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Frailty and the endocrine system

Andrew Clegg, Zaki Hassan-Smith

Frailty is a condition characterised by loss of biological reserves, failure of homoeostatic mechanisms, and vulnerability to adverse outcomes. The endocrine system is considered particularly important in frailty, because of its complex inter-relationships with the brain, immune system, and skeletal muscle. This Review summarises evidence indicating a key role for the hypothalamic–pituitary axis in the pathogenesis of frailty through aberrant regulation of glucocorticoid secretion, insulin-like growth factor signalling, and androgen production. Evidence also indicates a potential role for vitamin D and insulin resistance in the pathogenesis of frailty. The role of thyroid hormones in the pathogenesis of frailty remains uncertain. Key convergent pathological effects of frailty include loss of muscle mass and strength, with consequent impact on mobility and activities of daily living. Future translational research should focus on the understanding of endocrine mechanisms, to identify potential biomarkers of the condition, modifiable targets for treatment, and novel pharmacological drugs targeted at the endocrine components of frailty.

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Introduction

Frailty is a condition characterised by loss of biological reserves across multiple organ systems, failure of homoeostatic mechanisms, and vulnerability to physiological decompensation after minor stressor events.[1] Older people living with frailty are at increased risk of a range of adverse outcomes that have considerable importance from an individual, health service, and wider societal perspective.[1]

Frailty is closely linked to the ageing process, which results from the accumulation of damage caused by multiple mechanisms at a molecular and cellular level, leading to gradual physiological decline. However, with frailty the physiological decline appears to be accelerated, and accumulates across multiple inter-related physiological systems.[2,3] The endocrine system is considered one of the key systems in frailty, through complex inter-relationships with the brain, immune system, and skeletal muscle. The cardiovascular, respiratory, renal, and haematological systems are also considered of key importance in frailty. Evidence indicates that the absolute number of impaired physiological systems is more predictive of frailty than impairments in any particular system,[4] supporting the concept that frailty becomes evident when physiological decline reaches a cumulative, critical level.

The epidemiology of frailty

Evidence indicates that frailty affects around 10% of people aged 65 years and older, and between 25% and 50% of people older than 85 years.[5] Frailty is characterised by sudden, disproportionate changes in health after seemingly minor stressor events, such as an infection, new medication, or a minor surgical procedure. This initial stressor event is usually followed by an extended period of recovery, and subsequent inability to return to previous levels of function (figure 1). Consistent associations between frailty and important adverse outcomes have been reported in several large epidemiological studies. Adverse outcomes reported to be associated with frailty include falls (adjusted 3-year hazard ratio [HR] 1·23, 95% CI 1·00–1·68),[6] disability (adjusted 3-year HR 1·70, 1·47–2·17),[6] delirium (adjusted odds ratio [OR] 8·5, 95% CI 4·8–14·8),[7] nursing home admission (adjusted OR 2·60, 1·36–4·96),[8] hospitalisation (3-year HR 1·27, 1·11–1·46), and mortality (adjusted OR 3·69, 2·26–6·02).[8]

These frailty prevalence estimates and the independent associations of frailty with adverse outcomes that are discussed in this Review affect the planning and delivery of health and social care systems internationally. However, the estimated prevalence also shows that many older people do not have frailty, indicating that frailty is not an inevitable consequence of ageing. Frailty might be modifiable and is considered to have greater potential for reversibility than disability.[1,9] A better understanding of the pathophysiology of frailty would help in the development and targeting of novel approaches to prevention and treatment. Greater insight into the role of the endocrine system in the pathophysiology of frailty is likely to be especially important because potentially modifiable targets could be identified.

Models of frailty

The phenotype model[6] and the cumulative deficit model[10] are the two international frailty models that are best established. Both models have been extensively validated in large epidemiological studies, and demonstrate robust associations with a range of adverse outcomes.

The phenotype model identifies frailty on the basis of five physical characteristics: weight loss, exhaustion, low energy expenditure, slow gait speed, and reduced grip strength.[6] People without these physical characteristics are identified as fit, those with one or two of these physical characteristics are identified as pre-frail, and people with three or more of these are identified as frail.

The cumulative deficit model[10] identifies frailty on the basis of a range of deficit variables, including clinical signs, symptoms, diseases, disabilities, and abnormal

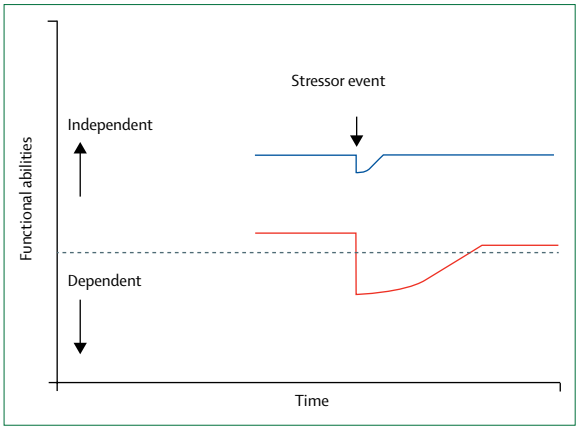

Figure 1: **Susceptibility of older people with frailty to a sudden change in health status after a minor stressor event**
The blue line represents a healthy older person who, after a minor stressor event such as an infection, has a small deterioration in function and then returns to baseline. The red line represents an older person with frailty who, after a similar stressor event, undergoes a larger deterioration (which might manifest as functional dependency) and then does not return to baseline. The horizontal dashed line represents the cutoff between functionally dependent and functionally independent. Adapted from reference 1.

Panel: **Measures to identify frailty recommended by the National Institute for Health and Care Excellence**

- Gait speed <0·8 m/s
- Timed up and go test score <12 s
- Self-reported health status score <6
- PRISMA-7 questionnaire >3
- Self-reported physical activity scale in the elderly score <56 in men or <59 in women

laboratory test values. The frailty index score can be calculated as the equally weighted number of deficits present in an individual in proportion to the total number of deficits possible in the model. For example, if nine of 36 deficits are present, the frailty index score would be 0·25. The model is useful because it is very flexible—a minimum of 30 deficits are required for a model to be valid.[11]

A prospective association between frailty, cognitive impairment, and dementia has been established, including when frailty is identified using the phenotype model, which does not explicitly include measures of cognition.[12] The cumulative deficit model incorporates measures of cognition as key deficit variables, and a prospective independent association between frailty and future dementia has been reported[13] using this approach.

Sarcopenia and frailty

Most older people with frailty also have sarcopenia, which is a syndrome characterised by the progressive and generalised loss of skeletal muscle mass and strength with age.[14,15] When present, sarcopenia is considered an especially important component of frailty, because loss of muscle mass and strength can lead to loss of physical function and independence as key adverse outcomes.[15]

Muscle power (the product of muscle torque and movement) might be more closely associated with functional physical performance than with static muscle strength, and declines more rapidly with age.[16] Therefore, muscle power might be more useful as a measure of physiological impairment and functional deficit. 2011 consensus criteria[15] for the diagnosis of sarcopenia recommend checking for low muscle mass, and either for low muscle strength or for low physical performance, because muscle strength and power do not depend entirely on muscle mass, and the relationship between strength and mass is non-linear. Observational studies[17] have reported between 1% and 3% losses of muscle strength per year in older people aged over 60 years, with even greater losses observed in older people aged over 80 years.

Identifying frailty in clinical practice

A range of simple tools and questionnaires to assess frailty are available and validated for use in clinical practice. The 2016 UK National Institute for Health and Care Excellence (NICE) guideline on the clinical assessment and management of multimorbidity recommends using one of the following measures to identify frailty: gait speed slower than 0·8 m/s, timed up and go test score higher than 12 s, self-reported health status score lower than 6; PRISMA-7[18] score higher than 3, and self-reported physical activity scale in the elderly score lower than 56 for men or lower than 59 for women (panel).[19] In addition, the FRAIL questionnaire[20] is a simple, validated measure made of five items, with a score greater than 3 indicating frailty. The NICE guideline cautions against using a performance-based tool to measure frailty in people who are acutely unwell, because the tool would not be able to differentiate between frailty and acute illness if, for example, gait speed was measured. However, the Clinical Frailty Scale and Reported Edmonton Frail Scale have been validated in acute hospital settings, so they are appropriate tools for the assessment of frailty in the context of acute illness.[21,22] An electronic frailty index supported by NICE guidance has been developed and validated in 2016, by use of routinely available primary care electronic health record data, and has been widely implemented across the UK to identify frailty in primary care settings.[23]

The endocrine system

The brain and endocrine system are intrinsically linked through the hypothalamic–pituitary axis, which controls metabolism and energy use via the signalling action of several homoeostatic hormones.[24] Accumulating evidence shows that the hypothalamic–pituitary axis has a crucial role in the regulation of ageing and frailty. Regulation of glucocorticoid secretion, insulin-like growth factor (IGF) signalling and androgen production are of key importance, because deficits in these hormonal

systems have been associated with adverse ageing profiles and frailty. In addition to the hypothalamic–pituitary axis, vitamin D and insulin resistance might have a potential role in the pathogenesis of frailty. Figure 2 shows the potential endocrine mechanisms involved in the development of frailty.

In their 2009 cross-sectional study,[25] Cappola and colleagues investigated the relationship between multiple anabolic hormones and frailty using data from 494 older women aged 70–79 years. The reported results indicated that the absolute number of hormone deficiencies was more predictive of frailty than the type of deficiency, suggesting that frailty could arise from a more generalised endocrine dysfunction, rather than from a particular hormonal deficiency.

Glucocorticoids

The hypothalamus receives and integrates multiple afferent inputs from diverse regions of the brain to coordinate a response to stress and inflammation, partly through the control of glucocorticoid secretion.[26] Basal glucocorticoid secretion is necessary for many cells to function normally, and concentrations of basal glucocorticoid are increased in response to any type of stress, including physical stress, psychological stress, and inflammation, to provide the altered physiology that is required to promote survival.[27] Age-related changes in the hypothalamic–pituitary–adrenal axis have been investigated in several studies, with evidence of blunting of the circadian rhythm,[28] reduced suppression of cortisol secretion,[29] and impaired recovery from stress,[30] although an overall increase in glucocorticoid secretion with age is uncertain.

Glucocorticoids affect the range of metabolically active tissues that are important in the development of the frailty phenotype, including skeletal muscle, bone, and the cardiovascular system.[31] Changes to the hypothalamic–pituitary–adrenal axis and glucocorticoid secretion in frailty have been researched. A cross-sectional study[32] with 214 women reported that frailty, measured using the phenotype model, was independently associated with chronically elevated diurnal cortisol concentrations, even after adjustment for depressive symptoms, which are themselves associated with increased cortisol concentrations. Persistently high concentrations of cortisol have been associated with increased catabolism of skeletal muscle,[33] so a link between chronically elevated cortisol and frailty is biologically plausible, with development of sarcopenia as a core component of the condition. Other aspects of the hypothalamic–pituitary–adrenal axis in the context of frailty have been assessed. Carvalhaes-Neto and colleagues[34] reported reduced post-dexamethasone suppression of cortisol in older care home residents aged 69 to 87 years with markers of frailty, compared with non-frail controls, suggesting dysregulation of hypothalamic–pituitary–adrenal axis feedback.

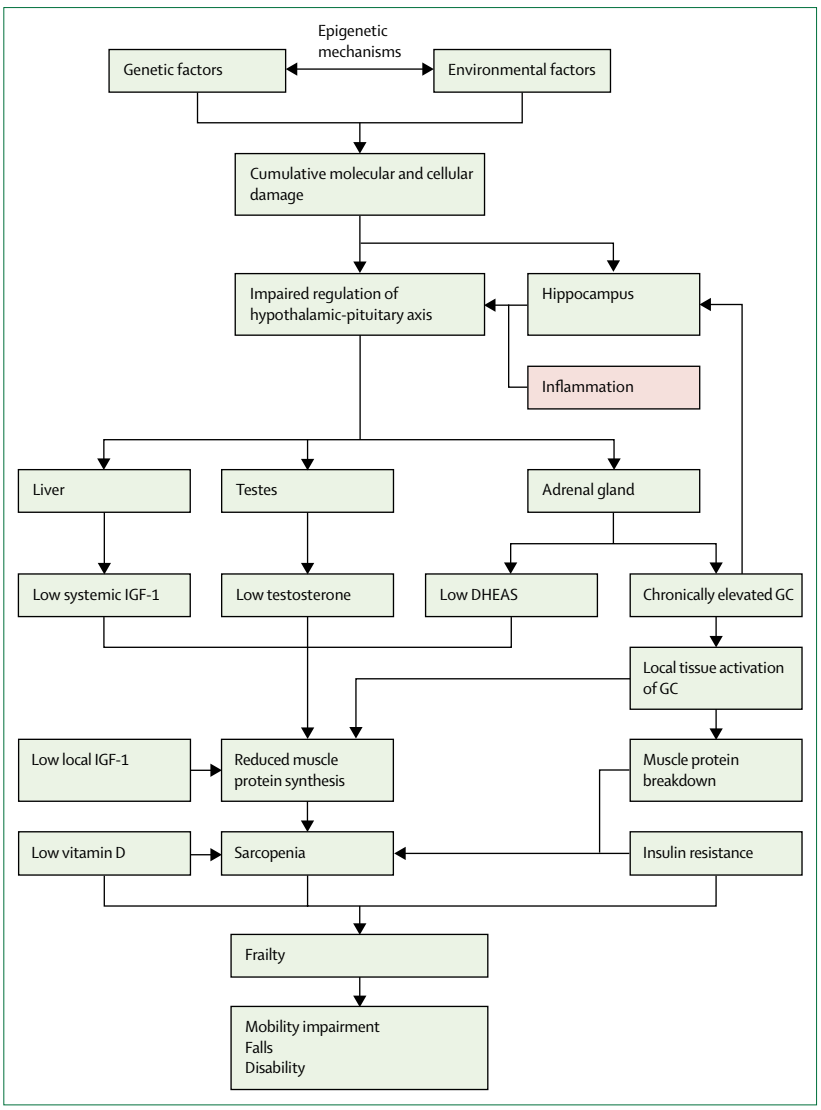

Figure 2: **Potential endocrine mechanisms involved in the development of frailty**
IGF-1=insulin-like growth factor 1. DHEAS=dehydroepiandrosterone. GC=glucocorticoid.

In their study[35] with 60 participants, Rao and colleagues reported that people with frailty had a reduced response to a low dose synacthen (1 µg adrenocorticotropic hormone [ACTH] stimulation test) compared with the controls. In a study[36] with a large community-dwelling cohort, Kumari and colleagues found that reduced diurnal cortisol rhythms were associated with poorer health outcomes later in life. Taken together, findings from these three studies[34–36] indicate that chronically elevated diurnal concentrations of cortisol in the context of frailty might be due to failure of homoeostatic control caused by impaired suppression of cortisol, rather than a result of an increased response to ACTH stimulation.

The effect of local tissue activation of cortisone to cortisol via 11β-HSD1 on features of the ageing phenotype has also been studied,[37] with evidence for an association

between higher concentrations of 11β-HSD1 and reduced grip strength, insulin resistance, and adverse body composition. Further studies with cohorts with well defined frailty are required to establish the clinical effect of local tissue activation of cortisol, and to establish whether 11β-HSD1 might be a potentially modifiable target for treatment.

Glucocorticoids and inflammation

Inflammation is a protective immune response that is triggered by conditions related to infection and tissue injury, including ischaemia, hypoxia, trauma, physical injury, and chemical injury.[38–40] Inflammation removes noxious stimuli and pathogens, restoring physiological homoeostasis; an inadequate inflammatory response would lead to multiple detrimental outcomes, including uncontrolled infections and absence of wound healing.[39] Moreover, if the inflammatory response is not tightly regulated, chronic molecular and cellular damage may occur, accelerating biological mechanisms that drive the development of frailty.[1] A large meta-analysis [41] supports the growing consensus that reactivity of the hypothalamic–pituitary–adrenal axis to inflammatory stimuli is greatly increased with age.

Detection of inflammation by the nervous system leads to activation of the hypothalamic–pituitary–adrenal axis and stimulation of cortisol release.[27,42] Glucocorticoid receptors in the brain are usually only occupied during stress and inflammation.[43] Circulating glucocorticoids are sensed by the hippocampus, which suppresses hypothalamic stimulation of glucocorticoid production in a negative feedback loop. Additional downstream effects, characterised by increased hippocampal activity, include increased metabolism and altered brain function.[44]

Uncontrolled inflammation has the potential to cause cellular damage, and a functional glucocorticoid system is an important component of the homoeostatic regulation of local and systemic inflammation. The loss of hippocampal neurons that is observed in both normal ageing and age-related conditions such as Alzheimer's disease might impair the glucocorticoid system's homoeostatic control, potentially causing uncontrolled inflammation and increased cellular damage, which would lead to accelerated ageing and frailty. Loss of homoeostatic control of the glucocorticoid system might promote further neurodegeneration, since chronically elevated concentrations of glucocorticoid have been postulated to increase hippocampal neuronal damage.[45] Figure 2 shows the potential role of glucocorticoid in the development of frailty, including reduced homoeostatic regulation.

Glucocorticoids and sarcopenia

Muscle homoeostasis is maintained through a balance between formation of new muscle cells, muscle cell hypertrophy, and loss of muscle cell protein. This balance is coordinated by the neuroendocrine system and immune system and is affected by nutritional factors and physical activity.

Glucocorticoids stimulate muscle atrophy by promoting myofibrillar degradation and inhibiting protein synthesis. Glucocorticoids also regulate muscle wasting caused by starvation, metabolic acidosis, and sepsis, so they probably play a key role in the characteristic loss of muscle mass and strength observed when older people with frailty are admitted to hospital for acute illness.[46]

Muscle strength and power are required for the basic mobility skills that are crucial to get out of bed, stand up from a chair, walk a short distance, and get off a toilet.[47] When an older person with frailty experiences an acute stressor event, their ability to perform these critical skills is often reduced, and there is an increased risk of immobility, causing further loss of muscle mass, and an increased risk of falls.[48] Indeed, sarcopenia has been independently associated with an increased risk of falls, functional decline, and mortality.[49]

IGFs and growth hormone

IGFs are a family of small peptides that increase anabolic activity in many cells. Their roles in neuronal plasticity and skeletal muscle strength are particularly important.[50] The main IGFs are IGF-1 and IGF-2. IGF-1 is synthesised in the liver in response to circulating growth hormone in a process regulated by the hypothalamic–pituitary axis.

Growth hormone secretion decreases at a rate of 14% per decade in adult life from the age of 20 years in a process called somatopause.[51] Growth hormone deficiency results in a body composition profile with increased fat mass and reduced lean mass. Welle and colleagues[52] assessed the benefits of recombinant growth hormone in older people, with evidence of improvements in body composition parameters but insufficient evidence of changes in muscle strength. Data on the dynamics between growth hormone and IGFs have been obtained only in cohorts with well defined frailty.

Many growth factors and hormones also stimulate local synthesis of IGF-1 by neurons, muscle cells, and white blood cells. The local autocrine and paracrine actions of IGF-1 are important for the promotion of neuronal plasticity and increased skeletal muscle strength.[50,53] Age-related impairments in the autocrine, paracrine, and endocrine activities of IGF-1 play a role in the development of neuronal senescence and sarcopenia, both of which are core components of frailty.[50,53]

IGF-1 regulates the production of many transcription factors that affect the expression of genes associated with inflammatory regulation and cellular autophagy, which are key mechanisms associated with frailty.[54] Evidence from nematode studies indicates that the downstream transcription factor DAF-16 might have an important role in the regulation of lifespan.[55] Additionally, genetic variations in the IGF signalling pathway have been

associated with increased life expectancy in human beings.[56] However, the relationships between regulatory mechanisms are complex. Both overexpression and suppression of growth hormone and IGF-1 are associated with increased mortality in pituitary disease, and there is no evidence of growth hormone resistance providing a survival advantage.[57–59]

IGFs are likely to have an important role in frailty. A 2009 cross-sectional study[25] with 494 older women reported that participants with IGF-1 deficiency, in combination with either dehydroepiandrosterone or testosterone deficiency, were more likely to have frailty (OR 2·79, 95% CI 1·06–7·32). A 2004 cross-sectional study[60] with 51 older participants reported significantly lower concentrations of IGF-1 in participants with frailty than in age-matched controls.[60] Frailty was measured with the phenotype model. An inverse correlation between IGF-1 and interleukin-6 levels was also reported, identifying a potential link between IGF-1 and inflammation that might be important in frailty.

A 2009 cross-sectional US study[61] with 696 older women identified a significant correlation between white blood cell counts and IGF-1. A complex U-shaped association between IGF-1, white blood cell count, and frailty was also reported. When IGF-1 concentrations were low, both low and high white blood cell counts were associated with increased risk of frailty. Conversely, when white blood cell counts were high, both low and high levels of IGF-1 were associated with frailty.

IGFs and sarcopenia

IGF-1 is considered essential for maintenance of muscle strength. The autocrine and paracrine effects of growth hormone-independent, local IGF-1 production by muscle cells in response to changes in the cellular microenvironment are thought to be particularly important for maintenance of muscle strength. Systemic, growth hormone-dependent IGF synthesis by the liver might also play a role in maintenance of muscle strength.[53]

IGF-1 increases muscle strength by stimulating an increased production of myocytes, activating muscle cell hypertrophy, and inhibiting muscle protein breakdown. Myocyte numbers are thought to increase through muscle stem cell proliferation and differentiation.[62] Muscle cell hypertrophy is caused by an IGF-mediated direct and indirect cascade of kinase enzymes, and by the nutrient sensing mTOR signalling pathway.[63] The breakdown of muscle protein is inhibited through downregulation of components of the ubiquitin-proteasome pathway.[64] IGF-1 secretion is modulated by nutrient intake, with fasting and low energy diets resulting in reduced circulating concentrations of the hormone. IGF-1 concentrations are also lower with increasing BMI.

A prospective cohort study with 558 participants did a multivariable analysis to identify a significant association between IGF-1 concentrations and sarcopenia as a key component of frailty.[65] Analysis of data from 1833 community-dwelling older people taking part in the I-Lan Longitudinal Aging Study[66] revealed a positive association between IGF-1 concentrations and improved muscle mass, grip strength, and bone mineral density. An additional observational study[67] with 3447 community-dwelling men aged between 70 and 89 years, reported that lower IGF-1 and higher insulin like growth factor binding protein 1 concentrations were associated with increased incident frailty, defined using the FRAIL score.

Androgens

The hypothalamic–pituitary–gonadal axis regulates testicular secretion of testosterone (the main human androgen) through pulsatile hypothalamic secretion of gonadotropin releasing hormone. Secretion of this hormone stimulates pituitary secretion of luteinising hormone, which binds to target cells to increase expression of steroidogenic acute regulatory protein. The adrenal gland is also a source of androgens such as dehydroepiandrosterone and androstenedione in women and men.

Androgens affect a range of target organs, including skeletal muscle, so they are of potential interest in frailty because they might be a modifiable determinant of the condition. Testosterone increases synthesis of muscle protein both through direct stimulation of muscle androgen receptors and through actions on the intramuscular IGF-1 system.[68,69] Testosterone concentrations have been shown to decrease with increasing age, with concentrations of bioavailable testosterone falling by around 2% per year in men.[70] Although these reductions can be considered part of the normal ageing process, many large epidemiological studies have reported consistent cross-sectional associations between low testosterone concentrations and frailty.[71–73] However, although there appears to be a consistent association between testosterone concentrations and frailty in cross-sectional studies, longitudinal studies reporting prospective associations have been equivocal, so testosterone might represent a surrogate marker for frailty, rather than a causal factor.[68]

Testosterone supplementation can increase skeletal muscle mass in younger and older men, mainly through promotion of myofibre hypertrophy and increased stem cell proliferation.[74] 790 men aged 65 years and older who had low concentrations of serum testosterone received either testosterone gel or a control gel in a 2016 randomised controlled trial.[75] Although improvements in sexual function and mood were reported, no benefits regarding vitality or mobility (measured with the 6-min walking distance)[76] were observed. One randomised trial of testosterone supplementation in 209 men aged 65 years and older with reduced mobility and low serum testosterone was terminated early because of safety concerns.[77] The intervention group had shown significant improvements in arm and leg strength compared with the placebo group; however, a higher rate of adverse

cardiovascular and respiratory events in the intervention group than in the placebo group led to a recommendation from the data and safety monitoring board that the trial be discontinued.

Other randomised trials of testosterone treatment have reported outcomes relevant to older people with frailty, with evidence of improvements in bone mineral density[78] and red blood cell count,[79] but no evidence of improvements in cognition,[80] and an increased size of coronary atheroma.[81] As in clinical practice for confirmed male hypogonadism, future trials of testosterone treatment should incorporate long-term safety monitoring for prostate cancer, polycythaemia, respiratory events, and cardiovascular events.

One cross-sectional study[82] reported an association between lower concentrations of dehydroepiandosterone and frailty, but the effect of comorbid conditions could not be confidently excluded. The role of dehydroepiandosterone in the pathogenesis of frailty might be more relevant as part of a generalised endocrine dysfunction.[25]

Vitamin D

Vitamin D deficiency is highly prevalent globally, with estimates of prevalence varying within individual populations based on ethnic diversity.[83,84] Vitamin D is central to the development and maintenance of bone health and calcium metabolism. Severe deficiency can cause rickets and osteomalacia.[85] Based on trial evidence, current guidelines recommend vitamin D supplementation to prevent osteoporotic fractures.[86–88] However, a 2017 meta-analysis[89] of calcium and vitamin D supplementation—separately or in combination—pooled data from 33 randomised trials with 51 145 participants and reported no overall reduction in total fracture risk.

Cross-sectional studies have found associations between vitamin D status and frailty. In the Concord Health and Ageing in Men Project[90] with 1659 participants, Hirani and colleagues found that low vitamin D status was associated with frailty, and independently associated with four out of five frailty components. In the Toledo Study for Healthy Aging[19] with 592 participants, Alvarez-Ríos and colleagues reported that low serum calcifediol was associated with frailty, defined with the phenotype model (odds ratio [OR] 1·65, 95% CI 1·02–2·67, p=0·04). Similar findings were reported by Tajar and colleagues[91] in their European study with 1504 participants and by Gutiérrez-Robledo and colleagues[92] in their Mexican study with 331 participants who were older than 70 years. A large Austrian study[93] with 940 participants also observed significant associations between low serum calcifediol and individual components of frailty, including physical exhaustion, inactivity, and reduced gait speed. A Taiwanese study with 215 participants reported a strong association between vitamin D status and frailty (OR 10·7, CI 2·6–44·3).[94]

Longitudinal studies have investigated whether vitamin D status can predict the development of frailty. One longitudinal US study[95] with 369 women reported an association between vitamin D concentrations and the incidence of frailty (HR 2·77, 95% CI 1·14–6·71). This association was significant before cardiometabolic diseases were accounted for. An Australian study[96] with 4203 men between 70 and 88 years old found that low vitamin D status was associated with an increased risk of incident frailty and mortality, independent of baseline frailty. Vogt and colleagues[97] followed up 727 non-frail participants over a mean of 2·9 years and found that low vitamin D status was associated with pre-frailty (OR 2·4, 95% CI 1·2–5·0), combined pre-frailty and frailty (OR 2·53, 95% CI 1·2–5·2), and mortality (OR 3·4, 95% 1·1–10·7). Longitudinal data from the US Third National Health and Nutrition Survey[98] with 4731 participants, and longitudinal data from the Italian Invecchiare in Chianti (InCHIANTI) study[99] with 1155 participants, indicate that low vitamin D status is associated with increased risk of incident frailty. However, in one US study[100] with 1606 men older than 65 years, Ensrud and colleagues reported no prospective association between frailty and vitamin D, despite the relation between frailty and vitamin D status that was found at baseline. A U-shaped association between frailty status and vitamin D at baseline was reported by Ensrud and colleagues in their US study[101] with 6307 women over 69 years old. They also observed a significant association between lower concentrations of serum calcifediol and incident frailty.

The effect of vitamin D supplementation has been assessed in meta-analyses of clinical trials. One meta-analysis[102] pooled data from 13 trials and found that daily vitamin D doses of 800 to 1000 IU had consistent positive effects on strength and balance. A 2014 meta-analysis[103] pooling data from 30 randomised trials with 5615 participants, reported a small positive effect of vitamin D supplementation on global muscle strength, but not on muscle mass or power. Another 2014 meta-analysis[104] pooling data from 20 randomised trials with 29 535 participants reported that vitamin D supplementation did not reduce the risk of falls, by a threshold of 15%.

Insulin resistance

Diabetes has been identified as a risk factor for frailty. In the past years, the role of insulin resistance in the development of frailty and as a target for prevention of frailty has been investigated. Insulin resistance and other components of metabolic syndrome are increasing in prevalence globally, due to industrialisation and the lifestyle changes associated with it.[105,106]

A prospective cohort study by Pérez-Tasigchana and colleagues,[107] with 1499 participants older than 60 years and a 3·5 year follow-up, reported an association between insulin resistance and frailty, defined with the phenotype model. Metabolic syndrome was associated with risk of frailty, and this association was mostly due to central

obesity. Metabolic syndrome also had an independent association with reduced grip strength. Another prospective study[108] with 3141 community-dwelling older people aged 69–74 years reported a positive association between insulin resistance and frailty (HR 1·15, 95% CI 1·02–1·31).

Hoogendijk and colleagues[109] analysed data from 1247 participants in the Longitudinal Aging Study Amsterdam (men and women older than 65 years) and found that although frailty appeared to contribute to the association between metabolic syndrome and mortality, comorbidities such as diabetes and cardiovascular disease contributed more to this association. A secondary analysis[110] of data from the Beijing Longitudinal Study of Ageing showed clustering of metabolic syndrome, frailty and mortality, but directionality or causality could not be established. Frailty index scores, calculated using the cumulative deficit model, increased with each cardiometabolic comorbidity, and those individuals with the highest frailty index scores had the greatest risk of mortality. Evidence from a single study has indicated that the metabolic syndrome might strengthen the association between frailty and impairment of executive function.[111]

Putative mechanisms have been identified that account for the associations between insulin resistance and frailty that are mentioned in this Series paper, including common pathways for dysregulated metabolic and contractile function of the skeletal muscle. Central to these associations is the interplay between adipose, muscle and bone, which are metabolically active tissues that are affected in frailty. Sarcopenic obesity should be studied further, because visceral adiposity and increased intramuscular lipid content has been shown to favour a pro-inflammatory, insulin resistant, catabolic state.[112] Clinical trials that evaluate interventions targeting components of metabolic syndrome (eg, insulin resistance) to prevent or treat frailty would be required.

The thyroid

Changes in thyroid hormone concentration with increasing age have been well characterised; thyroid-stimulating hormone (TSH) concentrations increase, free triiodothyronine (FT3) concentrations decrease, and free thyroxine (FT4) concentrations remain stable. Thyroid dysfunction can affect body composition, muscle strength, cognition, bone health, and cardiovascular health. However, data from defined frail cohorts are scarce.

Virgini and colleagues[113] associated subclinical hyperthyroidism with an increased prevalence of frailty (OR 2·48, 95% CI 1·15–5·34), but not with subsequent development of frailty, in a 5-year follow-up study with a cohort of older men. No associations were observed in the group with subclinical hypothyroidism. The study included 1455 men aged over 65 years and defined frailty with a modified phenotype model. A study[114] with 641 older women reported reduced risk of frailty, which had been defined with the phenotype model, in people with thyroglobulin and TPO antibodies, independent of their thyroid hormone status (OR 0·30, 95% CI 0·10–0·85). However, higher serum FT4 concentrations were associated with increased risk of frailty in men between 70 and 89 years old in a cross-sectional Australian study[115] with 3943 participants (OR 1·36, 95% CI 1·04–1·79. The study used the Fatigue, Resistance, Ambulation, Illnesses and Loss scale. The association held even with FT4 concentrations within the normal reference range.

In their 2017 study,[116] Bertoli and colleagues reported a significant inverse correlation between FT3 and frailty, defined using the Survey of Health, Ageing and Retirement in Europe Frailty Instrument (r=–0·436, $p<0·001$) in a cohort of 112 participants aged 65 years and older. 62 participants were inpatients with hip fractures and 50 controls were outpatients. Moderate, significant correlations were reported between FT3 and measures of nutritional status, disability, comorbidities, and grip strength were also observed. However, there were no correlations between TSH, FT4, and nutritional status, disability comorbidities, or grip strength. The main limitation of this study was that FT3 concentrations can be reduced because of several factors that predispose to non-thyroidal illness, including acute illness and surgery, and no evidence that supplementation would reduce this predisposition has been found. Nevertheless, the researchers proposed that FT3 could be used as a biomarker of frailty status. Reproducibility of the above findings involving the thyroid and frailty needs to be checked in well defined cohorts of people with frailty.

Conclusions

Frailty involves complex regulatory systems with changes in multiple hormone axes moderated by factors such as nutrition, exercise, and inflammation. Epidemiological evidence indicates that components of the hypothalamic–pituitary–adrenal axis, IGFs and androgens might be of particular importance, with emerging data identifying potential links between candidate hormones and frailty. However, available evidence indicates that in frailty, the cumulative burden of hormone deficiencies might be more important than the types of hormone deficiencies that comprise the generalised endocrine dysfunction.

Although there is evidence that vitamin D supplementation for people who are deficient is beneficial for reducing falls, trials of vitamin D supplementation to improve body composition and musculoskeletal and metabolic health have shown limited efficacy.

A better understanding of the role of the endocrine system in the development of frailty could lead to new pharmacological treatments. Future translational research should focus on the endocrine mechanisms of frailty to identify potential biomarkers of the condition, modifiable targets for treatment, and novel pharmacological drugs that target the endocrine components of frailty. Well

Search strategy and selection criteria

We developed a structured search strategy with the assistance of a research librarian at the University of Leeds, UK. We searched MEDLINE, Embase, CINAHL, Web of Science and the Cochrane database. All searches were from Jan 1, 2001, to May 31, 2017. We combined the search terms "frailty", "pre frailty", "sarcopenia", and "frail elderly" with a wide range of endocrine search terms, including "DHEAS", "testosterone", "IGF-1", "cortisol", and "insulin". Additional papers were identified from the reference lists of retrieved articles and from personal libraries. We prioritised studies that used a validated or operationalised measure to identify frailty in participants.

designed, appropriately powered, consortia based studies are required to establish the efficacy and long-term safety of potential therapeutic interventions, with a focus on clinically relevant outcomes that are highly relevant to older people living with frailty.

Contributors

AC led the development of the search strategy for this review. Both authors reviewed search results and retrieved relevant papers. Both authors contributed to the writing of the final manuscript, including development of figures.

Declarations of interests

We declare no competing interests.

References

1 Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet* 2013; **381:** 752–62.

2 Ferrucci L, Cavazzini C, Corsi A, et al. Biomarkers of frailty in older persons. *J Endocrinol Invest* 2002; **25** (suppl 10)**:** 10–15.

3 Taffett G. Physiology of aging. In: Cassell CK, Leipzig RM, Cohen HJ, et al, eds. Geriatric medicine: an evidence-based approach. New York, NY: Springer-Verlag, 2003: 27–35.

4 Fried LP, Xue QL, Cappola AR, et al. Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. *J Gerontol A Biol Sci Med Sci* 2009; **64:** 1049–57.

5 Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. *J Am Geriatr Soc* 2012; **60:** 1487–92.

6 Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; **56:** M146–56.

7 Eeles EM, White SV, O'Mahony SM, Bayer AJ, Hubbard RE. The impact of frailty and delirium on mortality in older inpatients. *Age Ageing* 2012; **41:** 412–16.

8 Rockwood K, Howlett SE, MacKnight C, et al. Prevalence, attributes, and outcomes of fitness and frailty in community-dwelling older adults: report from the Canadian study of health and aging. *J Gerontol A Biol Sci Med Sci* 2004; **59:** 1310–17.

9 Rodriguez-Mañas L, Fried LP. Frailty in the clinical scenario. *Lancet* 2015; **385:** e7–e9.

10 Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *Sci World J* 2001; **1:** 323–36.

11 Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr* 2008; **8:** 24.

12 Searle SD, Rockwood K. Frailty and the risk of cognitive impairment. *Alzheimers Res Ther* 2015; **7:** 54.

13 Song X, Mitnitski A, Rockwood K. Nontraditional risk factors combine to predict Alzheimer disease and dementia. *Neurology* 2011; **77:** 227–34.

14 Howard C, Ferrucci L, Sun K, et al. Oxidative protein damage is associated with poor grip strength among older women living in the community. *J Appl Physiol (1985)* 2007; **103:** 17–20.

15 Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010; **39:** 412–23.

16 Clark DJ, Patten C, Reid KF, Carabello RJ, Phillips EM, Fielding RA. Impaired voluntary neuromuscular activation limits muscle power in mobility-limited older adults. *J Gerontol A Biol Sci Med Sci* 2010; **65:** 495–502.

17 Doherty TJ. Invited review: aging and sarcopenia. *J Appl Physiol (1985)* 2003; **95:** 1717–27.

18 Hébert R, Raîche M, Dubois MF, Gueye NR, Dubuc N, Tousignant M. Impact of PRISMA, a coordination-type integrated service delivery system for frail older people in Quebec (Canada): a quasi-experimental study. *J Gerontol B Psychol Sci Soc Sci* 2010; **65B:** 107–18.

19 Alvarez-Ríos AI, Guerrero JM, García-García FJ, et al. Associations between frailty and serum N-terminal propeptide of type I procollagen and 25-hydroxyvitamin D in older Spanish women: the Toledo Study for Healthy Aging. *Exp Gerontol* 2015; **69:** 79–84.

20 Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging* 2012; **16:** 601–08.

21 Hilmer SN, Perera V, Mitchell S, et al. The assessment of frailty in older people in acute care. *Australas J Ageing* 2009; **28:** 182–88.

22 Juma S, Taabazuing MM, Montero-Odasso M. Clinical frailty scale in an acute medicine unit: a simple tool that predicts length of stay. *Can Geriatr J* 2016; **19:** 34–39.

23 Clegg A, Bates C, Young J, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. *Age Ageing* 2016; **45:** 353–60.

24 Bishop NA, Lu T, Yankner BA. Neural mechanisms of ageing and cognitive decline. *Nature* 2010; **464:** 529–35.

25 Cappola AR, Xue QL, Fried LP. Multiple hormonal deficiencies in anabolic hormones are found in frail older women: the Women's Health and Aging studies. *J Gerontol A Biol Sci Med Sci* 2009; **64:** 243–48.

26 Jankord R, Herman JP. Limbic regulation of hypothalamo-pituitary-adrenocortical function during acute and chronic stress. *Ann N Y Acad Sci* 2008; **1148:** 64–73.

27 Turnbull AV, Rivier CL. Regulation of the hypothalamic-pituitary-adrenal axis by cytokines: actions and mechanisms of action. *Physiol Rev* 1999; **79:** 1–71.

28 Sherman B, Wysham C, Pfohl B. Age-related changes in the circadian rhythm of plasma cortisol in man. *J Clin Endocrinol Metab* 1985; **61:** 439–43.

29 Wilkinson CW, Petrie EC, Murray SR, Colasurdo EA, Raskind MA, Peskind ER. Human glucocorticoid feedback inhibition is reduced in older individuals: evening study. *J Clin Endocrinol Metab* 2001; **86:** 545–50.

30 Traustadóttir T, Bosch PR, Cantu T, Matt KS. Hypothalamic-pituitary-adrenal axis response and recovery from high-intensity exercise in women: effects of aging and fitness. *J Clin Endocrinol Metab* 2004; **89:** 3248–54.

31 Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. *Lancet* 2006; **367:** 1605–17.

32 Varadhan R, Walston J, Cappola AR, Carlson MC, Wand GS, Fried LP. Higher levels and blunted diurnal variation of cortisol in frail older women. *J Gerontol A Biol Sci Med Sci* 2008; **63:** 190–95.

33 Attaix D, Mosoni L, Dardevet D, Combaret L, Mirand PP, Grizard J. Altered responses in skeletal muscle protein turnover during aging in anabolic and catabolic periods. *Int J Biochem Cell Biol* 2005; **37:** 1962–73.

34 Carvalhaes-Neto N, Huayllas MK, Ramos LR, Cendoroglo MS, Kater CE. Cortisol, DHEAS and aging: resistance to cortisol suppression in frail institutionalized elderly. *J Endocrinol Invest* 2003; **26:** 17–22.

35 Rao MY, Rao TS, Narayanaswamy RK. Study of hypothalamo pituitary adrenal axis in frail elderly subjects. *J Assoc Physicians India* 2012; **60:** 31–34.

36 Kumari M, Badrick E, Sacker A, Kirschbaum C, Marmot M, Chandola T. Identifying patterns in cortisol secretion in an older population. Findings from the Whitehall II study. *Psychoneuroendocrinology* 2010; **35:** 1091–99.

37 Hassan-Smith ZK, Morgan SA, Sherlock M, et al. Gender-specific differences in skeletal muscle 11β-HSD1 expression across healthy aging. *J Clin Endocrinol Metab* 2015; **100:** 2673–81.

38 Medzhitov R. Origin and physiological roles of inflammation. *Nature* 2008; **454:** 428–35.

39 Kumar V, Abbas A, Fausto N, Aster J. Robbins and Cotran pathological basis of disease. Philadelphia, PA: Elsevier, 2010.

40 Eltzschig HK, Carmeliet P. Hypoxia and inflammation. *N Engl J Med* 2011; **364:** 656–65.

41 Otte C, Hart S, Neylan TC, Marmar CR, Yaffe K, Mohr DC. A meta-analysis of cortisol response to challenge in human aging: importance of gender. *Psychoneuroendocrinology* 2005; **30:** 80–91.

42 Beishuizen A, Thijs LG. Endotoxin and the hypothalamo-pituitary-adrenal (HPA) axis. *J Endotoxin Res* 2003; **9:** 3–24.

43 Maclullich AM, Ferguson KJ, Miller T, de Rooij SE, Cunningham C. Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. *J Psychosom Res* 2008; **65:** 229–38.

44 Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr Rev* 2000; **21:** 55–89.

45 Conrad CD. Chronic stress-induced hippocampal vulnerability: the glucocorticoid vulnerability hypothesis. *Rev Neurosci* 2008; **19:** 395–411.

46 English KL, Paddon-Jones D. Protecting muscle mass and function in older adults during bed rest. *Curr Opin Clin Nutr Metab Care* 2010; **13:** 34–39.

47 Isaacs B. Clinical and laboratory studies of falls in old people. Prospects for prevention. *Clin Geriatr Med* 1985; **1:** 513–24.

48 Kortebein P, Ferrando A, Lombeida J, Wolfe R, Evans WJ. Effect of 10 days of bed rest on skeletal muscle in healthy older adults. *JAMA* 2007; **297:** 1772–74.

49 Beaudart C, Zaaria M, Pasleau F, Reginster JY, Bruyère O. Health outcomes of sarcopenia: a systematic review and meta-analysis. *PLoS One* 2017; **12:** e0169548.

50 Florini JR, Ewton DZ, Magri KA. Hormones, growth factors, and myogenic differentiation. *Annu Rev Physiol* 1991; **53:** 201–16.

51 Iranmanesh A, Lizarralde G, Veldhuis JD. Age and relative adiposity are specific negative determinants of the frequency and amplitude of growth hormone (GH) secretory bursts and the half-life of endogenous GH in healthy men. *J Clin Endocrinol Metab* 1991; **73:** 1081–88.

52 Welle S, Thornton C, Statt M, McHenry B. Growth hormone increases muscle mass and strength but does not rejuvenate myofibrillar protein synthesis in healthy subjects over 60 years old. *J Clin Endocrinol Metab* 1996; **81:** 3239–43.

53 Hameed M, Harridge SD, Goldspink G. Sarcopenia and hypertrophy: a role for insulin-like growth factor-1 in aged muscle? *Exerc Sport Sci Rev* 2002; **30:** 15–19.

54 Kenyon CJ. The genetics of ageing. *Nature* 2010; **464:** 504–12.

55 Amrit FR, Boehnisch CM, May RC. Phenotypic covariance of longevity, immunity and stress resistance in the caenorhabditis nematodes. *PLoS One* 2010; **5:** e9978.

56 Pawlikowska L, Hu D, Huntsman S, et al. Association of common genetic variation in the insulin/IGF1 signaling pathway with human longevity. *Aging Cell* 2009; **8:** 460–72.

57 Besson A, Salemi S, Gallati S, et al. Reduced longevity in untreated patients with isolated growth hormone deficiency. *J Clin Endocrinol Metab* 2003; **88:** 3664–67.

58 Holdaway IM, Bolland MJ, Gamble GD. A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly. *Eur J Endocrinol* 2008; 159: 89–95.

59 Laron Z. The GH-IGF1 axis and longevity. The paradigm of IGF1 deficiency. *Hormones (Athens)* 2008; **7:** 24–27.

60 Leng SX, Cappola AR, Andersen RE, et al. Serum levels of insulin-like growth factor-I (IGF-I) and dehydroepiandrosterone sulfate (DHEA-S), and their relationships with serum interleukin-6, in the geriatric syndrome of frailty. *Aging Clin Exp Res* 2004; **16:** 153–57.

61 Leng SX, Hung W, Cappola AR, Yu Q, Xue QL, Fried LP. White blood cell counts, insulin-like growth factor-1 levels, and frailty in community-dwelling older women. *J Gerontol A Biol Sci Med Sci* 2009; **64:** 499–502.

62 Gopinath SD, Rando TA. Stem cell review series: aging of the skeletal muscle stem cell niche. *Aging Cell* 2008; **7:** 590–98.

63 Rommel C, Bodine SC, Clarke BA, et al. Mediation of IGF-1-induced skeletal myotube hypertrophy by PI(3)K/Akt/mTOR and PI(3)K/Akt/GSK3 pathways. *Nat Cell Biol* 2001; **3:** 1009–13.

64 Glass DJ. Signalling pathways that mediate skeletal muscle hypertrophy and atrophy. *Nat Cell Biol* 2003; **5:** 87–90.

65 Payette H, Roubenoff R, Jacques PF, et al. Insulin-like growth factor-1 and interleukin 6 predict sarcopenia in very old community-living men and women: the Framingham Heart Study. *J Am Geriatr Soc* 2003; **51:** 1237–43.

66 Chen LY, Wu YH, Liu LK, et al. Association among serum insulin-like growth factor-1, frailty, muscle mass, bone mineral density, and physical performance among community-dwelling middle-aged and older adults in Taiwan. *Rejuvenation Res* 2017; published online May 9. DOI:10.1089/rej.2016.1882.

67 Yeap BB, Paul Chubb SA, Lopez D, Ho KK, Hankey GJ, Flicker L. Associations of insulin-like growth factor-I and its binding proteins and testosterone with frailty in older men. *Clin Endocrinol (Oxf)* 2013; **78:** 752–59.

68 Afilalo J. Androgen deficiency as a biological determinant of frailty: hope or hype? *J Am Geriatr Soc* 2014; **62:** 1174–78.

69 Urban RJ, Bodenburg YH, Gilkison C, et al. Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis. *Am J Physiol* 1995; **269:** E820–26.

70 Stanworth RD, Jones TH. Testosterone for the aging male; current evidence and recommended practice. *Clin Interv Aging* 2008; **3:** 25–44.

71 Eichholzer M, Barbir A, Basaria S, et al. Serum sex steroid hormones and frailty in older American men of the Third National Health and Nutrition Examination Survey (NHANES III). *Aging Male* 2012; **15:** 208–15.

72 Mohr BA, Bhasin S, Kupelian V, Araujo AB, O'Donnell AB, McKinlay JB. Testosterone, sex hormone-binding globulin, and frailty in older men. *J Am Geriatr Soc* 2007; **55:** 548–55.

73 Wu IC, Lin XZ, Liu PF, Tsai WL, Shiesh SC. Low serum testosterone and frailty in older men and women. *Maturitas* 2010; **67:** 348–52.

74 Sinha-Hikim I, Cornford M, Gaytan H, Lee ML, Bhasin S. Effects of testosterone supplementation on skeletal muscle fiber hypertrophy and satellite cells in community-dwelling older men. *J Clin Endocrinol Metab* 2006; **91:** 3024–33.

75 Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of testosterone treatment in older men. *N Engl J Med* 2016; **374:** 611–24.

76 ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care* Med 2002; **166:** 111–17.

77 Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med* 2010; **363:** 109–22.

78 Snyder PJ, Kopperdahl DL, Stephens-Shields AJ, et al. Effect of testosterone treatment on volumetric bone density and strength in older men with low testosterone: a controlled clinical trial. *JAMA Intern Med* 2017; **177:** 471–79.

79 Roy CN, Snyder PJ, Stephens-Shields AJ, et al. Association of testosterone levels with anemia in older men: a controlled clinical trial. *JAMA Intern Med* 2017; **177:** 480–90.

80 Resnick SM, Matsumoto AM, Stephens-Shields AJ, et al. Testosterone treatment and cognitive function in older men with low testosterone and age-associated memory impairment. *JAMA* 2017; **317:** 717–27.

81 Budoff MJ, Ellenberg SS, Lewis CE, et al. Testosterone treatment and coronary artery plaque volume in older men with low testosterone. *JAMA* 2017; **317:** 708–16.

82 Voznesensky M, Walsh S, Dauser D, Brindisi J, Kenny AM. The association between dehydroepiandosterone and frailty in older men and women. *Age Ageing* 2009; **38:** 401–06.

83 Hassan-Smith ZK, Hewison M, Gittoes NJ. Effect of vitamin D deficiency in developed countries. *Br Med Bull* 2017; **122:** 79–89.

84 Ford L, Graham V, Wall A, Berg J. Vitamin D concentrations in an UK inner-city multicultural outpatient population. *Ann Clin Biochem* 2006; **43:** 468–73.

85 Holick MF. Resurrection of vitamin D deficiency and rickets. *J Clin Invest* 2006; **116:** 2062–72.

86 Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. Dietary reference intakes for calcium and vitamin D. In: Ross AC, Taylor CL, Yaktine AL, et al, eds. Washington, DC: National Academies Press (US), 2011.

87 Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011; **96:** 1911–30.

88 Aspray TJ, Bowring C, Fraser W, et al. National Osteoporosis Society vitamin D guideline summary. *Age Ageing* 2014; **43:** 592–95.

89 Zhao JG, Zeng XT, Wang J, Liu L. Association between calcium or vitamin D supplementation and fracture incidence in community-dwelling older adults: a systematic review and meta-analysis. *JAMA* 2017; **318:** 2466–82.

90 Hirani V, Naganathan V, Cumming RG, et al. Associations between frailty and serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations in older Australian men: the Concord Health and Ageing in Men Project. *J Gerontol A Biol Sci Med Sci* 2013; **68:** 1112–21.

91 Tajar A, Lee DM, Pye SR, et al. The association of frailty with serum 25-hydroxyvitamin D and parathyroid hormone levels in older European men. *Age Ageing* 2013; **42:** 352–59.

92 Gutiérrez-Robledo LM, Ávila-Funes JA, Amieva H, et al. Association of low serum 25-hydroxyvitamin D levels with the frailty syndrome in Mexican community-dwelling elderly. *Aging Male* 2016; **19:** 58–63.

93 Pabst G, Zimmermann AK, Huth C, et al. Association of low 25-hydroxyvitamin D levels with the frailty syndrome in an aged population: results from the KORA-age Augsburg study. *J Nutr Health Aging* 2015; **19:** 258–64.

94 Chang CI, Chan DC, Kuo KN, Hsiung CA, Chen CY. Vitamin D insufficiency and frailty syndrome in older adults living in a Northern Taiwan community. *Arch Gerontol Geriatr* 2010; **50** (suppl 1)**:** S17–21.

95 Buta B, Choudhury PP, Xue QL, et al. The association of vitamin D deficiency and incident frailty in older women: the role of cardiometabolic diseases. *J Am Geriatr Soc* 2017; **65:** 619–24.

96 Wong YY, McCaul KA, Yeap BB, Hankey GJ, Flicker L. Low vitamin D status is an independent predictor of increased frailty and all-cause mortality in older men: the Health in Men Study. *J Clin Endocrinol Metab* 2013; **98:** 3821–28.

97 Vogt S, Decke S, de Las Heras Gala T, et al. Prospective association of vitamin D with frailty status and all-cause mortality in older adults: results from the KORA-Age Study. *Prev Med* 2015; **73:** 40–46.

98 Smit E, Crespo CJ, Michael Y, et al. The effect of vitamin D and frailty on mortality among non-institutionalized US older adults. *Eur J Clin Nutr* 2012; **66:** 1024–28.

99 Shardell M, D'Adamo C, Alley DE, et al. Serum 25-hydroxyvitamin D, transitions between frailty states, and mortality in older adults: the Invecchiare in Chianti Study. *J Am Geriatr Soc* 2012; **60:** 256–64.

100 Ensrud KE, Blackwell TL, Cauley JA, et al. Circulating 25-hydroxyvitamin D levels and frailty in older men: the osteoporotic fractures in men study. *J Am Geriatr Soc* 2011; **59:** 101–06.

101 Ensrud KE, Ewing SK, Fredman L, et al. Circulating 25-hydroxyvitamin D levels and frailty status in older women. *J Clin Endocrinol Metab* 2010; **95:** 5266–73.

102 Muir SW, Montero-Odasso M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc* 2011; **59:** 2291–300.

103 Beaudart C, Buckinx F, Rabenda V, et al. The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab* 2014; **99:** 4336–45.

104 Bolland MJ, Grey A, Gamble GD, Reid IR. Vitamin D supplementation and falls: a trial sequential meta-analysis. *Lancet Diabetes Endocrinol* 2014; **2:** 573–80.

105 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet* 2017; **390:** 2627–42.

106 Collaboration NCDRF, and the NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet* 2016; **387:** 1513–30.

107 Pérez-Tasigchana RF, León-Muñoz LM, Lopez-Garcia E, et al. Metabolic syndrome and insulin resistance are associated with frailty in older adults: a prospective cohort study. *Age Ageing* 2017; **46:** 807–12.

108 Barzilay JI, Blaum C, Moore T, et al. Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. *Arch Intern Med* 2007; **167:** 635–41.

109 Hoogendijk EO, Huisman M, van Ballegooijen AJ. The role of frailty in explaining the association between the metabolic syndrome and mortality in older adults. *Exp Gerontol* 2017; **91:** 5–8.

110 Tang Z, Wang C, Song X, et al. Co-occurrence of cardiometabolic diseases and frailty in older Chinese adults in the Beijing Longitudinal Study of Ageing. *Age Ageing* 2013; **42:** 346–51.

111 Lin F, Roiland R, Chen DG, Qiu C. Linking cognition and frailty in middle and old age: metabolic syndrome matters. *Int J Geriatr Psychiatry* 2015; **30:** 64–71.

112 Kob R, Bollheimer LC, Bertsch T, et al. Sarcopenic obesity: molecular clues to a better understanding of its pathogenesis? *Biogerontology* 2015; **16:** 15–29.

113 Virgini VS, Rodondi N, Cawthon PM, et al. Subclinical thyroid dysfunction and frailty among older men. *J Clin Endocrinol Metab* 2015; **100:** 4524–32.

114 Wang GC, Talor MV, Rose NR, et al. Thyroid autoantibodies are associated with a reduced prevalence of frailty in community-dwelling older women. *J Clin Endocrinol Metab* 2010; **95:** 1161–68.

115 Yeap BB, Alfonso H, Paul Chubb SA, et al. Higher free thyroxine levels are associated with frailty in older men: the Health In Men Study. *Clin Endocrinol (Oxf)* 2012; **76:** 741–48.

116 Bertoli A, Valentini A, Cianfarani MA, et al. Low FT3: a possible marker of frailty in the elderly. *Clin Interv Aging* 2017; **12:** 335–41.