Determinants of muscle preservation in individuals with cerebral palsy across the lifespan: a narrative review of the literature

Olaf Verschuren, Ana R.P. Smorenburg, Yvette Luiking, Kristie Bell, Lee Barber, Mark Peterson

Corresponding author:

Olaf Verschuren, PhD: Brain Center Rudolf Magnus and Center of Excellence for Rehabilitation Medicine, University Medical Center Utrecht and De Hoogstraat Rehabilitation, Utrecht, The Netherlands, Rembrandtkade 10, 3583TM, Utrecht, The Netherlands, Phone: +3130-2561211, Email: o.verschuren@dehoogstraat.nl

Ana Smorenburg, PhD: Nutricia Research, Advanced Medical Nutrition, Uppsalalaan 12, 3584 CT Utrecht, The Netherlands, Phone +3130-2095000, Email: ana.bonouvrie@nutricia.com

Yvette Luiking, PhD: Nutricia Research, Advanced Medical Nutrition, Uppsalalaan 12, 3584CT Utrecht, The Netherlands, Phone: +3130-2095000, Email: yvette.luiking@nutricia.com

Kristie L. Bell, PhD, Child Health Research Centre, The University of Queensland, Brisbane, Australia 4101; Lady Cilento Children's Hospital, South Brisbane, Queensland, Australia 4101. email: k.bell@uq.edu.au

Lee A. Barber, PhD: Queensland Cerebral Palsy and Rehabilitation Research Centre, Child Health Research Centre, Faculty of Medicine, The University of Queensland, Brisbane, Australia. Email: l.barber@uq.edu.au

Mark D. Peterson, PhD, M.S.: Department of Physical Medicine and Rehabilitation, University of Michigan, Ann Arbor, MI, USA. Email: mdpeterz@med.umich.edu

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jcsm.12287

Word count: 5565

ABSTRACT

In individuals with Cerebral Palsy (CP) smaller muscle and atrophy are present at young age. Many people with CP also experience a decline in gross motor function as they age, which might be explained by the loss of muscle mass. The clinical observation of muscle wasting has prompted a comparison to sarcopenia in older adults, and the term accelerated musculoskeletal aging is often used to describe the hallmark phenotype of CP through the lifespan. However, there has been very little research emphasis on the natural history of aging with CP, and even less with respect to the determinants or prevention of muscle loss with CP. Considering the burgeoning interest in the science of muscle preservation, this paper aims to: (a) describe the characteristics of accelerated musculoskeletal aging in people with CP (b) describe the pathophysiology of sarcopenia and parallels with CP; and (c) discuss possible therapeutic approaches, based on established approaches for sarcopenia.

Key words: cerebral palsy; sarcopenia; muscle; exercise

Cerebral palsy (CP) is the most common paediatric-onset physical disability, with a prevalence of 1.7–3.1 per 1000 livebirths in high-income countries, and higher prevalence in low-income countries[1, 2]. CP is caused by an insult to or malformation of the developing brain that affects motor control centres and leads to alterations in growth and development. **Although the brain lesion that causes CP is non-progressive, it affects overall health and especially mobility throughout the lifespan[3, 4].** Following the central nervous system lesion, the damage to the descending pathways causes paresis – a reduction or failure of voluntary activation and muscle over activity which can be described as spasticity, spastic dystonia, and spastic co-contraction. Although the primary brain lesion is static, these neural changes result in a cascade of secondary musculoskeletal complications that are progressive, including soft tissue contracture and bone deformity[5, 6]. Research pertaining to the structure and physiology of skeletal muscle of children and young adults with CP has highlighted several abnormalities. In vivo studies of muscle in ambulant individuals with CP report structural differences between CP and typically developed (TD) muscle including reduced muscle size[7-10] and abnormal proportions of contractile and non-contractile tissue[11-13]. While loss of muscle mass and function is apparent at higher ages in the general population, smaller muscle and early atrophy are already present at young age in individuals with CP[14, 15]. Individual differences determine the extent to which this impacts physical performance, mobility and functional ability.

In fact, approximately 75% of the individuals with CP who were once mobile eventually stop ambulating[16]. It is also well documented that even high-functioning children with CP are at increased risk to lose ambulatory skills or turn to assistive devices in adulthood[17], which leads to substantial declines in functional skills, activities of daily living and/or mobility, and independence[18-21]. These clinical observations have prompted a comparison to older adults without CP, and the term “accelerated musculoskeletal aging” has been proposed to describe the hallmark phenotype of CP through lifespan[22]. However, there has been very little research emphasis on the natural history of aging with CP, and even less with respect to the determinants or prevention of muscle loss in CP.

In an attempt to stimulate research pertaining to clinically observed, age-related muscle atrophy and weakness, the term “sarcopenia” was first introduced in 1989[23]. Despite the exponential growth in this area of research over the past 30 years[24], there have been substantial obstacles with adopting a consensus definition for the diagnosis of sarcopenia in clinical settings. Although the initial definition of sarcopenia was limited to describing age-related muscle atrophy, muscle loss can also occur with disuse, chronic inflammation, and inadequate macro- and micronutrient intake, or is associated with acute and chronic disease, all of which are not necessarily age-related[25, 26]. Therefore, the term (primary) sarcopenia indicates muscle wasting related to aging, while “secondary sarcopenia” refers to muscle loss related to disuse, inflammation, or malnutrition[25]. In the elderly, however, the aetiology of sarcopenia can be multi-factorial so the distinction between ‘primary and secondary sarcopenia’ can be difficult to make[25].

Considering the burgeoning interest in the science of muscle preservation in individuals with CP, it is time to consider the knowledge and evidence related to sarcopenia in the general population as **it** pertains to people with CP. This paper aims to: (a) describe the characteristics of accelerated musculoskeletal aging in people with CP; (b) describe the pathophysiology of sarcopenia and parallels with CP; and (c) discuss possible therapeutic approaches – what can we learn from approaches in sarcopenia prevention/treatment?

A. Characteristics of muscle and muscle growth in people with CP: Is CP characterized by accelerated musculoskeletal aging?

In 2010, the European sarcopenia consensus definition was published[25], which (re)defined sarcopenia as a condition in which at least 2 of these 3 criteria apply: 1) low muscle mass; 2) low muscle strength and/or 3) low physical performance. In this paragraph we discuss characteristics of muscle and muscle growth in people with CP and examine whether the criteria of sarcopenia can also be applied to individuals with CP.

1. Muscle size and composition

Muscle **size (e.g., cross-sectional area or volume)** are important morphological properties and indicators of muscle force-producing capacity[27], as well as insight into the amount of metabolically active lean tissue available for glucose storage and metabolism[28]. In individuals with CP, the muscles in the impaired limb are smaller than the muscles in the unimpaired limb, and both are smaller compared to a muscle of a TD child.[7] Cross-sectional studies investigating muscle volume in individuals with CP and TD peers report differences in muscle size that are evident early in development, with as much as 22% smaller calf muscle size in children with CP present by pre-school age[29]. The **differences** in muscle volume of ambulant individuals with CP compared to TD peers increase with age to over 45% smaller calf muscle size in young adults with CP[22]. **In individuals with unilateral CP, the often considered "unaffected limb" has muscle that is more similar to the impaired limb with smaller volume and altered muscle quality compared to TD peers[30]. Muscle size differences between individuals with CP and TD peers, have also been reported for the volume of nine large lower limb muscles in adolescents and cross-sectional area of the psoas muscle in adults[8, 31]. Among adults, a previous study using computed tomography demonstrated that the psoas muscle in CP is significantly smaller and less dense, indicating greater muscle fat infiltration and lower muscle quality[32].**

Muscle is composed of contractile and non-contractile tissues. The contractile tissue is the force generating tissue that causes movement. It is comprised of sarcomeres, the building blocks that form muscle fibres, and bundles of muscle fibres that form fascicles. The contractile tissue is highly metabolic. The non-contractile tissue comprises predominantly connective tissue in series (i.e. tendons) and parallel (aponeuroses, muscle cell framework), as well as inter- and intramuscular fat. **Muscles of the lower limb of individuals with CP have greater connective tissue fraction[12] and more inter- and intramuscular fat on magnetic resonance imaging (MRI) and computed tomography (CT), and have altered**

echo intensity parameters, indicative of increased non-contractile tissue, on B-mode ultrasound compared to TD peers[11, 13, 33, 30]. Therefore, the proportion of muscle volume that includes the contractile tissue may be less. Ex vivo studies of muscle from ambulant and non-ambulant children with CP compared to TD children further report reduced myofibre cross-sectional area[34], altered fibre type distribution[35], shorter and stiffer muscle cells[36], and longer and fewer sarcomere in-series[37].

Reduced muscle volume with greater connective tissue and fatty infiltration in individuals with CP greatly reduces the force generation capacity of muscle[31], and also reduces the pool of metabolic lean tissue **compared** to TD individuals. Moreover, altered muscle fibre and sarcomere structure further reduces the force and movement generating capabilities. To date, no studies have quantified muscle structure and composition of the upper limb in individuals with CP or investigated the muscle changes throughout adulthood with CP.

2. Muscle growth

There is limited published information describing muscle growth in individuals with CP. To date, there has been only one longitudinal study describing the growth of lower limb muscle in children with CP[15]. **It was shown that in pre-school aged children with CP, growth of the calf muscle was significant at 12 months follow-up, even after lower limb botulinum toxin treatment (an established treatment to reduce muscular hyperactivity due to spasticity in children and adults with CP).** However, the **overall muscle growth of the spastic muscle in children with CP** over 12 months was 60% lower than in TD peers. Recent cross-sectional studies report calf muscle volume increases linearly with age in CP; however, the muscle volume increased to a lesser extent than in TD children[10, 14]. In a combined group of children with unilateral and bilateral CP, muscle growth, as indicated by the slope of the age-volume relationship, was almost half that of TD children[14]. Moreover, the muscles of children with unilateral CP developed at a slower rate than the muscles of children with bilateral CP, with muscle growth at 23% and 65% of the TD muscle growth rate, respectively[10]. The lower muscle growth rate results in a greater disparity of calf muscle volumes between the CP groups as children progress into adolescence and adulthood.

The limited research investigating muscle growth in individuals with CP has focussed on the early childhood years. This period often includes standard care treatments that aim to reduce spasticity, slow contracture development, and maintain walking ability in these children[38]. Treatments including serial casting and intramuscular botulinum toxin injections may also compromise muscle growth[39-41]. However, current studies have not differentiated between the effects of treatments, and the underlying mechanisms that lead to reduced growth in CP in general, as compared with TD children. Surgical interventions for lower limb soft tissue contracture reduce muscle growth, but muscle volume was found to recover one year after surgery[42].

The natural history of muscle growth and decline with age in individuals with CP remains unknown. Moreover, the specific reasons for reduced longitudinal muscle growth,

development of contractures and peripheral factors responsible for muscular weakness also remain poorly understood. It is plausible that this may stem from the brain lesion causing CP, with the impact of reducing total muscle fibre number in an impaired muscle[43]. Furthermore, genetic alterations have been identified in spastic CP muscle, which give rise to competing pathways for muscle hypertrophy and decrease in anabolic growth factors. The efficiency of protein uptake and synthesis (amongst other building processes) remains unknown in CP.

3. Strength and function

Structural abnormalities in the muscle among individuals with CP, including reduced muscle size and abnormal composition, combined with altered neural control (e.g. increased co-contraction and selective activation[44, 45]), contribute to reduced muscle strength and power compared to TD individuals[31, 46-49]. **Muscle strength varies widely among individuals, but also among disability severity, as classified by the Gross Motor Function Classification System (GMFCS; function deteriorates from level I to V)[50]. The muscle strength of children classified as GMFCS Level I and Level II ranges between 50-100% of predicted normal for all muscle groups of the lower extremity except ankle dorsiflexors (which is lower). For children classified as GMFCS level III muscle strength is less than 50% of predicted normal for all muscle groups of the lower extremity except knee extensors (which is higher)[51].**

While loss of muscle mass and function is expected in the general aging population, gradual loss of physical performance and functional ability is present even at young ages in individuals with CP. Hanna et al.[52] showed that stability of the gross motor function trajectories varies over time when children and adolescents with CP transition into young adulthood. In children classified as GMFCS levels III-V the average gross motor function score peaks before it declines when children become adolescents and young adults. These findings indicate that adolescents classified as GMFCS levels III-V are at risk of losing motor function and physical performance. Throughout adulthood a gradual decline in functional ability is reported across all GMFCS levels[53]. Approximately 75% of individuals with CP included in the study by Murphy et al. [16] who were once mobile eventually stopped ambulating. Adolescents with CP enter adult life with reduced strength and functional reserve, with one third of adults with CP experiencing a decline in walking ability before the age of 35 years[18]. It is also well-documented that even high-functioning children with CP are at increased risk to lose ambulatory skills or turn to assistive devices in adulthood[17], which leads to substantial declines in functional skills, activities of daily living and/or mobility[19], and ultimately a loss of independence[18-21].

In children and young adults with CP, lower limb muscle strength is closely related to independent mobility with muscle adaptations resulting in reduced walking speed and distance, as well as more frequent tripping and falling.[4, 16] The reduced trajectory of muscle strength through development may be the critical factor that determines functional capacity and mobility in CP[22].

B. The Pathophysiology of Sarcopenia: A Multifactorial Concept caused by a Combination of Interrelated Factors.

Several factors underlie the loss of muscle mass and function with advanced age in TD individuals, such as anabolic resistance, impaired muscle quality, and nutritional factors. This section describes these factors in sarcopenia, and analogues what is known in people with CP.

1. Anabolic resistance and contributing factors like inactivity, inflammation, and oxidative stress

Muscle mass is the result of a balance between continuous synthesis and degradation of skeletal muscle proteins. Net protein balance is defined as the difference between skeletal muscle protein synthesis (MPS) and breakdown (MPB). A positive net protein balance (i.e., when MPS exceeds MPB) can result in the accretion of skeletal muscle proteins (anabolism). Conversely, a negative net protein balance (i.e., MPB exceeds MPS) will result in a loss of skeletal muscle protein (catabolism). During the ageing process, protein turnover declines[54], and a blunted response of muscle protein synthesis to anabolic stimuli in a meal has been reported[55]. This so-called "anabolic resistance" is suggested as the major contributor to loss of muscle mass in TD adults and elderly[56]. Several factors can contribute to anabolic resistance, such as inactivity, chronic inflammation ("inflammaging"), and oxidative stress[57, 58].

Indeed, a more sedentary lifestyle plays an important role in the development of sarcopenia[59]. However, aging is also characterized by an increased incidence of enforced bed-rest periods, secondary to injury or disease. These periods of total inactivity contribute directly to the sarcopenia process as it has been shown that the rate of muscle mass loss is accelerated in older persons undergoing a period of bed-rest[60]. Disuse atrophy is characterized by a reduction in muscle fibre cross sectional area. The consequences of inactivity-induced muscle wasting include reduced strength and muscle quality, with deleterious effects on quality of life and independence in daily activities. Furthermore, this reduction in metabolically active lean tissue results in decreased capacities of whole-body glucose storage and metabolism[28, 61], which contributes to insulin resistance, and a lower whole-body metabolic rate[62]. Muscle disuse has been studied after a variety of interventions including bed rest, casting, limb suspension and spaceflight. Whenever human MPS has been measured after inactivity, a marked decline has been observed in 24-h MPS, due to lowered fasted MPS and a reduced postprandial MPS response to an anabolic stimulus. The reduced MPS occurs relatively early in immobilization (within 10 days of bed rest) and does not decline further[60]. Thus, anabolic resistance is not always age-related. It can also be a direct consequence of disuse and deconditioning. In young adults who have been typically developing, a reduction in physical activity through cast-induced immobilization of the legs blunts basal and amino-acid stimulated rates of MPS[63-65]. Thus, it is apparent that disuse induces anabolic resistance in skeletal muscle regardless of age. Recent work also indicates

that even short-term abrupt sedentary behaviour, leading to a reduced relative loading of skeletal muscles, resulted in loss of muscle mass in the legs[66].

In addition, oxidative stress and chronic inflammation play important roles in muscle atrophy[67]. The interaction of these factors affects the balance between MPS and MPB, inducing skeletal muscle cell death ("apoptosis"), which leads to significant loss of muscle mass. The state of oxidative stress seems to trigger the pathogenesis of muscle wasting in chronic diseases[68]. The deleterious effect of oxidative stress on the muscle can also be explained through its participation to the low-grade inflammation status by triggering the release of inflammatory cytokines or by participating to the reduced sensitivity of muscle to leucine anabolic action[69]. Elevated levels of low-grade inflammation induced by oxidative stress are detrimental to skeletal muscle in humans[70], as well as in animal models[71]. Age-related low-grade inflammation has been associated with a decrease in muscle mass and strength[72], and a loss of physical function[73].

Analogue CP: To the best of our knowledge there are currently no studies that have examined anabolic resistance in people with CP. However, children with CP have one of the most sedentary lifestyles across paediatric disabilities[74]. From 2-3 years of age, children with CP show significantly more sedentary behaviour than TD children and, not surprisingly, GMFCS level correlates with sedentary behaviour, with more sedentary behaviour occurring in those with levels IV and V[75]. Decreased activity levels lead to muscle weakness, disuse muscle atrophy, and muscle shortening, but also lead to further activity limitations which prompt a vicious circle of inactivity and disuse[76]. Despite the lack of studies to directly measure anabolic response in children with CP, the low physical activity levels and related disuse make it plausible that children with CP have decreased anabolic responses to dietary amino acids and protein, to a similar extent seen in the elderly with sarcopenia.

In children with CP, oxidative stress may be caused by a deficiency in vitamin and food intake, environmental factors **(i.e. passive smoking and fruit juice intake)** and epileptic seizures[77]. However, the few studies that have examined oxidative stress markers in children with CP have yielded inconclusive findings. Aycicek and Iscan[77] showed that children with CP have increased lipid hydroperoxide levels (a marker for oxidative stress) and decreased antioxidant levels when compared to TD children. The authors concluded that children with CP have an impaired oxidative/antioxidative balance when compared to TD children. In contrast, Kulak et al.[78] showed that children with CP have similar lipid hydroperoxide levels as TD children. At the same time, some antioxidant enzyme levels were found to be lower in children with CP, whereas other antioxidant enzyme levels were higher, which led the authors to conclude that children with CP do not show elevated levels of oxidative stress compared to their TD peers.

2. ***Impaired muscle quality, i.e. muscle strength per mass unit, and muscle function with underlying factors like intramuscular fat, impaired mitochondrial function, muscle fibre type changes, and neuromuscular innervation***

Apart from the decrease in muscle mass, which is reflected by a decrease of up to 50% in the size and number of muscle fibres from 20 to 90 years of age[79], there are also composition changes in the muscle that occur with age. Specifically, there is a selective age-related atrophy of type 2 fibers (glycolytic fibers, predominant in fast-twitch muscles)[80]. Moreover, there is an age-dependent increase in muscle fat content, which is known to be positively correlated with whole-body fat[81]. Age-related muscle fat infiltration can be part of the sarcopenia process, as it is associated with lower muscle strength[82] and an increased risk of developing mobility limitations[83]. Moreover, specific loss of α-motor neurons[84] leads to multiple processes of denervation-renervation of muscle fibers and consequently to the decline in coordinated muscle action and reduction in muscle strength. Another factor in the pathogenesis of sarcopenia is the age-related decrease in mitochondria number and function. This is the consequence of an alteration in the expression of genes encoding mitochondria protein[85], a decrease in mitochondria protein synthesis[86], a decrease in mitochondria oxidative capacity, and ATP production rates[85]. This can have a major impact on endurance capacity and muscle fatigue, which in turn can contribute to the decreased physical function observed in elderly. A new study suggests that mitochondrial dysfunction, reduced insulin sensitivity, and reduced physical endurance are related, at least in part, to physical inactivity and to increases in adiposity rather than to aging alone[87].

Analogue CP: Muscles of the lower limb of ambulant individuals with CP have greater connective tissue fraction[12] and more inter- and intramuscular fat[11, 13, 33, 88] compared to TD peers. Furthermore, Johnson et al.[13] showed that children with quadriplegic CP (GMFCS III-V) had 2.3-fold higher intermuscular adipose tissue in the mid-thigh muscles than control subjects, and this was related to their low levels of physical activity. At a muscle fiber level, Ito et al.[89] showed a type 1 fiber predominance in spastic muscles of individuals with CP, and a type 2b fiber deficiency with significant variation in fiber size. **It is also reported that spastic muscle in CP show myofibrillar disorganization in poorly defined areas ("moth-eaten fibres'), fibres with rounded contours in cross-section (versus normal polygonal contours) and in some cases, an increased extracellular matrix and fibrotic increase in passive stiffness [43].** Taken together, these studies show that children with CP have lower muscle quality than TD children, which might contribute to impaired muscle function in this particular patient group.

3. Nutritional factors: deficiencies of protein and vitamin D

Although older adults may decrease their overall energy intake, the actual need for certain macronutrients and micronutrients may increase with age. Inadequate nutrition or malabsorption and/or maldigestion are suggested as one of the underlying mechanisms involved in the onset or progression of sarcopenia[25]. Certain nutrients are referred to as musculoskeletal nutrients, i.e. protein, calcium, vitamin D, magnesium and phosphorus[90]. The relation between nutrients and muscle parameters has been extensively reviewed by Mithal et al.[91] for protein, vitamin D and the B vitamins, and by Robinson et al.[92] for antioxidants and long-chain polyunsaturated fatty acids. However, nutritional

recommendations for sarcopenia mainly apply to consideration of adequate protein intake and adequate vitamin D status[93], as the evidence for these nutrients is most evident. Considering the role of malnutrition in the pathophysiology of sarcopenia[25], adequate energy intake is important **to prevent muscle loss.**

Adequate protein intake is especially relevant for stimulation of MPS in conditions of anabolic resistance. This is intuitive, as muscle is the largest protein reservoir in the body, with muscle proteins being replaced at a rate of 1-2% per day. A dietary intake study in a large cohort showed that protein intake decreases with age[94]. High daily protein intake in healthy older adults is associated with a reduced loss of muscle mass, as shown in several cohort studies in older people[95]. Indeed, individuals with sarcopenia showed a lower intake of dietary protein compared with non-sarcopenic individuals[96, 97]. Among 55-77 year old ambulatory men and women, 14-days of controlled dietary protein intake at the recommended level (RDA: 0.8g protein/kg body weight (bw)/day), resulted in a significant decrease of the mid-thigh muscle area and a decrease in urinary nitrogen excretion[98]. This also implies that a protein intake greater than the RDA in elderly is required to maintain nitrogen balance, fat free mass, and muscle mass[98]. Explorative studies suggest that healthy older people may require a minimum protein intake of 1.0 to 1.5 g/kg bw/day to achieve a null nitrogen balance, and to preserve muscle mass, strength and function[99]. A recent consensus paper by the dietary protein needs with aging (PROT-AGE) group advised that older adults should consume 1.0-1.2 g protein/kg bw/day, and even higher amounts are recommended for older adults who are malnourished[100].

Moreover, protein intake varies throughout the day. This is important as it is hypothesized that 25-30g high-quality protein per meal is needed for adequate stimulation of MPS to counteract anabolic resistance with ageing[101]. Habitual protein intake is highest at lunch or evening meals, but is especially low at breakfast[102-105]. The habitual low protein intake at breakfast may therefore prevent maximal muscle protein synthesis. One recent publication indicated that the distribution of protein intake over the day differs between frail and non-frail community-dwelling seniors, with the lowest intake at breakfast in the frail[106].

The lack of specific (anabolic) nutrients is responsible for the loss of muscle mass; however, an adequate caloric intake is also needed to facilitate metabolic processes. If nutrients intake is insufficient to meet the needs, resulting in malnutrition, body fat and muscle will be catabolized to provide energy[107]. Therefore, meeting the daily energy recommendation is important for the maintenance of muscle mass and physical performance.

Age-related declines in vitamin D receptor can also contribute to the loss of muscle strength[108]. The importance of adequate vitamin D status is recognized, but low serum vitamin D levels are also commonly reported. Houston et al. reported inadequate levels (<50nmol/L 25(OH)D) in 75% of older women and 50% of older men (InCHIANTI cohort).[95] The vitamin D intake through nutrition was found to be low in elderly in Europe,[109] and inadequate vitamin D intake is indeed a health concern. Also, the reduced time spent outdoors and the skin's decreased ability to make vitamin D contribute to low vitamin D status with aging. Several observational studies found an association between

vitamin D status and muscle strength, physical performance (e.g. balance, chair stand), physical activity, fall occurrence and activities of daily living[110, 111]. Describing the exact working mechanism of vitamin D and its receptor in muscle is outside the scope of this review (for a review on this topic see Hamilton, 2009[112]). In short, vitamin D is involved in the transcription of a range of proteins, including those involved in calcium metabolism, which is critical for skeletal muscle function. It is also widely believed that vitamin D has a rapid effect on membrane calcium channels thereby being a critical modulator of muscle function[112]. Another mechanism by which vitamin D acts on muscle is through increasing the sensitivity of MPS to an anabolic stimulus, as shown for leucine in muscle cells under vitamin D deficient and supplemented conditions[113]. Vitamin D thus seems essential for muscle function.

Analogue CP: Some of the nutritional factors that contribute to the development of sarcopenia might also play a role in the muscle function of people with CP. The prevalence of malnutrition, which may result in an inadequate protein intake, is also elevated in the CP population[114]. Adequate dietary protein intake may therefore be a critical key factor for maintaining skeletal muscle mass in people with CP. This is supported by the findings of Arrowsmith et al.[115] who found low total body protein levels **(as measured by neutron activation analysis)** in children with spastic quadriplegic CP. This could be the result of reduced muscle mass due to inactivity, or, malnutrition coupled with the inactivity, and consequently decrement in muscle volume. There are many possible reasons people with CP fail to consume enough protein to meet their needs. Medical conditions (food processing and swallowing problems), physical and mental disabilities that limit shopping and food preparation, and food insecurity due to financial and social limitations, are commonly reported reasons[114].

Despite the feeding and swallowing difficulties in a great proportion of the children with CP, different studies showed no differences in protein intake between children with CP and their TD peers[116-119]. However, to date it remains unclear whether children with CP have similar protein requirements as TD children. Many people with CP participate in intensive (strengthening) exercise programs and since exercise causes muscle micro-damage, it is important to replace and rebuild this tissue to allow for hypertrophy and strength increases[120]. Therefore, it may be argued that for children with CP it is crucial that a regular dietary intake of high-quality proteins is necessary and that there is even a higher need for these proteins than for children without CP.

Adequate vitamin D intake is essential for preservation of muscle strength and function. Individuals with CP may be at heightened risk for hypovitaminosis D-induced osteopenia and impaired bone mass accrual. The risk of secondary health complications associated with or exaggerated by the combination of insufficient vitamin D, chronic sedentary behaviour, and obesity may also be higher. Indeed, about 30% of the children with CP have insufficient vitamin D status;[121, 122] however, a major difficulty in comparing literature on this topic is the use of different cut-off points for vitamin D deficiency. Therefore, it is difficult to say

whether the percentages in CP are high or similar compared to the general population in which a deficiency prevalence of 2-60% is reported[123, 124]. Although present across all GMFCS levels, vitamin D deficiency is more prominent in children classified at GMFCS levels IV and V, who might have reduced outdoor activity. One of the factors that could contribute to vitamin D deficiency is the use of anticonvulsants[125]. About 41% of children with CP have epilepsy and anticonvulsant use is common. It can therefore be assumed that vitamin D deficiency is common in this population. Moreover, in a recent study with CP adults, more than 50% were either vitamin D insufficient or deficient, and abdominal adiposity was a strong independent predictor for low vitamin D levels[126].

C. Therapeutic approaches in sarcopenia with focus on a) protein (quantity per day and at each meal; protein quality); b) vitamin D; and c) combination with exercise

Recommending dietary modifications, nutritional supplements and exercise therapy separately or in combination can be appropriate steps to stimulate muscle growth, and combat muscle deterioration in people with CP. Maximizing muscle mass can improve functionality, strength, endurance, and general metabolic health. Based on the pathophysiology of sarcopenia and prevalent nutritional deficiencies, therapeutic approaches with protein, vitamin D and/or exercise have been applied. This section discusses what we can learn from these approaches for possible future interventions in individuals with CP.

Protein interventions

It is well-established that dietary protein ingestion stimulates skeletal MPS and inhibits protein breakdown, resulting in a positive protein balance and net muscle mass gain[127, 128]. Net protein balance is maintained by ingestion of protein-containing meals which results in systemic hyperaminoacidemia that is stimulatory for the synthesis of new proteins[129-131]. The ingested protein dose and source dictates the amplitude and duration of the rise in essential amino acids in the blood, which, in turn, affects the degree of MPS[127, 132]. In addition to increasing the total dose of protein or (essential) amino acids in a meal[133], a diminished anabolic responsiveness with aging can be overcome by increasing the proportion of the amino acid leucine[134], especially at low protein intake[135]. Only one study measuring MPS was performed in sarcopenic older adults and demonstrated an increase of MPS after a leucine-enriched whey protein supplement[136].

Vitamin D

While the recommendations for older sarcopenic adults are in favor of vitamin D supplementation, randomized controlled trials on muscle strength show non-conclusive results. Both positive effects[137-139] and absence of effects[140-142] were observed with vitamin D supplementation. These contradictory results may be attributed to the differences in study design, for instance baseline vitamin D levels, vitamin D dosing schedule (daily, weekly or monthly), the dosage of vitamin D supplemented or the duration of the intervention.

Supplementation of at least 800IU (20µg) showed, however, an effect on muscle strength[137, 138]. The evidence to support vitamin D supplementation for falls and fracture prevention is more apparent, indicating a beneficial effect of vitamin D supplementation[143, 144]. Based on 5 RCTs involving 1237 participants, Bischoff-Ferrari et al.[110] concluded that vitamin D supplementation appears to reduce the odds of falling by 22% compared with patients receiving calcium supplements or placebo. It has been suggested that this beneficial effect of vitamin D on falling could be explained by 1.25 hydroxyvitamin D binding to a highly specific nuclear receptor in muscle tissue, leading to improved muscle function and thereby reduced risk of falling. In a 2- month intervention of elderly ambulatory women, vitamin D plus calcium supplementation improved body sway **by** 9% when compared with calcium supplementation alone[145]. Similarly musculoskeletal function increased by 4-11% in institutionalized elderly women after an intervention with vitamin D and calcium compared to calcium alone. Moreover, the combination of adequate vitamin D and anabolic leucine optimized the MPS response in vitamin D deficient muscle cells.[113] Along the same lines, sufficient baseline 25OHD levels and protein intake may be required to increase muscle mass as a result of an intervention with a vitamin D and protein supplement in sarcopenic older adults[97].

Exercise

The synergistic effect of protein ingestion with exercise potentiates the muscle synthetic response, swinging net balance in favour of muscle protein accretion[146], thereby permitting muscle hypertrophy when practiced frequently over time[147]. Regular exercise may also help normalize some aspects of age-related mitochondrial dysfunction, and in turn improve muscle function[87].

Exercise is known to improve muscle strength and function in both the young and the elderly. An updated meta-analysis by Sherrington et al.[148] showed that exercise as a single intervention can prevent falls in community-dwelling older people. In particular exercise programmes that challenge balance and are of a high intensity have larger effects. It thus seems that exercise alone can already help preventing falls in (healthy) elderly. However, it is also known that protein ingestion after a single bout of resistance type exercise stimulates muscle protein accretion during post-exercise recovery. Nutrition in combination with exercise is considered optimal for maintaining muscle function[149]. Consequently it is believed that protein supplementation can augment the effects of resistance-type exercise training. Cermak et al.[150] performed a systematic review to define whether this is indeed the case. Based on 22 RCTs that included 680 subjects they concluded that protein supplementation after prolonged (>6 weeks) resistance-type exercise training has a positive effect on fat free mass and one repetition maximum leg press strength in younger and older subjects. This suggests that a combination of nutrition with exercise could be optimal for maintaining muscle function[149].

***Analogue CP:* Although comparable nutritional intervention studies in people with CP are lacking, a recent systematic review has highlighted that there is preliminary evidence that strength training leads to muscle hypertrophy in children and adolescents**

with CP[48]. However, nutritional supplementation in combination with resistance training or a physical activity intervention has not been investigated in people with CP.

Summary and conclusion

In this review, we highlight the evidence for early and accelerated musculoskeletal aging in CP, which may be comparable to sarcopenia among older adults without CP. Given the fact that nutritional interventions (combined with exercise training) have shown promising effects for mitigating sarcopenia and improving muscle mass and function, future studies should investigate the effect of these interventions as a primary preventive strategy among individuals with CP.

Acknowledgements
The authors certify that they comply with the ethical guidelines for authorship of the Journal of Cachexia, Sarcopenia and Muscle (von Haelings S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle. J Cachexia Sarcopenia Muscle 2015:4:315-316.

Olaf Verschuren, Ana Smorenburg, Yvette Luiking, Kristie Bell, Lee Barber and Mark Peterson declare that they have no conflict of interest.

The authors have stated that they had no interests which might be perceived as posing a conflict or bias.

REFERENCES

1. Sellier E, Platt MJ, Andersen GL, Krageloh-Mann I, De La Cruz J, Cans C et al. Decreasing prevalence in cerebral palsy: a multi-site European population-based study, 1980 to 2003. Dev Med Child Neurol. 2016;58(1):85-92. doi:10.1111/dmcn.12865.
2. Yeargin-Allsopp M, Van Naarden Braun K, Doernberg NS, Benedict RE, Kirby RS, Durkin MS. Prevalence of cerebral palsy in 8-year-old children in three areas of the United States in 2002: a multisite collaboration. Pediatrics. 2008;121(3):547-54. doi:10.1542/peds.2007-1270.
3. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D et al. A report: the definition and classification of cerebral palsy April 2006. Developmental Medicine and Child Neurology. 2007;49(s109):8-14.
4. Green LB, Hurvitz EA. Cerebral palsy. Phys Med Rehabil Clin N Am. 2007;18(4):859-82, vii. doi:10.1016/j.pmr.2007.07.005.
5. Gough M, Shortland AP. Could muscle deformity in children with spastic cerebral palsy be related to an impairment of muscle growth and altered adaptation? Developmental Medicine and Child Neurology. 2012;54(6):495–9. doi:10.1111/j.1469-8749.2012.04229.x.
6. Morrell DS, Pearson JM, Sauser DD. Progressive bone and joint abnormalities of the spine and lower extremities in cerebral palsy. Radiographics. 2002;22(2):257-68.

7. Barrett R, Lichtwark G. Gross muscle morphology and structure in spastic cerebral palsy: a systematic review. Developmental Medicine and Child Neurology. 2010;52(9):794-804.
8. Noble JJ, Fry NR, Lewis AP, Keevil SF, Gough M, Shortland AP. Lower limb muscle volumes in bilateral spastic cerebral palsy. Brain Dev. 2014;36(4):294-300. doi:10.1016/j.braindev.2013.05.008.
9. Barber L, Barrett R, Lichtwark G. Passive mechanical properties of the medial gastrocnemius muscle in young adults with cerebral palsy. Journal of Biomechanics. 2011;44(3):2496-500. doi:10.1016/j.jbiomech.2011.06.008.
10. Barber LA, Read F, Lovatt Stern J, Lichtwark G, Boyd RN. Medial gastrocnemius muscle volume in ambulant children with unilateral and bilateral cerebral palsy aged 2 to 9 years. Dev Med Child Neurol. 2016;58(11):1146-52. doi:10.1111/dmcn.13132.
11. Noble J, Charles-Edwards GD, Keevil SF, Lewis AP, Gough M, Shortland AP. Intramuscular fat in ambulant young adults with bilateral spastic cerebral palsy. BMC Musculoskeletal Disorders. 2014;15:236. doi:10.1186/1471-2474-15-236.
12. Booth CM, Cortina-Borja MJ, Theologis TN. Collagen accumulation in muscles of children with cerebral palsy and correlation with severity of spasticity. Developmental Medicine and Child Neurology. 2001;43(5):314-20.
13. Johnson DL, Miller F, Subramanian P, Modlesky CM. Adipose tissue infiltration of skeletal muscle in children with cerebral palsy. J Pediatr. 2009;154(5):715-20. doi:10.1016/j.jpeds.2008.10.046.
14. Herskind A, Ritterband-Rosenbaum A, Willerslev-Olsen M, Lorentzen J, Hanson L, Lichtwark G et al. Muscle growth is reduced in 15-month-old children with cerebral palsy. Dev Med Child Neurol. 2015. doi:10.1111/dmcn.12950.
15. Barber L, Hastings-Ison T, Baker R, Kerr Graham H, Barrett R, Lichtwark G. The effects of botulinum toxin injection frequency on calf muscle growth in young children with spastic cerebral palsy: a 12-month prospective study. Journal of children's orthopaedics. 2013;7(5):425-33. doi:10.1007/s11832-013-0503-x.
16. Murphy KP, Molnar GE, Lankasky K. Employment and social issues in adults with cerebral palsy. Arch Phys Med Rehabil. 2000;81(6):807-11.
17. Bottos M, Feliciangeli A, Sciuto L, Gericke C, Vianello A. Functional status of adults with cerebral palsy and implications for treatment of children. Dev Med Child Neurol. 2001;43(8):516-28.
18. Day SM, Wu YW, Strauss DJ, Shavelle RM, Reynolds RJ. Change in ambulatory ability of adolescents and young adults with cerebral palsy. Dev Med Child Neurol. 2007;49(9):647-53. doi:10.1111/j.1469-8749.2007.00647.x.
19. Ando N, Ueda S. Functional deterioration in adults with cerebral palsy. Clin Rehabil. 2000;14(3):300-6.
20. Tarsuslu T, Livanelioglu A. Relationship between quality of life and functional status of young adults and adults with cerebral palsy. Disabil Rehabil. 2010;32(20):1658-65. doi:10.3109/09638281003649904.
21. Strauss D, Ojdana K, Shavelle R, Rosenbloom L. Decline in function and life expectancy of older persons with cerebral palsy. NeuroRehabilitation. 2004;19(1):69-78.
22. Shortland A. Muscle deficits in cerebral palsy and early loss of mobility: can we learn something from our elders? Developmental Medicine and Child Neurology. 2009;51(Supp 4):59-63.
23. Rosenberg I. Summary comments: epidemiological and methodological problems in determining nutritional status of older persons. . Am J Clin Nutr. 1989;50:1231-3.

24. Cao L, Morley JE. Sarcopenia Is Recognized as an Independent Condition by an International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) Code. Journal of the American Medical Directors Association. 2016;17(8):675-7. doi:10.1016/j.jamda.2016.06.001.
25. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412-23. doi:10.1093/ageing/afq034.
26. Pagotto V, Silveira EA. Applicability and agreement of different diagnostic criteria for sarcopenia estimation in the elderly. Arch Gerontol Geriatr. 2014;59(2):288-94. doi:10.1016/j.archger.2014.05.009.
27. Fukunaga T, Miyatani M, Tachi M, Kouzaki M, Kawakami Y, Kanehisa H. Muscle volume is a major determinant of joint torque in humans. Acta Physiol Scand. 2001;172(4):249-55. doi:10.1046/j.1365-201x.2001.00867.x.
28. Stein TP, Wade CE. Metabolic consequences of muscle disuse atrophy. J Nutr. 2005;135(7):1824S-8S.
29. Barber L, Hastings-Ison T, Baker R, Barrett R, Lichtwark G. Medial gastrocnemius muscle volume and fascicle length in children aged 2 to 5 years with cerebral palsy. Dev Med Child Neurol. 2011;53(6):543-8. doi:10.1111/j.1469-8749.2011.03913.x.
30. Obst SJ, Boyd R, Read F, Barber L. Quantitative 3-D Ultrasound of the Medial Gastrocnemius Muscle in Children with Unilateral Spastic Cerebral Palsy. Ultrasound Med Biol. 2017;43(12):2814-23. doi:10.1016/j.ultrasmedbio.2017.08.929.
31. Barber L, Barrett R, Lichtwark G. Medial gastrocnemius muscle fascicle active torque-length and Achilles tendon properties in young adults with spastic cerebral palsy. Journal of Biomechanics. 2012;45(15):2526-30. doi:10.1016/j.jbiomech.2012.07.018.
32. Peterson MD, Zhang P, Haapala HJ, Wang SC, Hurvitz EA. Greater Adipose Tissue Distribution and Diminished Spinal Musculoskeletal Density in Adults With Cerebral Palsy. Arch Phys Med Rehabil. 2015;96(10):1828-33. doi:10.1016/j.apmr.2015.06.007.
33. Pitcher CA, Elliott CM, Panizzolo FA, Valentine JP, Stannage K, Reid SL. Ultrasound characterization of medial gastrocnemius tissue composition in children with spastic cerebral palsy. Muscle Nerve. 2014. doi:10.1002/mus.24549.
34. Castle ME, Reyman TA, Schneider M. Pathology of spastic muscle in cerebral palsy. Clin Orthop Relat Res. 1979(142):223-32.
35. Rose J, Haskell WL, Gamble JG, Hamilton RL, Brown DA, Rinsky L. Muscle pathology and clinical measures of disability in children with cerebral palsy. J Orthop Res. 1994;12(6):758-68. doi:10.1002/jor.1100120603.
36. Friden J, Lieber RL. Spastic muscle cells are shorter and stiffer than normal cells. Muscle and Nerve. 2003;27(2):157-64.
37. Smith LR, Lee KS, Ward SR, Chambers HG, Lieber RL. Hamstring contractures in children with spastic cerebral palsy result from a stiffer extracellular matrix and increased in vivo sarcomere length. Journal of Physiology. 2011;589(Pt 10):2625-39. doi:10.1113/jphysiol.2010.203364.
38. Graham HK, Rosenbaum P, Paneth N, Dan B, Lin JP, Damiano DL et al. Cerebral palsy. Nat Rev Dis Primers. 2016;2:15082. doi:10.1038/nrdp.2015.82.
39. Schroeder AS, Ertl-Wagner B, Britsch S, Schroder JM, Nikolin S, Weis J et al. Muscle biopsy substantiates long-term MRI alterations one year after a single dose of botulinum toxin injected into the lateral gastrocnemius muscle of healthy volunteers. Movement Disorders. 2009;24(10):1494-503. doi:10.1002/mds.22661.

40. Chen CM, Stott NS, Smith HK. Effects of botulinum toxin A injection and exercise on the growth of juvenile rat gastrocnemius muscle. Journal of Applied Physiology. 2002;93(4):1437-47. doi:10.1152/japplphysiol.00189.2002.
41. Longino D, Frank C, Leonard TR, Vaz MA, Herzog W. Proposed model of botulinum toxin-induced muscle weakness in the rabbit. Journal of Orthopaedic Research. 2005;23(6):1411-8. doi:10.1016/j.orthres.2005.02.016.1100230625.
42. Fry NR, Gough M, McNee AE, Shortland AP. Changes in the volume and length of the medial gastrocnemius after surgical recession in children with spastic diplegic cerebral palsy. Journal of Pediatric Orthopaedics. 2007;27(7):769-74.
43. Lieber RL, Steinman S, Barash IA, Chambers H. Structural and functional changes in spastic skeletal muscle. Muscle Nerve. 2004;29(5):615-27. doi:10.1002/mus.20059.
44. Rose J, McGill KC. Neuromuscular activation and motor-unit firing characteristics in cerebral palsy. Developmental Medicine and Child Neurology. 2005;47(5):329-36.
45. Stackhouse S, Binder-Macleod SA, Lee SC. Voluntary muscle activation, contractile properties, and fatigability in children with and without cerebral palsy. Muscle and Nerve. 2005;31(5):594-601. doi:10.1002/mus.20302.
46. Dallmeijer AJ, Rameckers EA, Houdijk H, de Groot S, Scholtes VA, Becher JG. Isometric muscle strength and mobility capacity in children with cerebral palsy. Disabil Rehabil. 2017;39(2):135-42. doi:10.3109/09638288.2015.1095950.
47. Wiley ME, Damiano DL. Lower-extremity strength profiles in spastic cerebral palsy. Dev Med Child Neurol. 1998;40(2):100-7.
48. Gillett J, Boyd R, Carty C, Barber L. The impact of strength training on skeletal muscle morphology and architecture in children and adolescents with spastic cerebral palsy: A systematic review. Res Dev Disabil. 2016;56:183-96. doi:10.1016/j.ridd.2016.06.003.
49. Wiley ME, Damiano DL. Lower-extremity strength profiles in spastic cerebral palsy. Dev Med Child Neurol. 1998;40:100-7.
50. Palisano RJ, Rosenbaum P, Walter S. The development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol. 1997;39:214-23.
51. Eek MN, Beckung E. Walking ability is related to muscle strength in children with cerebral palsy. Gait Posture. 2008;28(3):366-71.
52. Hanna SE, Rosenbaum PL, Bartlett DJ, Palisano RJ, Walter SD, Avery L et al. Stability and decline in gross motor function among children and youth with cerebral palsy aged 2 to 21 years. Dev Med Child Neurol. 2009;51(4):295-302.
53. Bottos M, Feliciangeli A, Sciuto L, Gericke C, Vianello A. Functional status of adults with cerebral palsy and implications for treatment of children. Developmental Medicine & Child Neurology. 2001;43(8):516-28.
54. Short KR, Vittone JL, Bigelow ML, Proctor DN, Nair KS. Age and aerobic exercise training effects on whole body and muscle protein metabolism. Am J Physiol Endocrinol Metab. 2004;286(1):E92-101. doi:10.1152/ajpendo.00366.2003.
55. Volpi E, Mittendorfer B, Rasmussen BB, Wolfe RR. The response of muscle protein anabolism to combined hyperaminoacidemia and glucose-induced hyperinsulinemia is impaired in the elderly. J Clin Endocrinol Metab. 2000;85(12):4481-90. doi:10.1210/jcem.85.12.7021.
56. Cuthbertson D, Smith K, Babraj J, Leese G, Waddell T, Atherton P et al. Anabolic signaling deficits underlie amino acid resistance of wasting, aging muscle. FASEB J. 2005;19(3):422-4. doi:10.1096/fj.04-2640fje.

57. Boirie Y. Fighting sarcopenia in older frail subjects: protein fuel for strength, exercise for mass. Journal of the American Medical Directors Association. 2013;14(2):140-3. doi:10.1016/j.jamda.2012.10.017.
58. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. The journals of gerontology Series A, Biological sciences and medical sciences. 2014;69 Suppl 1:S4-9. doi:10.1093/gerona/glu057.
59. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc. 2002;50(5):889-96.
60. 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(16):1772-4. doi:10.1001/jama.297.16.1772-b.
61. Wolfe RR. The underappreciated role of muscle in health and disease. Am J Clin Nutr. 2006;84(3):475-82.
62. Johnstone AM, Murison SD, Duncan JS, Rance KA, Speakman JR. Factors influencing variation in basal metabolic rate include fat-free mass, fat mass, age, and circulating thyroxine but not sex, circulating leptin, or triiodothyronine. Am J Clin Nutr. 2005;82(5):941-8.
63. Wall BT, Gorissen SH, Pennings B, Koopman R, Groen BB, Verdijk LB et al. Aging Is Accompanied by a Blunted Muscle Protein Synthetic Response to Protein Ingestion. PLoS One. 2015;10(11):e0140903. doi:10.1371/journal.pone.0140903.
64. Wall BT, Dirks ML, Snijders T, van Dijk JW, Fritsch M, Verdijk LB et al. Short-term muscle disuse lowers myofibrillar protein synthesis rates and induces anabolic resistance to protein ingestion. American journal of physiology Endocrinology and metabolism. 2016;310(2):E137-47. doi:10.1152/ajpendo.00227.2015.
65. de Boer MD, Selby A, Atherton P, Smith K, Seynnes OR, Maganaris CN et al. The temporal responses of protein synthesis, gene expression and cell signalling in human quadriceps muscle and patellar tendon to disuse. J Physiol. 2007;585(Pt 1):241-51. doi:10.1113/jphysiol.2007.142828.
66. Krogh-Madsen R, Thyfault JP, Broholm C, Mortensen OH, Olsen RH, Mounier R et al. A 2-wk reduction of ambulatory activity attenuates peripheral insulin sensitivity. J Appl Physiol (1985). 2010;108(5):1034-40. doi:10.1152/japplphysiol.00977.2009.
67. Kregel KC, Zhang HJ. An integrated view of oxidative stress in aging: basic mechanisms, functional effects, and pathological considerations. Am J Physiol Regul Integr Comp Physiol. 2007;292(1):R18-36. doi:10.1152/ajpregu.00327.2006.
68. Moylan JS, Reid MB. Oxidative stress, chronic disease, and muscle wasting. Muscle Nerve. 2007;35(4):411-29. doi:10.1002/mus.20743.
69. Marzani B, Balage M, Venien A, Astruc T, Papet I, Dardevet D et al. Antioxidant supplementation restores defective leucine stimulation of protein synthesis in skeletal muscle from old rats. J Nutr. 2008;138(11):2205-11.
70. Howard C, Ferrucci L, Sun K, Fried LP, Walston J, Varadhan R et al. Oxidative protein damage is associated with poor grip strength among older women living in the community. J Appl Physiol (1985). 2007;103(1):17-20. doi:10.1152/japplphysiol.00133.2007.
71. Siu PM, Pistilli EE, Alway SE. Age-dependent increase in oxidative stress in gastrocnemius muscle with unloading. J Appl Physiol (1985). 2008;105(6):1695-705. doi:10.1152/japplphysiol.90800.2008.
72. Visser M, Pahor M, Taaffe DR, Goodpaster BH, Simonsick EM, Newman AB et al. Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: the Health ABC Study. J Gerontol A Biol Sci Med Sci. 2002;57(5):M326-32.

73. Taaffe DR, Harris TB, Ferrucci L, Rowe J, Seeman TE. Cross-sectional and prospective relationships of interleukin-6 and C-reactive protein with physical performance in elderly persons: MacArthur studies of successful aging. J Gerontol A Biol Sci Med Sci. 2000;55(12):M709-15.
74. Longmuir P, Bar-Or O. Factors influencing the physical activity levels of youths with physical and sensory disabilities. Adapted Phys Educ Q. 2000;17:40-53.
75. Verschuren O, Peterson MD, Balemans AC, Hurvitz EA. Exercise and physical activity recommendations for people with cerebral palsy. Dev Med Child Neurol. 2016;58(8):798-808. doi:10.1111/dmcn.13053.
76. Moreau NG, Li L, Geaghan JP, Damiano DL. Contributors to fatigue resistance of the hamstrings and quadriceps in cerebral palsy. Clinical biomechanics. 2009;24(4):355-60. doi:10.1016/j.clinbiomech.2009.01.012.
77. Aycicek A, Iscan A. Oxidative and antioxidative capacity in children with cerebral palsy. Brain research bulletin. 2006;69(6):666-8. doi:10.1016/j.brainresbull.2006.03.014.
78. Kulak W, Sobaniec W, Solowej E, Sobaniec H. Antioxidant enzymes and lipid peroxides in children with cerebral palsy. Life sciences. 2005;77(24):3031-6. doi:10.1016/j.lfs.2005.02.031.
79. Lexell J, Taylor CC, Sjostrom M. What is the cause of the ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men. J Neurol Sci. 1988;84(2-3):275-94.
80. Vandervoort AA. Aging of the human neuromuscular system. Muscle Nerve. 2002;25(1):17-25.
81. Ryan AS, Nicklas BJ. Age-related changes in fat deposition in mid-thigh muscle in women: relationships with metabolic cardiovascular disease risk factors. Int J Obes Relat Metab Disord. 1999;23(2):126-32.
82. Goodpaster BH, Carlson CL, Visser M, Kelley DE, Scherzinger A, Harris TB et al. Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. J Appl Physiol. 2001;90(6):2157-65.
83. Visser M, Goodpaster BH, Kritchevsky SB, Newman AB, Nevitt M, Rubin SM et al. Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. J Gerontol A Biol Sci Med Sci. 2005;60(3):324-33. doi:60/3/324 [pii].
84. Edstrom E, Altun M, Bergman E, Johnson H, Kullberg S, Ramirez-Leon V et al. Factors contributing to neuromuscular impairment and sarcopenia during aging. Physiol Behav. 2007;92(1-2):129-35.
85. Short KR, Bigelow ML, Kahl J, Singh R, Coenen-Schimke J, Raghavakaimal S et al. Decline in skeletal muscle mitochondrial function with aging in humans. Proc Natl Acad Sci U S A. 2005;102(15):5618-23.
86. Rooyackers OE, Adey DB, Ades PA, Nair KS. Effect of age on in vivo rates of mitochondrial protein synthesis in human skeletal muscle. Proc Natl Acad Sci U S A. 1996;93(26):15364-9.
87. Lanza IR, Short DK, Short KR, Raghavakaimal S, Basu R, Joyner MJ et al. Endurance exercise as a countermeasure for aging. Diabetes. 2008;57(11):2933-42. doi:10.2337/db08-0349.
88. Whitney DG, Singh H, Miller F, Barbe MF, Slade JM, Pohlig RT et al. Cortical bone deficit and fat infiltration of bone marrow and skeletal muscle in ambulatory children with mild spastic cerebral palsy. Bone. 2017;94:90-7. doi:10.1016/j.bone.2016.10.005.
89. Ito J, Araki A, Tanaka H, Tasaki T, Cho K, Yamazaki R. Muscle histopathology in spastic cerebral palsy. Brain Dev. 1996;18(4):299-303.
90. Sharkey JR, Giuliani C, Haines PS, Branch LG, Busby-Whitehead J, Zohoori N. Summary measure of dietary musculoskeletal nutrient (calcium, vitamin D, magnesium, and phosphorus) intakes is

associated with lower-extremity physical performance in homebound elderly men and women. Am J Clin Nutr. 2003;77(4):847-56.
91. Mithal A, Bonjour JP, Boonen S, Burckhardt P, Degens H, El Hajj Fuleihan G et al. Impact of nutrition on muscle mass, strength, and performance in older adults. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2013;24(5):1555-66. doi:10.1007/s00198-012-2236-y.
92. Robinson S, Cooper C, Aihie Sayer A. Nutrition and sarcopenia: a review of the evidence and implications for preventive strategies. J Aging Res. 2012;2012:510801. doi:10.1155/2012/510801.
93. Morley JE, Argiles JM, Evans WJ, Bhasin S, Cella D, Deutz NE et al. Nutritional recommendations for the management of sarcopenia. Journal of the American Medical Directors Association. 2010;11(6):391-6. doi:10.1016/j.jamda.2010.04.014.
94. Feart C, Jutand MA, Larrieu S, Letenneur L, Delcourt C, Combe N et al. Energy, macronutrient and fatty acid intake of French elderly community dwellers and association with socio-demographic characteristics: data from the Bordeaux sample of the Three-City Study. Br J Nutr. 2007;98(5):1046-57.
95. Houston DK, Cesari M, Ferrucci L, Cherubini A, Maggio D, Bartali B et al. Association between vitamin D status and physical performance: the InCHIANTI study. The journals of gerontology Series A, Biological sciences and medical sciences. 2007;62(4):440-6.
96. Ter Borg S, de Groot LC, Mijnarends DM, de Vries JH, Verlaan S, Meijboom S et al. Differences in Nutrient Intake and Biochemical Nutrient Status Between Sarcopenic and Nonsarcopenic Older Adults-Results From the Maastricht Sarcopenia Study. Journal of the American Medical Directors Association. 2016;17(5):393-401. doi:10.1016/j.jamda.2015.12.015.
97. Verlaan S, Aspray TJ, Bauer JM, Cederholm T, Hemsworth J, Hill TR et al. Nutritional status, body composition, and quality of life in community-dwelling sarcopenic and non-sarcopenic older adults: A case-control study. Clinical nutrition. 2017;36(1):267-74. doi:10.1016/j.clnu.2015.11.013.
98. Campbell WW, Trappe TA, Wolfe RR, Evans WJ. The recommended dietary allowance for protein may not be adequate for older people to maintain skeletal muscle. The journals of gerontology Series A, Biological sciences and medical sciences. 2001;56(6):M373-80.
99. Wolfe RR, Miller SL. The recommended dietary allowance of protein: a misunderstood concept. JAMA. 2008;299(24):2891-3. doi:10.1001/jama.299.24.2891.
100. Bauer JM, Verlaan S, Bautmans I, Brandt K, Donini LM, Maggio M et al. Effects of a vitamin D and leucine-enriched whey protein nutritional supplement on measures of sarcopenia in older adults, the PROVIDE study: a randomized, double-blind, placebo-controlled trial. J Am Med Dir Assoc. 2015;16(9):740-7. doi:10.1016/j.jamda.2015.05.021.
101. Paddon-Jones D, Rasmussen BB. Dietary protein recommendations and the prevention of sarcopenia. Curr Opin Clin Nutr Metab Care. 2009;12(1):86-90. doi:10.1097/MCO.0b013e32831cef8b.
102. Tieland M, Borgonjen-Van den Berg KJ, Van Loon LJ, de Groot LC. Dietary Protein Intake in Dutch Elderly People: A Focus on Protein Sources. Nutrients. 2015;7(12):9697-706. doi:10.3390/nu7125496.
103. Tieland M, Borgonjen-Van den Berg KJ, van Loon LJ, de Groot LC. Dietary protein intake in community-dwelling, frail, and institutionalized elderly people: scope for improvement. Eur J Nutr. 2012;51(2):173-9. doi:10.1007/s00394-011-0203-6.

104. Paddon-Jones D, Campbell WW, Jacques PF, Kritchevsky SB, Moore LL, Rodriguez NR et al. Protein and healthy aging. Am J Clin Nutr. 2015;Apr 29 (Epub 10.3945/ajcn.114.084061). doi:10.3945/ajcn.114.084061.
105. Rousset S, Patureau Mirand P, Brandolini M, Martin JF, Boirie Y. Daily protein intakes and eating patterns in young and elderly French. Br J Nutr. 2003;90(6):1107-15.
106. Bollwein J, Diekmann R, Kaiser MJ, Bauer JM, Uter W, Sieber CC et al. Distribution but not amount of protein intake is associated with frailty: a cross-sectional investigation in the region of Nurnberg. Nutr J. 2013;12(1):109.
107. Newman AB, Lee JS, Visser M, Goodpaster BH, Kritchevsky SB, Tylavsky FA et al. Weight change and the conservation of lean mass in old age: the Health, Aging and Body Composition Study. Am J Clin Nutr. 2005;82(4):872-8; quiz 915-6.
108. Ceglia L. Vitamin D and its role in skeletal muscle. Curr Opin Clin Nutr Metab Care. 2009;12(6):628-33. doi:10.1097/MCO.0b013e328331c707.
109. Raats M, de Groot L, van Staveren W. Food for the ageing population. . Cambridge, England: Woodhead Publishing Limited.; 2009.
110. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Hu FB, Zhang Y, Karlson EW et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or =60 y. Am J Clin Nutr. 2004;80(3):752-8. doi:80/3/752 [pii].
111. Suzuki T, Kwon J, Kim H, Shimada H, Yoshida Y, Iwasa H et al. Low serum 25-hydroxyvitamin D levels associated with falls among Japanese community-dwelling elderly. J Bone Miner Res. 2008;23(8):1309-17. doi:10.1359/jbmr.080328.
112. Hamilton B. Vitamin D and human skeletal muscle. Scandinavian journal of medicine & science in sports. 2010;20(2):182-90. doi:10.1111/j.1600-0838.2009.01016.x.
113. Salles J, Chanet A, Giraudet C, Patrac V, Pierre P, Jourdan M et al. 1,25(OH)2-vitamin D3 enhances the stimulating effect of leucine and insulin on protein synthesis rate through Akt/PKB and mTOR mediated pathways in murine C2C12 skeletal myotubes. Mol Nutr Food Res. 2013;57(12):2137-46. doi:10.1002/mnfr.201300074.
114. Rempel G. The importance of good nutrition in children with cerebral palsy. Physical medicine and rehabilitation clinics of North America. 2015;26(1):39-56. doi:10.1016/j.pmr.2014.09.001.
115. Arrowsmith FE, Allen JR, Gaskin KJ, Gruca MA, Clarke SL, Briody JN et al. Reduced body protein in children with spastic quadriplegic cerebral palsy. Am J Clin Nutr. 2006;83(3):613-8.
116. Grammatikopoulou MG, Daskalou E, Tsigga M. Diet, feeding practices, and anthropometry of children and adolescents with cerebral palsy and their siblings. Nutrition. 2009;25(6):620-6. doi:10.1016/j.nut.2008.11.025.
117. Schoendorfer N, Tinggi U, Sharp N, Boyd R, Vitetta L, Davies PS. Protein levels in enteral feeds: do these meet requirements in children with severe cerebral palsy? Br J Nutr. 2012;107(10):1476-81. doi:10.1017/S0007114511004533.
118. Walker JL, Bell KL, Stevenson RD, Weir KA, Boyd RN, Davies PS. Relationships between dietary intake and body composition according to gross motor functional ability in preschool-aged children with cerebral palsy. Ann Nutr Metab. 2012;61(4):349-57. doi:10.1159/000342557.
119. Kalra S, Aggarwal A, Chillar N, Faridi MM. Comparison of micronutrient levels in children with cerebral palsy and neurologically normal controls. Indian J Pediatr. 2015;82(2):140-4. doi:10.1007/s12098-014-1543-z.
120. Verschuren O, Peterson MD. Nutrition and physical activity in people with cerebral palsy: opposite sides of the same coin. Dev Med Child Neurol. 2016;58(5):426. doi:10.1111/dmcn.13107.

121. Finbraten AK, Syversen U, Skranes J, Andersen GL, Stevenson RD, Vik T. Bone mineral density and vitamin D status in ambulatory and non-ambulatory children with cerebral palsy. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2015;26(1):141-50. doi:10.1007/s00198-014-2840-0.
122. Ware T, Whitelaw C, Flett P, Parameswaran V. Vitamin d status in tasmanian children with cerebral palsy. J Paediatr Child Health. 2013;49(4):E349-50. doi:10.1111/jpc.12144.
123. Forrest KY, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. Nutr Res. 2011;31(1):48-54. doi:10.1016/j.nutres.2010.12.001.
124. Spiro A, Buttriss JL. Vitamin D: An overview of vitamin D status and intake in Europe. Nutr Bull. 2014;39(4):322-50. doi:10.1111/nbu.12108.
125. Lee SH, Yu J. Risk factors of vitamin D deficiency in children with epilepsy taking anticonvulsants at initial and during follow-up. Ann Pediatr Endocrinol Metab. 2015;20(4):198-205. doi:10.6065/apem.2015.20.4.198.
126. Peterson MD, Haapala HJ, Chaddha A, Hurvitz EA. Abdominal obesity is an independent predictor of serum 25-hydroxyvitamin D deficiency in adults with cerebral palsy. Nutr Metab (Lond). 2014;11:22. doi:10.1186/1743-7075-11-22.
127. Pennings B, Boirie Y, Senden JM, Gijsen AP, Kuipers H, van Loon LJ. Whey protein stimulates postprandial muscle protein accretion more effectively than do casein and casein hydrolysate in older men. Am J Clin Nutr. 2011;93(5):997-1005. doi:10.3945/ajcn.110.008102.
128. Rennie MJ, Tipton KD. Protein and amino acid metabolism during and after exercise and the effects of nutrition. Annual review of nutrition. 2000;20:457-83. doi:10.1146/annurev.nutr.20.1.457.
129. Burd NA, West DW, Rerecich T, Prior T, Baker SK, Phillips SM. Validation of a single biopsy approach and bolus protein feeding to determine myofibrillar protein synthesis in stable isotope tracer studies in humans. Nutrition & metabolism. 2011;8:15. doi:10.1186/1743-7075-8-15.
130. Bohe J, Low A, Wolfe RR, Rennie MJ. Human muscle protein synthesis is modulated by extracellular, not intramuscular amino acid availability: a dose-response study. J Physiol. 2003;552(Pt 1):315-24. doi:10.1113/jphysiol.2003.050674.
131. Fujita S, Dreyer HC, Drummond MJ, Glynn EL, Cadenas JG, Yoshizawa F et al. Nutrient signalling in the regulation of human muscle protein synthesis. J Physiol. 2007;582(Pt 2):813-23. doi:10.1113/jphysiol.2007.134593.
132. Tang JE, Moore DR, Kujbida GW, Tarnopolsky MA, Phillips SM. Ingestion of whey hydrolysate, casein, or soy protein isolate: effects on mixed muscle protein synthesis at rest and following resistance exercise in young men. J Appl Physiol (1985). 2009;107(3):987-92. doi:10.1152/japplphysiol.00076.2009.
133. Volpi E, Mittendorfer B, Wolf SE, Wolfe RR. Oral amino acids stimulate muscle protein anabolism in the elderly despite higher first-pass splanchnic extraction. The American journal of physiology. 1999;277(3 Pt 1):E513-20.
134. Katsanos CS, Kobayashi H, Sheffield-Moore M, Aarsland A, Wolfe RR. A high proportion of leucine is required for optimal stimulation of the rate of muscle protein synthesis by essential amino acids in the elderly. American journal of physiology Endocrinology and metabolism. 2006;291(2):E381-7. doi:10.1152/ajpendo.00488.2005.
135. Casperson SL, Sheffield-Moore M, Hewlings SJ, Paddon-Jones D. Leucine supplementation chronically improves muscle protein synthesis in older adults consuming the RDA for protein. Clinical nutrition. 2012;31(4):512-9. doi:10.1016/j.clnu.2012.01.005.

136. Kramer IF, Verdijk LB, Hamer HM, Verlaan S, Luiking YC, Kouw IW et al. Both basal and post-prandial muscle protein synthesis rates, following the ingestion of a leucine-enriched whey protein supplement, are not impaired in sarcopenic older males. Clinical nutrition. 2016. doi:10.1016/j.clnu.2016.09.023.
137. Gallagher JC, Rapuri PB, Smith LM. An age-related decrease in creatinine clearance is associated with an increase in number of falls in untreated women but not in women receiving calcitriol treatment. J Clin Endocrinol Metab. 2007;92(1):51-8. doi:10.1210/jc.2006-1153.
138. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. Osteoporos Int. 2009;20(2):315-22. doi:10.1007/s00198-008-0662-7.
139. Sato Y, Iwamoto J, Kanoko T, Satoh K. Low-dose vitamin D prevents muscular atrophy and reduces falls and hip fractures in women after stroke: a randomized controlled trial. Cerebrovasc Dis. 2005;20(3):187-92. doi:10.1159/000087203.
140. Brunner RL, Cochrane B, Jackson RD, Larson J, Lewis C, Limacher M et al. Calcium, vitamin D supplementation, and physical function in the Women's Health Initiative. J Am Diet Assoc. 2008;108(9):1472-9. doi:10.1016/j.jada.2008.06.432.
141. Bunout D, Barrera G, Leiva L, Gattas V, de la Maza MP, Avendano M et al. Effects of vitamin D supplementation and exercise training on physical performance in Chilean vitamin D deficient elderly subjects. Exp Gerontol. 2006;41(8):746-52. doi:10.1016/j.exger.2006.05.001.
142. Latham NK, Anderson CS, Lee A, Bennett DA, Moseley A, Cameron ID. A randomized, controlled trial of quadriceps resistance exercise and vitamin D in frail older people: the Frailty Interventions Trial in Elderly Subjects (FITNESS). J Am Geriatr Soc. 2003;51(3):291-9. doi:jgs51101 [pii].
143. Bergman GJ, Fan T, McFetridge JT, Sen SS. Efficacy of vitamin D3 supplementation in preventing fractures in elderly women: a meta-analysis. Curr Med Res Opin. 2010;26(5):1193-201. doi:10.1185/03007991003659814.
144. Bischoff-Ferrari HA, Willett WC, Orav EJ, Lips P, Meunier PJ, Lyons RA et al. A pooled analysis of vitamin D dose requirements for fracture prevention. N Engl J Med. 2012;367(1):40-9. doi:10.1056/NEJMoa1109617.
145. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. J Bone Miner Res. 2000;15(6):1113-8. doi:10.1359/jbmr.2000.15.6.1113.
146. Rennie MJ, Wackerhage H, Spangenburg EE, Booth FW. Control of the size of the human muscle mass. Annual review of physiology. 2004;66:799-828. doi:10.1146/annurev.physiol.66.052102.134444.
147. Hartman JW, Tang JE, Wilkinson SB, Tarnopolsky MA, Lawrence RL, Fullerton AV et al. Consumption of fat-free fluid milk after resistance exercise promotes greater lean mass accretion than does consumption of soy or carbohydrate in young, novice, male weightlifters. Am J Clin Nutr. 2007;86(2):373-81.
148. Sherrington C, Michaleff ZA, Fairhall N, Paul SS, Tiedemann A, Whitney J et al. Exercise to prevent falls in older adults: an updated systematic review and meta-analysis. Br J Sports Med. 2016. doi:10.1136/bjsports-2016-096547.
149. Boirie Y. Physiopathological mechanism of sarcopenia. The journal of nutrition, health & aging. 2009;13(8):717-23.

150. Cermak NM, Res PT, de Groot LC, Saris WH, van Loon LJ. Protein supplementation augments the adaptive response of skeletal muscle to resistance-type exercise training: a meta-analysis. Am J Clin Nutr. 2012;96(6):1454-64. doi:10.3945/ajcn.112.037556.