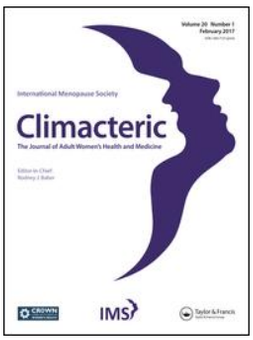

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REVIEW

A pas de deux of osteoporosis and sarcopenia: osteosarcopenia

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ABSTRACT

The musculoskeletal conditions osteoporosis and sarcopenia are highly prevalent in older adults. Osteoporosis is characterized by low bone mass and microarchitectural deterioration of bone, whereas sarcopenia is identified by the loss of muscle strength, function and mass. Osteoporosis represents a major health problem contributing to millions of fractures worldwide on an annual basis, whereas sarcopenia is associated with a range of adverse physical and metabolic outcomes. They both affect physical and social function, confidence and quality of life as well as contributing to high health-care costs worldwide. Osteosarcopenia is the term given when both conditions occur concomitantly and it has been suggested that interactions between these two conditions may accelerate individual disease progression as co-existence of osteoporosis and sarcopenia is associated with higher morbidity from falls, fracture, disability as well as mortality. In this review, we will outline the epidemiology, pathogenesis and clinical consequences of osteosarcopenia and discuss available management strategies.

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Introduction

Musculoskeletal health disorders including osteoporosis and sarcopenia are highly prevalent in older adults. Osteoporosis, a disease characterized by low bone mass and structural deterioration of bone tissue, is the most common chronic metabolic bone disease and represents a major global health problem, contributing to 8.9 million fractures worldwide on an annual basis [1]. Osteoporosis incurred an estimated £1.8 billion in UK health costs in 2000; this is predicted to increase to £2.2 billion by 2025 [2]. Sarcopenia is characterized by progressive and generalized decline in muscle strength, function and muscle mass with increasing age or secondary to disease [3]. It is associated with a range of adverse physical and metabolic outcomes in terms of disability, morbidity, impaired quality of life and mortality [4], and has also been identified as a predictor of fracture risk [5]. In terms of cost, sarcopenia incurred an estimated $18.5 billion in health-care costs to the USA in 2000. In the UK, the annual excess cost associated with muscle weakness was estimated to be £2.5 billion [6,7]. Several varying definitions of sarcopenia have contributed to differences in prevalence estimates worldwide, ranging from 3 to 30% [4,8–10]. Currently, a global consensus definition for sarcopenia does not exist but there are well-constructed diagnostic algorithms that provide a mechanism for clinical case finding [4].

Growing interest has emerged in the coexistence of osteoporosis and sarcopenia in some individuals, which is often termed osteosarcopenia, and is associated with higher morbidity from falls, fracture, disability as well as mortality [11,12]. Knowledge of the overlap in the pathophysiology of osteoporosis and sarcopenia can inform the development of potential treatments for osteosarcopenia [13]. Given the urgent need to educate clinicians and researchers on the importance of identifying osteosarcopenia early, this article aims to review and appraise relevant and available literature on osteosarcopenia, providing an update on the epidemiology (prevalence, risk factors and diagnosis) and management for osteosarcopenia.

Coexistence of poor bone and muscle measurements

The concept that individuals with low bone mass might also have low muscle mass has been investigated previously in several studies. For example, in 1998, a study assessed the relationship between whole-body bone mineral content and lean mass in males and females between 2 and 87 years of age, indicating that bone mass is closely and linearly associated with muscle mass throughout life [14]. In other studies, lean mass was a better predictor of whole-body bone mineral density (BMD) than fat mass as well as incident fractures [15–17]. In the Hertfordshire Cohort Study, muscle size and muscle strength were positively associated with bone size and strength [18]. Greater loss of bone mass was noted in

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osteosarcopenic patients compared to osteoporotic patients in a study conducted in Ecuador dominated by female participants [19]. A positive relationship between muscle and bone mass decline over a year was recognized in older individuals in the SarcoPhAge study [20], whereas an increase in the risk of fracture and a decline in muscle strength were associated with a decrease in spine and hip BMD [20]. In the Copenhagen Sarcopenia Study, BMD was lower among individuals with sarcopenia [21] and a large study of women in Japan showed that the relative skeletal muscle index was positively correlated with BMD of the lumbar spine and total hip [22]. Finally, in a cross-sectional study of premenopausal, perimenopausal and postmenopausal women, a linear decline in both muscle mass and bone density was noted, showing significant changes in postmenopausal compared to premenopausal women [23].

Approaches to defining osteosarcopenia

Awareness of complex muscle and bone interrelationships will inform construction of diagnostic pathways for osteosarcopenia and allows the construction of a pathway to identify coexistence of osteoporosis and sarcopenia (Figure 1).

In clinical practice, falls, fractures, slower gait speed, difficulty rising from a chair, weight loss, low body mass index or muscle wasting should all highlight the need for further diagnostic evaluation for osteoporosis and sarcopenia. There are available tools at the clinician's disposal to aid the identification of both sarcopenia and osteoporosis separately. SARC-F, a 5-point sarcopenia self-questionnaire, has high specificity but low sensitivity, making it the most accurate in detecting those with sarcopenia [24] (Table 1). The most widely used definition for sarcopenia has been proposed by the European Working Group on Sarcopenia in Older People (EWGSOP2) [4]. The EWGSOP2 diagnostic algorithm uses normative grip strength reference values for young healthy adults where possible, with cut-off points usually set at −2 or −2.5 standard deviations compared to mean reference values [4]. In recent years, there has been much more emphasis on muscle strength as the primary parameter characterizing sarcopenia, as opposed to muscle mass [4,8]. Sarcopenia is probable when low muscle strength is present; this is assessed by grip strength (measured with the use of a hand-held dynamometer) or time taken to complete five chair rises (Table 2). A diagnosis of sarcopenia is confirmed by the presence of low muscle quantity measured, for example, by dual-energy X-ray absorptiometry. A diagnosis of severe sarcopenia is made when low muscle strength is accompanied by low muscle quantity and decline in physical performance (i.e. slower gait speed) (Table 2). Other modalities of imaging previously used to measure muscle mass include bioelectrical impedance analysis, but equations used to derive lean mass values are population and device specific, and lack standardization [25]; the same difficulties apply to ultrasound scanning use but interest in its application is growing, especially in view of the ready access to equipment [26,27]. Computed tomography and magnetic resonance imaging are mostly used in research settings or when other diseases or conditions are suspected [25].

The FRAX score is now widely used as a validated tool for risk stratification for osteoporosis, so decisions can be facilitated in the need for treatment in all postmenopausal women and men aged 50 years or over who have risk factors for fracture [28,29]. The diagnosis of osteopenia and of osteoporosis is made using dual-energy X-ray absorptiometry scanning. According to World Health Organization (WHO) criteria, *T*-scores of BMD below −1 and −2.5 standard deviations categorize the patient as osteopenic and osteoporotic, respectively [30].

As already discussed, the presence of sarcopenia associated with low BMD (osteopenia or osteoporosis) with or without clinical fracture has been defined as osteosarcopenia by some researchers (Figure 1).

Prevalence of osteosarcopenia

The prevalence of osteosarcopenia among community-dwelling populations increases with age and is greater in women than in men [31,32]. Estimates vary considerably, between 5 and 37% depending on the population and definition of sarcopenia used. The highest rates were observed in those with fractures [21,31]. In a study of 316 community-dwelling Chinese adults aged 65 years and over, 10.4% of men and 15.1% of women were found to be osteosarcopenic [33]. The prevalence of osteosarcopenia was found to be 37% in 680 community-dwelling older individuals in Australia with a history of falls [11]. The prevalence of sarcopenia was found to be 58% among 313 older women following hip fractures in an Italian study [34]. BMD values were significantly lower in sarcopenic older women, and sarcopenic adults had a fourfold higher risk of having co-existing osteoporosis compared with non-sarcopenic adults in a Belgian study [35]. Lastly, studies have shown that being diagnosed with sarcopenia was associated with a high risk of having osteoporosis and vice versa [20–22,36–38].

Risk factors and pathophysiology

Many factors have been implicated in the pathology of osteosarcopenia. Data from the UK Biobank show that muscle strength is partially genetically regulated and genetic factors are important in the achievement of peak bone mass [39,40]. No single gene or single nucleotide polymorphisms have been associated with the loss of bone mass, muscle strength or mass in conjunction, but genome-wide association studies have identified several genes that are associated with bone and muscle wasting, with *GDF8* the most well characterized [41]. Genetic background might also determine responsivity of the muscle–bone unit to mechanical stimuli; several quantitative trait loci have been associated with the specific response to mechanical stimulation [42].

The mechanostat hypothesis first described by Frost suggests that increasing loads imposed by larger muscle forces on bone in childhood and adolescence lead to higher bone strength in midlife [43,44]. Conversely, a decline in muscle

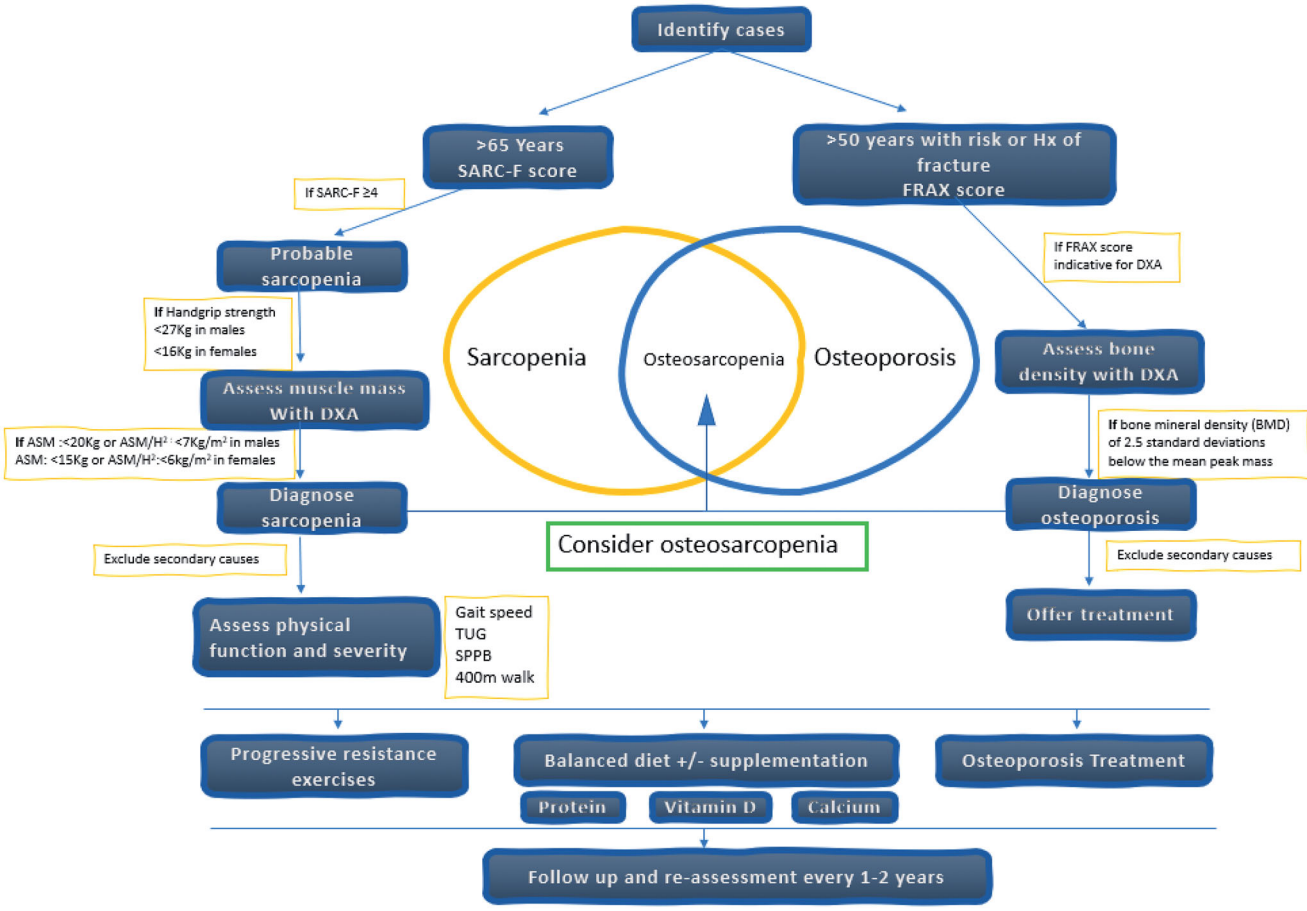

Figure 1. Risk stratification strategy for osteosarcopenia. ASM, appendicular skeletal muscle mass; DXA, dual-energy X-ray absorptiometry; H, height; Hx, history; SPPB, Short Physical Performance Battery; TUG, timed up and go.

Table 1. SARC-F questionnaire: 5-point sarcopenia self-questionnaire for detecting those with sarcopenia.

Component	*Question*	*Scoring*
Strength	Difficulty in lifting and carrying 10 pounds?	None = 0 Some = 1 A lot or unable = 2
Walking	Difficulty walking across a room?	None = 0 Some = 1 A lot or unable = 2
Chair rise	Difficulty transferring from a chair or bed?	None = 0 Some = 1 A lot or unable = 2
Stairs	Difficulty climbing a flight of 10 stairs?	None= 0 Some= 1 A lot or unable = 2
Falls	Times have you fallen in the past year?	None = 0 Some = 1 A lot or unable = 2

SARC-F score ≥4 best predicts the need for further, more comprehensive evaluation to confirm evidence of sarcopenia.

strength with age put bones into partial disuse and remodeling [44]. This highlights the importance of mechanical loading in the maintenance of the muscle–bone unit as loss of both bone and muscle mass are intrinsically linked to the reduction in physical performance observed with aging [45].

Aging is a significant risk factor for both osteoporosis and sarcopenia [46]. However, the molecular mechanisms linking bone to muscle function as we age are not very well defined. Factors known as myokines (released from muscle, such as myostatin or irisin) and osteokines (released from bone, such as osteocalcin) are thought to be the mechanism of communication between the two tissues. Myostatin and the Wnt–β-catenin signaling pathway have been extensively studied in mediating muscle–bone crosstalk by controlling both osteoblastic activity and muscle regeneration [47,48].

Inflamm-aging, the chronic low-level and long-term physiological stimulation of the immune system, occurs as a consequence of lifelong exposure to antigenic stimuli interacting with complex genetic, environmental and age-related mechanisms, including mitochondrial dysfunction [49,50]. These changes can affect muscle proteolysis and lead to a reduction in bone mineralization [51], while it has been suggested that low-grade and chronic inflammation can shift mesenchymal stem cell lineage toward adipogenesis instead of myogenesis and osteoblast genesis, resulting in decreased muscle and bone quality [52]. Finally, fat infiltration is one of the hallmarks of sarcopenia and osteoporosis, as high levels of marrow adipose tissue are associated with bone loss and osteoporosis, and myosteatosis is associated with a decrease in myocyte dysfunction and impaired muscle quality [52].

Sex hormones have several effects on muscle and bone. Notably, with aging, their concentration and activity on tissues alter. Menopause, which is characterized by a sharp decline in circulating prostaglandin estradiol in women, is an important influence on the further decline in muscle and bone; the same abrupt decline does not apply to men. Early menopause without treatment is a strong risk factor for

Table 2. Clinical tools and cut-offs for measurement of muscle strength, lean mass and physical performance in sarcopenia according to the EWGSOP2 criteria and pathway.

Criterion		*Tool*	*Cut-offs for women*	*Cut-offs for men*
Identify cases		SARC-F	≥ 4	
Assess sarcopenia	Muscle strength	Grip strength or	<16 kg	<27 kg
		chair stand test	>15 s for 5 rises	
Confirm sarcopenia	Muscle quantity or quality	ASM by DXA or	<15 kg	<20 kg
		ASM/height^2	<5.5 kg/m^2	<7 kg/m^2
Assess severity	Physical performance	Gait speed or	≤0.8 m/s	
		SPPB or	≤8-point score	
		TUG or	≥20 s	
		400-m walk	≥6 min for completion or non-completion	

ASM, appendicular skeletal muscle mass; DXA, dual-energy X-ray absorptiometry; EWGSOP2, European Working Group on sarcopenia in Older People; SPPB, Short Physical Performance Battery; TUG, timed up and go.

future fragility fracture [53] and hormone replacement therapy in postmenopausal women is able to both preserve bone and muscle mass [54]. Growth hormone (GH) and insulin growth factor-1 both exert a positive influence on osteoblasts in addition to their anabolic actions on muscle [55].

Lifestyle factors such as nutrition, alcohol and smoking have been shown to have effects on bone and muscle. Active smoking is associated with worse bone health in female smokers [56] and has been linked to the development of sarcopenia [57,58]. While moderate alcohol intake is not thought to be associated with low muscle mass, heavy alcohol consumption is likely to lead to low muscle mass secondary to poor nutrition, lower physical activity and hormonal abnormalities [59].

Specific nutrients affect both bone and muscle. Low levels of vitamin D are commonly found in osteosarcopenic patients [11]. In a study conducted in Korea, vitamin D deficiency was associated with low BMD and was more pronounced in those with sarcopenia [60], while low Appendicular Lean Mass (ALM) was associated with low vitamin D in the Minocycline to Improve Neurologic Outcome in Stroke (MINOS) study [57]. Low vitamin D levels are likely to contribute to muscle weakness and increased risk of falls in addition to increased bone fragility [61,62]. Finally, vitamin K is essential for the effective function of proteins including those involved for bone remodeling and it has been shown that *in vitro* vitamin K improves the proliferation and migration of primary bovine skeletal satellite cells, with potential in maintaining normal muscle function, as well as facilitating several pathways in muscle–bone crosstalk [63,64].

Management of osteosarcopenia

Non-pharmacological management – lifestyle and nutritional modifications

Both sarcopenia and osteoporosis are amenable to preventative and therapeutic interventions in the form of exercise and nutritional support, the multicomponent nature of which remains the core of osteosarcopenia management.

Physical exercise has been shown to have a positive impact on muscle mass and function, with greater benefits on physical performance in adults over the age of 60 years [65]. Furthermore, a meta-analysis of 14 prospective studies has shown a significant inverse relationship between increasing level of physical activity and risk of hip fracture in older women [66]. Randomized controlled trials have demonstrated the efficacy of progressive resistance exercise to stimulate osteoblastogenesis and muscle protein synthesis [67,68]. Low-repetition, light-load power training also showed improved pelvis BMD and knee extensor strength over the course of 6 weeks in a small study of postmenopausal women with sarcopenia [69]. Emphasis on resistance training for individuals with osteoporosis is also given [70]. A recent systematic review showed that chronic resistance training is safe and effective in improving characteristics of osteosarcopenia such as lumbar spine BMD, muscle mass, strength and quality, but not physical performance [71]. Multimodal programs that incorporate traditional and high-velocity progressive resistance training, weight-bearing exercises and balance/mobility activities might be the best approach for osteosarcopenia [72].

A nutritional approach focuses on vitamin D, calcium and protein intake. Despite the lack of information regarding the intake of high-quality protein in older individuals, it has been suggested that adequate intake should be ensured. The recommended dietary allowance for protein of 0.8 g protein/kg/day might be inadequate for older people to meet their metabolic and physiological needs and should be increased to 1.5 g protein/kg/day [73]. Higher protein intake was protective against physical function decline in older individuals, including those with a previously sufficient protein intake, independent of physical activity [74]. Protein supplementation above the recommended daily amount in combination with resistance exercise or endurance type exercises is advised [75]. This combination has demonstrated an increase in muscle and bone mass, muscle strength, balance and functional capacity [68,76]. A recent systematic review suggested that protein supplementation and muscle strengthening exercise were associated with gain in lean muscle mass in people at risk of sarcopenia [77]. Enhanced protein intake has benefited patients with osteosarcopenia [78]. Dairy food provides nutrients such as calcium, phosphate and protein that are important in the maintenance of bone health [79], but there have been mixed reports regarding their benefit [76,80,81].

An adequate vitamin D status is associated with better BMD, muscle mass and function [82,83] and reduced number of falls in postmenopausal women [84]. The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) recommends a vitamin D intake of 800 IU/daily to maintain

25(OH)D levels >50 nmol/l in postmenopausal women [85]. Conversely, an annual oral administration of high-dose cholecalciferol was associated with an increased risk of falls and fractures [86]. However, to date no interventional and randomized controlled studies have been performed to assess its effect on osteosarcopenic patients [87]. Finally creatine has also been reported to increase muscle mass and strength as well as bone density, but studies are required to show benefit in osteosarcopenic patients [75].

Pharmacologic treatments

Commonalities in pathophysiology could lead to the identification of potential pharmacological targets for treatment of osteosarcopenia [88,89]. Currently, however, there are no randomized controlled trials of drug treatments for osteosarcopenia.

Interventions with drugs that have anti-inflammatory properties including non-steroidal anti-inflammatory drugs (NSAIDs) have been examined in sarcopenia [90]. Their exact mechanism of action is still not clearly described, but some studies have shown that cyclooxygenase-inhibiting NSAIDs might be effective in improving muscle protein metabolism [91], and participants in a cross-sectional study taking long-term NSAIDs had a lower risk of sarcopenia compared to non-NSAID users [92]. On the contrary, a negative effect of skeletal muscle regeneration has also been reported [93]. Due to conflicting results from studies and the potential side effects associated with NSAIDs, long-term use is not recommended, especially in older adults.

Testosterone replacement in men has demonstrated positive effects in muscle strength, gait and volumetric BMD [94,95]. Hormone replacement therapy in women at the onset of menopause has been shown to preserve muscle strength [96] and prolonged use is associated with high muscle mass [97]. Hormone replacement therapy use also reduces fractures, although the unfavorable risk/benefit balance in older postmenopausal women limits its use to younger postmenopausal women who are at high risk of fracture and also have menopausal symptoms [28]. Side effects and variable anabolic actions seen in studies of selective androgen receptor modulators, classes of androgen receptor ligands that display tissue selective anabolic and androgenic activity, have precluded their widespread use. For example, though andarine and ostarine use were associated with an increase lean mass and physical function in older males and postmenopausal females [98,99], no clear advantage was shown for bone health.

GH supplementation has shown no clear benefit in muscle mass, function or strength, despite initial reports that low GH levels contribute to a decrease lean mass and increase in adipose tissue [89]. GH replacement has been shown to be possibly beneficial in the management of postmenopausal women with osteoporosis; a recent meta-analysis indicated a role in fracture prevention although not an increase in BMD [100].

In conclusion, there are currently no approved pharmacological agents for osteosarcopenia, although treatments for osteoporosis have been explored to understand whether their actions outwit their effects on bone. For example, denosumab has shown beneficial effects on falls risk [101], has been associated with increased handgrip strength and lean body mass [102], and has been associated with reduced fear of falling, better balance and physical action [103] when compared to intravenous zoledronic acid.

Considering novel therapies, lower levels of myostatin, a negative regulator of muscle development and growth [104], have been found in animal and human studies of increased musculature and strength [105–107]. Myostatin inhibitors have been suggested as a possible treatment for osteosarcopenia. However, in a phase II trial in older adults with a history of falls, myostatin inhibition was associated with an increase in lean body mass and improved functional measures but no benefit in bone health [108]. Initial reports of bimagrumab, a human monoclonal antibody that binds to type II activin receptors and prevents the binding of myostatin and activin A, has demonstrated significant increases in lean body mass and strength in older adults [109], but those results were not sustained [110]. Irisin, another myokine, has also been suggested as a target to treat osteosarcopenic subjects as it retrieves disuse-induced bone loss and muscle atrophy in mice [111] and is proposed as a biomarker for sarcopenia in postmenopausal women [112]. Finally, prevention of fat infiltration [113] and use of melatonin [114], adiponectin [115] and exosomes [116] have been proposed as potential therapeutic targets, but further research and studies are needed.

Conclusion

Osteoporosis and sarcopenia are age-related conditions and are associated with significant morbidity and mortality. Their prevalence is expected to increase over the years with important consequences for individuals and health-care systems. These two conditions share common pathophysiological mechanisms, resulting in an interest in and attempts to treat and manage these pathologies simultaneously. Early recognition and intervention of both conditions is important to decrease morbidity and mortality and preserve independence of older individuals. Combined resistance and balance exercises with nutritional supplementation and treatment of osteoporosis are the current strategies to manage osteosarcopenia. Further basic science research to gain a better insight into biomarkers with potential diagnostic and therapeutic value as well as epidemiological studies to understand the life course influences leading to osteosarcopenia are needed.

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