cortisol is due to different alterations of the HPA axis, showing a reduction of type I (mineralocorticoid receptor) and type II (glucocorticoid receptor) corticosteroid receptors as a function of age (Veldhuis et al., 2013; Yau et al., 2002). While mRNA and protein levels of both receptors decrease with age (Veldhuis et al., 2013), an age-related elevation of the number of corticotropin-releasing hormone (CRH) neurons, causing an increased CRH secretion, has been observed at the hypothalamic level (Zhou and Swaab, 1999). The consequence is an age-related increase in the subsequently released adrenocorticotropin-releasing hormone (ACTH) and cortisol secretion (Ice, 2005; Nater et al., 2013; Van Cauter et al., 1996). A consistent picture emerges of an age-related hyperactive basal HPA axis regulation, caused by a decreased sensitivity to the negative feedback loop at the hypothalamic level, central nervous system (CNS) modifications, as well as slower metabolic clearance rates of CRH, ACTH or cortisol (Ferrari et al., 1995).

4. Steroid hormones as markers of healthy aging

4.1. Steroid hormones as markers of body composition in women

The body composition of premenopausal women is characterized by subcutaneous body fat and a gynoid (pear-like) body shape, whereas postmenopausal women show an increased accumulation of body fat in visceral depots, resulting in a more central or android (apple-like) shape (Arner et al., 1991). Moreover, muscle strength, muscle mass (Messier et al., 2011) and BMD decline with age and from pre- to postmenopause (Seifert-Klauss et al., 2012). This change in body composition, and especially the increase in metabolically active visceral body fat, is linked to an increase in metabolic risk (Arner et al., 1991), sarcopenia (Sakuma and Yamaguchi, 2012) and frailty (Nedergaard et al., 2013).

A longitudinal study revealed a parallel decline in fat mass and testosterone over time in middle-aged women, but reversed effects in men (Bann et al., 2015), and a recent study found testosterone to be a predictor of fat accumulation, but only in hypo-gonadal women (He et al., 2018). In healthy, non-obese postmenopausal women, however, higher testosterone levels were associated with lower body fat mass (Casson et al., 2010). These results suggest a mediating role of the aromatase activation in visceral body fat and its transformation of testosterone to estradiol. In fact, estrogens play a crucial role for body fat, due to its effects on appetite, energy expenditure and body fat distribution, which are mediated by the estrogen receptors (ER) ERα and ERα:ERβ ratio (Palmer and Clegg, 2015). Studies have consistently reported a positive relationship between estradiol and both fat mass (e.g. Mahabir et al., 2006) and fat distribution (e.g. Paxton et al., 2013). Findings on the estrogen and testosterone precursor DHEA are rather inconsistent, with studies revealing a positive (Barrett-Connor and Ferrara, 1996), a negative (De Pergola et al., 1994), or no association with body fat (He et al., 2018).

Only a small number of studies have examined the effect of endogenous testosterone on muscle mass and strength in women, but the existing literature generally suggests a positive association (e.g. van Geel et al., 2009; Yuki et al., 2015). A review on exogenous testosterone proposed a lower risk of chronic states such as sarcopenia with higher testosterone, although the effects are not as clear as for men (Sakuma and Yamaguchi, 2012).

Glucocorticoids regulate the protein and glucose metabolism in skeletal muscles and are therefore important indicators of the age-related change in muscle composition. According to Bodine and Furlow

(2015), a transient glucocorticoid activation exerts beneficial effects on skeletal muscles by maintaining high circulating glucose levels. For a wider timeframe such as in aging, lower cortisol levels seem to be more beneficial, since they were found to be linked to a lower age-related muscle loss and atrophy compared to higher cortisol levels (Vitale et al., 2016). Skeletal muscle gene expression of 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1) leads to the local conversion of inactive cortisone to active cortisol, which shows an age-related increase in women (Gathercole et al., 2013). In one study, a reduced gene expression was associated with higher grip strength, lower body fat and total cholesterol, and better functional outcomes (Hassan-Smith et al., 2015).

Regarding BMD, a prospective longitudinal study revealed a rapid loss in BMD in perimenopausal women, despite normal or high levels of estradiol (Seifert-Klauss et al., 2012), and there is evidence that DHEA-S (Park et al., 2017), but not testosterone (Arpaci et al., 2015), plays a crucial role in the BMD of postmenopausal women. As a combined morbidity outcome, the risk of frailty may increase with higher estradiol (Carcaillon et al., 2012), lower DHEA-S (Voznesensky et al., 2009), and lower testosterone levels (Wu et al., 2010), although the effect of estradiol was not visible for all age groups and the findings need to be replicated in longitudinal analyses.

In summary, the impact of testosterone on body fat is unclear, possibly due to the mediating effects of estradiol. There is evidence that higher testosterone and lower cortisol levels have positive effects on muscle mass and functional outcomes, while the results on DHEA-S are inconsistent. There is support for a positive effect of DHEA-S on BMD and a higher risk of frailty with lower testosterone and DHEA-S, and higher estradiol levels, although there are no longitudinal studies to support these findings.

4.2. Steroid hormones as markers of body composition in men

Frailty and the risk of falls increase with age. In men, the lifetime fracture risk after the age of 50 years lies at around 20% (Lippuner et al., 2009). The prevalence of age-related sarcopenia, a clinical condition defined as below-threshold muscle mass, lies at up to 15% in over-65-year-olds (Melton et al., 2000).

In a large cohort study, higher endogenous testosterone levels were independently associated with lower BMI and better body composition in men (Clifton et al., 2016). Increased testosterone levels were further associated with increased muscle mass and strength in aging men (Roy et al., 2002), as well as reduced frailty as identified in the European Male Aging Study (Tajar et al., 2011). In a prospective cohort study of older men, lower testosterone was independently associated with frailty at baseline and at six-year follow-up (Hyde et al., 2010), while another longitudinal study revealed that higher testosterone levels were associated with reduced loss of lean mass at 4.5-year follow-up (LeBlanc et al., 2011). A cross-sectional study of older men identified low free testosterone (below 243 pmol/L) and high SHBG (above 66 nmol/L) to be associated with a 4- and 3-fold increased odds of frailty, respectively (Eichholzer et al., 2012). Reanalysis of the data of the European Male Aging Study further indicated that low free testosterone rather than low total testosterone is responsible for poorer body composition and bone mineral density, underlining a pivotal role of SHBG in the male frailty syndrome (Antonio et al., 2016). In line with this, reduced bone mineral density and increased risk of fractures have been reported in patients undergoing androgen deprivation therapy due to prostate cancer treatment (Shahinian et al., 2005; Wadhwa et al., 2009).

A study examining the differential effects of testosterone and estradiol on body composition in men used a 5-alpha reductase inhibitor, which inhibits the conversion of testosterone to estradiol, in one of two groups. In both groups, testosterone levels were chemically depleted (Finkelstein et al., 2013). By subsequently administering testosterone alone or in combination with the inhibitor, the authors identified that decreased estradiol levels accounted for increased fat mass, while decreased testosterone accounted for decreased muscle mass. As in women, estradiol may contribute to increased body fat. However, higher estradiol levels were further shown to be particularly important for increased BMD, by promoting bone anabolism and inhibiting bone resorption in elderly men (Hoppé et al., 2011). Interestingly, male sex is a major protective factor against fractures in older age, which is due to increased cortical bone expansion during pubertal peak bone mass acquisition and superior skeletal maintenance during aging (Vanderschueren et al., 2014). While estradiol possesses important properties which increase bone mineral density, testosterone reduces fracture risk via additional effects on bone maintenance, although mainly through extra skeletal determinants such as increased lean mass and muscle strength (Vanderschueren et al., 2014).

For DHEA/-S, early reports described associations of higher DHEA-S levels with lower BMI, more lean mass, less fat mass, and increased physical fitness in older men (Abbasi et al., 1998). In the European Male Aging Study, higher DHEA-S levels were associated with reduced frailty (Tajar et al., 2011), and another longitudinal study showed that reduced DHEA-S and an increased cortisol: DHEA-S ratio were significantly associated with increased odds of frailty at 10-year follow-up (Baylis et al., 2013). In line with this, a recent large-scale longitudinal study confirmed a reduced risk of falls and fractures with higher levels of DHEA and DHEA-S, while this effect was largely independent of levels of muscle mass, strength, or balance (Ohlsson et al., 2018).

Given the fact that cortisol is a catabolic hormone exerting direct action on bone cells and indirect effects on calcium absorption, several studies in older men found that increased cortisol was associated with frailty, reduced bone formation, persistent bone destruction and increased osteocyte and osteoblast apoptosis and osteoporosis (Warriner and Saag, 2013). This is in line with previous studies on healthy older men which showed endogenous cortisol to be associated with bone mineral density and involutional bone loss (Dennison et al., 1999a, 1999b), while for elevated peak plasma cortisol, accelerated loss of bone mineral density was reported (Reynolds et al., 2005). Although there are some inconsistent reports regarding the association between body composition and cortisol levels, with findings of no association between endogenous cortisol levels and body fat or fat free mass in men (Ragnarsson et al., 2016), the vast majority of studies report positive associations between cortisol levels and body mass index and waist circumference (Fraser et al., 1999; Stalder et al., 2013). This has recently been confirmed meta-analytically for hair cortisol (Stalder et al., 2017).

Taken together, testosterone has consistently been found to be associated with increased muscle mass and reduced frailty, while low levels of estradiol in men seem to be associated with increased fat mass and decreased BMD. DHEA/-S is associated with reduced frailty, and higher cortisol levels have consistently been linked to increased frailty and worse body composition.

4.3. Sex steroids as markers of cognition women

A high variability in the age-related cognitive decline among older individuals is reported (Lupien et al., 1999). A meta-analysis on cognition across the menopausal stages revealed that postmenopausal women showed the lowest performance on delayed verbal memory tasks and a lower performance on phonemic verbal fluency tasks compared to perimenopausal women but not compared to premenopausal women, indicating a mediating role of sex steroids (Weber et al., 2014).

Estrogens promote neural growth and survival and show neuroprotective effects. ERs were identified in brain areas which are important for cognitive function, such as the prefrontal cortex and the hippocampus (McEwen, 2002). In a study in peri- and postmenopausal women, higher estradiol levels were associated with better overall cognitive function (Hu et al., 2017). In early but not late postmenopause, women with higher free estradiol performed better on

semantic memory tests (Henderson et al., 2013), and postmenopausal women with higher estradiol performed better on verbal (Wolf and Kirschbaum, 2002) and semantic (Ryan et al., 2012) memory tests. A steady decline in estradiol, as reached in natural as opposed to surgical menopause, was associated with better cognitive function outcomes in a prospective longitudinal study (Burger et al., 1999). However, these findings are not consistently reported (Barrett-Connor and Goodman-Gruen, 1999; Carlson and Sherwin, 2000; Hogervorst et al., 2004). Although testosterone also exerts neuroprotective effects, it is proposed that these effects are mediated by estradiol due to the mutual effects of the two hormones on androgen and estrogen receptors (Pike et al., 2009). While testosterone supplementation studies do not support the estradiol mediation hypothesis (Davis and Wahlin-Jacobsen, 2015), findings on endogenous hormones across cognitive domains and menopausal stages are contradictory. While one study did not find an association of either testosterone or estradiol with any cognitive function outcome in postmenopausal women (Henderson et al., 2013), another study found a positive relationship of both estradiol and testosterone with verbal memory (Wolf and Kirschbaum, 2002). Only one study, by Ryan et al. (2012), has explicitly tested whether the testosterone: estradiol ratio is associated with semantic and verbal episodic memory. The results revealed that a lower ratio was associated with better memory outcomes.

Despite some findings regarding the effects of exogenous testosterone on cognitive function, there is still not enough evidence to recommend testosterone therapy in order to stabilize or increase cognitive performance in women (Davis and Wahlin-Jacobsen, 2015). A recent review reached a similar conclusion for DHEA-S. While the majority of studies found an overall positive association between DHEA-S levels and cognitive function outcomes, they did not support any enhancing effects of DHEA replacement in unimpaired individuals (De Menezes et al., 2016).

4.4. Sex steroids as markers of cognition in men

In men, an association between low androgen levels and cognitive decline or dementia has been extensively debated, and is biologically plausible due to the fact that testosterone possesses neuroprotective properties and is associated with increased neuronal survival (Hammond et al., 2001). Men with clinical conditions causing low testosterone levels show impaired cognitive abilities in certain domains (Almeida et al., 2004; Bussiere et al., 2005). Large cohort studies revealed positive linear associations between testosterone and cognitive dimensions such as visuospatial abilities or memory (Moffat et al., 2002; Yaffe et al., 2002a; Yeap et al., 2008), while others found curvilinear associations between testosterone and cognitive performance when considering the entire age spectrum in males, with positive associations emerging predominantly in the older men (70–80 years) (Muller et al., 2005). A recent longitudinal study using a 10-year follow-up supported these findings by showing a markedly increased risk of developing dementia with low testosterone levels (Ford et al., 2018). However, there is also conflicting literature which found no association between testosterone and cognition in aging men after adjusting for confounders (Fonda et al., 2005).

In a study of older men, low estradiol and high testosterone levels predicted better cognitive performance in a four-year follow up (Barrett-Connor et al., 1999a,b), while another cohort study in older men replicated the negative association for estradiol (Yaffe et al., 2002b). Several longitudinal studies further showed that elevated estradiol levels in men were associated with reduced cognitive performance and incidence of Alzheimer's dementia (Fonda et al., 2005; Muller et al., 2009). However, as outlined above, there is also conflicting literature indicating that estradiol and testosterone might be positively associated with cognition in older women while showing no association with cognition in older men (Wolf and Kirschbaum, 2002).

Although positive associations between DHEA levels and cognition have been reported in men (Goldman and Glei, 2007), some studies failed to identify an association between circulating DHEA levels and cognitive performance (Moffat et al., 2000), or only reported a positive link to specific domains of cognition (Hildreth et al., 2013). Data from the Massachusetts Male Aging Study revealed DHEA and DHEA-S to be beneficially associated with cognitive function only in unadjusted models, while these effects diminished after including covariates (Fonda et al., 2005).

4.5. Glucocorticoids as markers of cognition in women and men

In both women and men, intensive and chronic stress can impair cognitive performance, particularly with respect to tasks that depend on the hippocampus and the prefrontal cortex. According to the glucocorticoid cascade hypothesis, prolonged stress leads to an impairment of the negative cortisol feedback, resulting in an elevated glucocorticoid release and ultimately damage to brain structures such as the hippocampus (Sapolsky et al., 1986). A great deal of support for this assumption stems from recent experimental rodent studies, which showed dendritic spine remodeling and attrition due to prolonged corticosterone exposure (Anderson et al., 2016). However, only some human studies have been able to establish an effect of higher cortisol on more hippocampal atrophy and poorer performance on memory tests (Comijs et al., 2010; Lee et al., 2007; Lupien et al., 1999). More recent human studies further showed that elevated cortisol levels are associated with reduced white matter integrity (Cox et al., 2015) or prefrontal cortex surface (Stomby et al., 2016). In addition, large cohort studies in older men have indicated that when adjusting for moderating variables, cortisol is clearly associated with poorer cognitive performance (Fonda et al., 2005). As Harris et al. (2017) states, however, it is unclear whether in "normal" aging, cortisol levels would become sufficiently high to explain the cognitive decline. Nevertheless, there is recent evidence that in specific populations, increased nighttime cortisol levels are associated with neurological deficits, brain atrophy, or worse white matter integrity, underlining the detrimental effects of too much nighttime cortisol on the human brain (Tene et al., 2018). In line with this, administration of an intracellular 11-hydroxysteroid dehydrogenase (11-HSD) type 1 inhibitor – which blocks the regeneration of inactive cortisone to active cortisol – was shown to improve cognitive function by maintaining low cortisol levels (Sandeep et al., 2004).

To summarize, findings on the contribution of estradiol to cognitive function in women are inconsistent. The effect of testosterone on cognition in women might be mediated by estradiol, but more evidence is needed to support this hypothesis. For cortisol, a negative association emerges with regard to cognition in women. The pattern of findings in men is mixed, with many studies indicating a positive association between androgens and cognitive performance, although some studies have questioned this hypothesis. Lower levels of estradiol and cortisol seem to be associated with better cognitive performance in men.

4.6. Steroids as markers of mood in women

Across the whole lifespan, women are twice as likely to develop depressive symptoms and depressive disorders as men (Kessler et al., 1993). Biological explanations for this sex difference may lie, among other factors, in women's sensitivity to strong ovarian sex hormone changes, which occur, for example, during the menopausal transition (Freeman et al., 2006) or in differences in the response to stress (Llaneza et al., 2012).

Estrogen receptors are distributed throughout the entire brain, and estrogens therefore have an important impact on neurotransmitter systems. Moreover, they act as neurosteroids on the pituitary and hypothalamus, influencing the activation of the HPA axis (McEwen, 2002). It is suggested that some women are more sensitive to hormonal fluctuations, and show larger mood changes in response to an acute trigger such as estradiol withdrawal or the start of a prolonged

hypogonadism, as seen in perimenopause (Schmidt and Rubinow, 2009). In a study by Gordon et al. (2016), week-to-week estradiol fluctuations were found to have an impact on mood and depressive symptoms in perimenopausal women, but only if they were currently depressed. Women in a healthy state seemed to be unaffected by fluctuating estradiol levels.

Cross-sectional and longitudinal studies have investigated the contribution of androgens to depression in women. A large longitudinal study encompassing more than 3000 women in the menopausal transition reported that lower testosterone levels across the eight-year measurement period and more stable testosterone levels from baseline to follow-up were associated with lower depressive symptoms (Bromberger et al., 2010). These findings are in line with the results of a cohort study of older women, in which higher free testosterone levels were associated with lower depression scores (Morsink et al., 2007), but differ from a longitudinal study on the menopausal transition which did not find any association with testosterone (Woods et al., 2008). Since testosterone is a down-stream product of DHEA, studies have investigated the effect of DHEA and its sulfate DHEA-S on depressive symptoms, with conflicting findings. Some studies reported a protective effect of higher baseline DHEA-S levels on the onset of depressive symptoms (Souza-Teodoro et al., 2016; Veronese et al., 2015) or a positive association of DHEA-S with depressive symptoms but not with a diagnosis of major depression (Morrison et al., 2011). However, other longitudinal studies did not find an association (Bromberger et al., 2010; Dennerstein et al., 2002). The methodological differences between these studies, and especially the differences in menopausal status at the time of study enrollment, need to be mentioned and may account for at least some of the differences in outcomes.

Depression involves changes in the HPG axis, which are possibly mediated by the suprachiasmatic nucleus, resulting in changes in cortisol secretion (Bao et al., 2008). When confronted with a stressor, older as well as more severely depressed men and women show a more blunted cortisol response, without changes in the recovery phase (Burke et al., 2005). In middle-aged women, diurnal cortisol slopes are steeper in those with lower depression scores, with this difference being mostly due to higher morning cortisol levels (Woods et al., 2010). The above-mentioned study by Gordon reported evidence of HPA axis dysregulation in the pathophysiology of perimenopausal depression. Estradiol increase from one week to the next was associated with higher weekly waking cortisol in previously and currently depressed perimenopausal women, but not in healthy perimenopausal women (Gordon et al., 2016).

To summarize, the literature supports the notion that some women are more vulnerable to estradiol changes. Moreover, there is evidence supporting the involvement of an HPA axis dysregulation with changes in cortisol in the development of age- and menopause-related mood changes and depressive symptoms. Probably due to methodological differences in the study design, findings on testosterone and DHEA-S remain inconclusive.

4.7. Steroids as markers of mood in men

With regard to men, investigations of the relation between testosterone levels and mood have revealed a mixed picture. Although several studies have provided evidence that men with low testosterone levels also show more depressive symptoms (Almeida et al., 2008; Barrett-Connor et al., 1999b; Ford et al., 2016), some cohort studies do not support this (Kische et al., 2017; T'sjoen et al., 2005; Wu et al., 2010). However, more consistent findings, relating low testosterone levels to worse mood, are reported when carefully examining specific subgroups of men such as older men, men infected with human immunodeficiency virus (HIV), men with dysthymia, or carriers of deviant numbers of CAG repeats in the androgen receptor gene affecting testosterone action in the CNS (Amiaz and Seidman, 2008; Booth et al., 1999; Seidman et al., 2002, 2001). Increased age is associated with decreased testosterone levels and increased levels of depressive symptoms (Baer et al., 2013; T'sjoen et al., 2005). The finding that elevated levels of depression intensify age-related testosterone decline (Walther et al., 2016) further points to an interdependent triad comprising age, testosterone levels, and depressive symptoms determining health and disease in older men. In support of this, in older men, longitudinal changes in testosterone levels instead of baseline testosterone seem to predict depressive symptoms (Kische et al., 2018).

With regard to DHEA, in a cohort study, lower depressive symptoms at 4-year follow-up were associated with higher DHEA levels at baseline (Souza-Teodoro et al., 2016). However, a large cohort study in healthy elderly men identified a positive association between depressive mood and DHEA-S levels (T'sjoen et al., 2005). However, the reported finding of a positive association between DHEA-S and depressive symptoms is surprising, and another large cohort study in elderly individuals identified higher DHEA levels as protective against the incidence of depression (Veronese et al., 2015), which seemed to be particularly robust in older men but not older women in third cohort study (Michikawa et al., 2013). A meta-analysis examining DHEA-S protein expression in a large meta-sample concluded that low levels of DHEA-S expression were independently associated with depression (Hu et al., 2015).

The study by T'sjoen et al. (2005) further identified a positive association between depressive symptoms and estradiol in men, which is mostly consistent with the literature (Barrett-Connor et al., 1999b; Vogel et al., 1978), although there is a conflicting study showing an additional negative effect of low estradiol levels on mood in men receiving androgen blockade due to prostate cancer (Almeida et al., 2004). To disentangle the mutually influencing effects of testosterone and estradiol on depressive symptoms, further experimental studies using 5-alpha reductase inhibitors, which hinder the conversion from testosterone to estradiol, are needed.

As outlined above, aging is accompanied by an increased cortisol secretion (Karlamangla et al., 2013). Furthermore, one of the most consistent findings in the pathophysiology of depressive disorders is elevated cortisol levels (Bhagwagar et al., 2005; Ehlert et al., 2001; Mannie et al., 2007; Pariante, 2017). Researchers have therefore suggested that the association between elevated cortisol levels and depression is stronger in older individuals, and a thorough meta-analysis indeed showed that the link between increased cortisol levels and more depressive symptoms is strongest in older individuals, irrespective of sex (Stetler and Miller, 2011). However, there are also contradictory reports pointing to a more complex pattern, suggesting that only certain subtypes of depression are associated with reduced cortisol levels, while other subtypes show increased levels and that age and sex critically influence these associations (Juruena et al., 2018; Stalder et al., 2017).

Taken together, higher androgen levels have been shown to be associated with better mood and lower depressive symptoms in certain subgroups of men such as older men, while elevated estradiol levels seem to be associated with worse mood and higher levels of depressive symptoms in older men. Cortisol shows consistently positive associations with depressive symptoms.

4.8. Steroids as markers of sexual function in women

A decline in sexual function is observed across the menopausal transition. Compared to premenopausal women, postmenopausal women were found to have a 2.3-fold increased risk of developing sexual dysfunction (Gracia et al., 2007), and Avis et al. (2017) reported a decline in sexual function approximately 20 months before reaching the FMP, which slowed but did not cease about one year after the FMP.

A vast amount of studies showed that estrogens have an effect on sexual function (reviewed in Santoro et al., 2016). This effect is explained by, among other factors, the impact of estradiol on the thickness of the vaginal epithelium, leading to more blood flow and vasodilatation and therefore to a stronger genital sensation (Berman, 2005). Moreover, higher estradiol levels reduce climacteric vasomotor

symptoms, which are often bothersome and can impair sexual function (Santoro et al., 2016). The effect of androgens and the androgen and estrogen precursor DHEA on sexual function has been neglected for a long time, but has become one focus of research in the last decade. A prospective longitudinal study showed that total testosterone was associated with the frequency of masturbation and desire in the last six months, and testosterone values above the upper quartile were linked to a higher frequency of masturbation, more desire, and higher arousal (Randolph et al., 2015). In a prospective study, middle-aged women with the lowest testosterone fluctuations revealed the lowest decrease in libido (Gracia et al., 2004). Davis et al. (2005) found a link between higher DHEA-S, but not testosterone, and better sexual responsiveness, more arousal and more pleasure in older women. However, even though the likelihood of low sexual function increased with low DHEA-S levels in this study, not all women with low levels of DHEA-S levels reported low sexual function.

The HPA axis has suppressive effects on the HPG axis (Viau, 2002), and the few existing studies support a negative relationship between chronic stress and sexual arousal in men and women (Bodenmann et al., 2006; Hamilton et al., 2008). Laboratory studies in older women showed that moderate levels of stress can either be enhancing (Brauer et al., 2007) or inhibiting (Bradford and Meston, 2006), supporting the notion that sexual arousal could have short-term cortisol-buffering effects. Studies suggest a moderating effect of cortisol on the relationship between testosterone and social behavior (Lozza et al., 2017; Mehta and Josephs, 2010). One study in young women found a negative association between testosterone and dyadic desire, but only in women with high cortisol, whereas solitary desire was directly and negatively related to testosterone levels (Van Anders, 2012). The studies on cortisol and sexual function in older women are still scarce and represent a research gap with potential for future investigations.

In summary, studies support a link between estradiol and sexual function through direct and indirect action on the female physiology. There is evidence supporting the involvement of testosterone and DHEA-S in sexual function. Some studies suggest a bidirectional effect of cortisol and sexual function, but there is still limited evidence with potential for future studies.

4.9. Steroids as markers of sexual function in men

Sexuality remains an important quality-of-life consideration in men until late life (Hyde et al., 2012). However, sexual health severely decreases with age and males over 40 years show high rates of erectile dysfunction, with a prevalence of 61% for 40-69-year-olds and 77% for ≥70-year-olds (Wagle et al., 2012). There is a consistently reported positive relation between T and sexual function, including sexual interest and erectile function, in men. Several large cohort studies have independently confirmed this finding (Martin et al., 2012; O'Connor et al., 2011; Shi et al., 2014), although a smaller number of studies report only an association of low testosterone with a lack of sexual desire, but not with other complaints (e.g. erectile dysfunction; ED) (Hyde et al., 2012), or no association between testosterone as a predictor of sexual function (Marberger et al., 2011). The age-related increase in symptoms of erectile dysfunction has been found to be buffered when men show higher testosterone levels (Walther et al., 2017). Furthermore, in two independent studies, low testosterone levels were identified as the primary reason for decreased erectile function, but concomitantly increased estradiol levels seemed to additionally contribute to reduced sexual function (Basar et al., 2005; El-Sakka, 2013). By contrast, in an experimental study in which endogenous testosterone and estradiol levels were chemically depleted, different dosages of testosterone were administered to all participants and a subgroup received anastrozole in parallel (to suppress the conversion of testosterone to estradiol), a decline in both testosterone and estradiol was found to contribute to decreased sexual function (Finkelstein et al., 2013).

For DHEA/-S, an association between sexual dysfunction and low DHEA-S levels was reported (Basar et al., 2005). This is consistent with large cohort studies reporting a decreased prevalence of erectile dysfunction with higher DHEA-S levels (Feldman et al., 1994). In addition, the age-related increase in symptoms of erectile dysfunction has been shown to be buffered by higher DHEA levels (Walther et al., 2017).

There is a lack of studies examining the potential contribution of cortisol to sexual dysfunction in aging men, which is surprising given the well-described age-related increase in cortisol and sexual dysfunction. Therefore, studies including middle-aged men or men with certain conditions may reveal a pattern for older men as well. For example, patients with Cushing's syndrome exhibiting chronic hypercortisolism show decreased sexual desire (Starkman and Schteingart, 1981). While some studies failed to identify a positive association of increased cortisol levels with erectile dysfunction in middle-aged men (Derouet et al., 2002; Gray et al., 1991), others did report some evidence for this association. For instance, one study found that in middle-aged depressed men, cortisol levels showed significant negative associations with different dimensions of sexual function such as erectile function and sexual desire (Kobori et al., 2009). Another study including middle-aged men with ED reported that higher levels of perceived stress were related to decreased orgasmic and erectile function, while elevated morning cortisol levels showed a negative association with sexual desire (Kalaitzidou et al., 2014).

Taken together, increased testosterone and estradiol are associated with increased sexual function. For DHEA, endogenous levels are consistently, though only weakly, associated with sexual function. Since cortisol levels are negatively associated with sexual function in men and increase with age, the potential association with sexual dysfunction should be taken into account in the treatment of elderly men with ED.

4.10. Emerging clinical implications for women

Recent reviews and meta-analyses on modifiable lifestyle factors propose that older individuals can actively modulate their health. For example, regular physical activity has a positive effect on the maintenance of well-being in older life (Daskalopoulou et al., 2017). One of the mechanisms by which physical activity and exercise promote health lies in their effects on the physiological and psychological stress reactivity (Kennedy et al., 2016). It is suggested that a healthy diet, for instance the Mediterranean diet supplemented with extra virgin olive oil, promotes global cognition and memory. Moreover, mindfulness-based exercise such as tai chi or yoga are suggested to improve global cognition (Lehert et al., 2016) and might even have a beneficial influence on hormonal balance (Walther et al., 2018). Studies showed that skeletal muscles remain sensitive to training until old age, and exercise can counteract some of the age-related loss in muscle strength (Daskalopoulou et al., 2017) and androgen levels (Sato et al., 2016). While some of the results on modifiable lifestyle factors are still preliminary in nature and need to be replicated, these results show that the aging organism is still placid enough to benefit from lifestyle changes and intervention programs into old age (Dumas, 2017).

With regard to hormone therapy in women, it is important to consider the clinical recommendations and to thoroughly monitor physiological changes such as bleeding patterns as well as psychological changes such as mood swings (Shifren and Gass, 2014; Soares, 2017). Estradiol withdrawal has been proposed to have an effect on mood (Gordon et al., 2016; Schmidt and Rubinow, 2009). However, these negative effects might be minimized through the application or intake of exogenous estradiol. Transdermal, vaginal, and intrauterine application of cream, tablet, ring, or pessary offer non-oral routes of administration, with the potential advantage of bypassing the first-pass hepatic effect (Pinkerton et al., 2017). As recently reviewed, randomized controlled trials on transdermal estrogen therapy (ET) in perimenopause show promising results, with remission rates of depression ranging from 60 to 80% (Soares, 2017), but the effects are only

beneficial within the critical time window around the FMP (Rubinow et al., 2015; Soares, 2017). A recent study on transdermal estradiol and micronized progesterone in euthymic peri- or early postmenopausal women provided first evidence of a preventive effect on the development of depressive symptoms over a 12-month study period (Gordon et al., 2018). In the same line, one study has suggested that hormone therapy (HT) and oral contraceptives may exert protective effects on cognition, but only if started before the FMP (Greendale et al., 2009). Androgens play a critical role in women`s physiology, but it is still unclear whether androgen therapy is suitable for women, since there are neither clear values for androgen deficiency, nor specific products for women, and long-term studies are needed to evaluate safety and efficacy on health-related outcomes (Davis and Wahlin-Jacobsen, 2015; Shifren and Davis, 2017). Finally, it is crucial to consider pre-existing diagnoses, the menopausal status, and the general health when deciding whether to prescribe a supplement and if so which one. The North American Menopause Society (NAMS) recommendations state that women with an intact uterus should receive a combination of exogenous estrogens and an adapted dose of progesterone to prevent endometrial overgrowth (Pinkerton et al., 2017). Moreover, the clinical care recommendations of the NAMS highlight the importance of a close dialogue between women and healthcare practitioners to enhance informed decision-making for women and to improve health-related practices (Shifren and Gass, 2014).

4.11. Emerging clinical implications for men

Testosterone therapy is receiving increased attention for its beneficial effects in different dimensions of healthy aging, but is recommended only for men presenting hormonally verified testosterone deficiency with according symptoms (Bhasin et al., 2018). Meta-analyses report an overall positive effect for body composition (Corona et al., 2016), mood and well-being (Amanatkar, 2014; Elliott et al., 2017), and sexual function (Corona et al., 2014; Elliott et al., 2017). The majority of studies included in these analyses were administration studies in men with low testosterone levels. However, there is no testosterone concentration level that reliably distinguishes between men who will respond to treatment and those who will not (Morgentaler et al., 2016). In addition, basal testosterone levels prior to treatment are usually not identified as moderators of the treatment effect in meta-analytic approaches (Amanatkar, 2014). Therefore, older men with normal testosterone levels might still benefit from exogenous supplementation, although this needs further study. With regard to older men, the largest RCT administering testosterone in older men so far, “The Testosterone Trials (TTT)”, was able to show similar findings for older men (Snyder et al., 2014). While others reported a beneficial effect of testosterone supplementation in lean body mass in older men (Emmelot-Vonk et al., 2008), TTT showed an improvement in bone mineral density and thus a reduction in the risk of frailty and falls (Snyder et al., 2017). In line with others (Emmelot-Vonk et al., 2008), TTT failed to provide further evidence of a beneficial effect with respect to cognitive function (Resnick et al., 2017). TTT further demonstrated a beneficial effect of testosterone on mood in older men, and a moderate benefit for sexual function (Snyder et al., 2016). However, re-analysis of the data revealed that participants receiving testosterone showed improvements in sexual desire and activity related to the magnitude of increases in testosterone and estradiol (Cunningham et al., 2016).

In contrast to testosterone, DHEA supplementation in men did not hold the long-held promise of an anti-aging treatment and was largely dismissed. Studies on DHEA supplementation did not reveal beneficial effects on body composition or bone mineral density in older men (Baulieu et al., 2000; Nair et al., 2006). However, meta-analytic findings indicate that DHEA supplementation may support a reduction of fat mass in older men (Corona et al., 2013). Similar to testosterone, a systematic review of RCTs on cognitive function in middle-aged and older men also concluded that there is no evidence of a beneficial effect of DHEA supplementation (Grimley Evans et al., 2006). Early supplementation studies further indicated DHEA as a potential antidepressant (Rabkin et al., 2000; Wolkowitz et al., 1999), while others were unable to replicate these results (Kritz-Silverstein et al., 2008; Wolf et al., 1997). Although a recent meta-analysis indicated a beneficial effect of DHEA on depressive symptoms (Peixoto et al., 2018), the analysis had some methodological shortcomings and needs to be considered with caution. By contrast, a thorough meta-analysis did not identify an effect of DHEA on sexual function in men (Corona et al., 2013), and thus supported more recently conducted DHEA supplementation studies showing no effects (Bloch et al., 2013; Morales et al., 2009).

Therefore, in older men, meta-analyses and individual reports suggest testosterone more than DHEA supplementation as a potent therapy for various areas of life such as body composition, quality of life, mood, and sexual function (Amanatkar, 2014; Elliott et al., 2017), but not for cognition (Resnick et al., 2017). Although there are concerns regarding the safety of testosterone supplementation (Vigen et al., 2013), there is no support for increased adverse events with testosterone supplementation (Elliott et al., 2017). However, long-term safety of testosterone therapy is still a matter of current debate, since sufficiently powered trials with long-term monitoring of adverse events do not exist (Bhasin et al., 2018; Snyder et al., 2018). The restoration of lowered testosterone levels only due to aging, without being symptomatic for testosterone deficiency, is not an authorized reason for the use of testosterone therapy.

Instead, modifiable lifestyle factors and intervention programs for males are recommended as primary approaches for the prevention of symptoms related to androgen loss and for the promotion of good health into old age. Although both factors have been shown to beneficially influence testosterone and DHEA levels, higher physical activity was shown to elicit larger effects on testosterone or DHEA secretion compared to lifestyle modifications such as diet (Kumagai et al., 2016). Furthermore, 150 min of vigorous physical activity per week was directly related to successful aging in a 12-year follow-up including 12’201 older men (Almeida et al., 2014). Very recently, a 12-week aerobic exercise intervention program in middle-aged obese men was successful in increasing testosterone levels, suggesting aerobic exercise as a crucial intervention factor in maintaining health-promoting androgen levels in older men (Kumagai et al., 2018).

5. Future directions

Middle-aged and older men and women should be provided with information on healthy lifestyles in order to counteract the age-related hormonal changes and at best prevent chronic conditions. Moreover, besides their family doctor, older individuals should have access to endocrinologists, psychiatrists, and psychotherapists in order to seek support if needed. In individual cases, hormone replacement can help to overcome the age-related steroid hormone alterations and restore levels that enable better physical functioning and wellbeing. Healthy aging is a public health concern and therefore a highly important research topic. Steroid hormones in healthy aging represent an understudied although promising research field, and future studies should investigate age-related steroid hormone changes with regard to health-related outcomes.

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