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Title

Vitamin D and muscle strength throughout the life course: a review of epidemiological and intervention studies

Running Head

Vitamin D and muscle strength

Authors

Elaine K. McCarthy[1] and Mairead Kiely[1, 2]

Institution

[1] Vitamin D Research Group, School of Food and Nutritional Sciences, University College Cork, Ireland and [2] The Irish Centre for Fetal and Neonatal Translational Research, University College Cork, Ireland.

Corresponding Author

Mairead Kiely, School of Food and Nutritional Sciences, University College Cork, Republic of Ireland. Email: m.kiely@ucc.ie, Phone: 00353214903394, Fax: 00353214270244.

Role of Authors

Both authors contributed equally to this review.

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Abstract

The putative role for vitamin D in muscle function and strength throughout the life course is of interest as muscle strength is required for engagement in physical activity at all ages. As vitamin D deficiency is widely reported in the population, especially in countries at high latitude, the potential importance of vitamin D in muscle function throughout life, and potential impacts on growth and development, participation in physical activity and effects on skeletal and cardio-metabolic health, is an important topic for discussion. This review provides an overview of muscle function and summarises the role of the vitamin D receptor and proposed molecular mechanisms of action of vitamin D in muscle cells. In addition, the review provides a comprehensive assessment of the clinical evidence surrounding the association between vitamin D and muscle strength. Among adults, particularly older adults, cross-sectional and cohort studies reported a positive association between vitamin D status and muscle strength. These associations have been largely confirmed by intervention studies. Limited research has been carried out in adolescents and children; two cross-sectional studies in adolescents have suggested an association between serum 25-hydroxyvitamin D concentrations and muscle strength. However, the two intervention studies in adolescents have yielded conflicting results. Other than a single observational study, data in young children are very limited and further investigation in under 12's is warranted.

Introduction

The adverse outcomes of vitamin D deficiency, such as nutritional rickets in children and adolescents and osteomalacia and osteoporosis in adults, are well-documented (Institute of Medicine, 2011). However, vitamin D deficiency has also been linked with muscle weakness in both children and adults, suggesting additional indirect benefits of vitamin D on skeletal health beyond its well-established role in calcium homeostasis (van der Heyden *et al.*, 2004). Muscle weakness, particularly affecting proximal muscles with symptoms such as delayed onset of walking in infants and difficulty climbing stairs in adolescents, is a clinical manifestation of vitamin D deficiency, which may coexist with skeletal features such as rickets and hypocalcaemia (Shaw and Mughal, 2013). The aim of this review is to examine the association between vitamin D and muscle strength throughout the life course, with a particular emphasis on the available clinical evidence.

Searches for this review were conducted in PubMed and Web of Science and terms (Mesh terms where applicable) included "Vitamin D" OR "Ergocalciferols" OR "Vitamin D Deficiency" OR "Cholecalciferol" OR "Vitamin D Receptor" AND "Muscles" OR "Muscle Strength" OR "Muscle Cells" OR "Muscle Development" OR "Muscle Weakness" OR "Genomic Pathway" OR "Non-genomic Pathway". A manual search of bibliographies of relevant primary journal articles was also conducted, with searches restricted to articles in English and citations up to June 2014.

A brief summary of some studies in older adults has been provided, including results from meta-analyses, as research into this area is well developed. For younger adults, adolescents and children, this review provides a complete and exhaustive review of all relevant studies on this topic to date.

Background

Vitamin D

Decreased serum 25-hydroxyvitamin D (25(OH)D) concentrations and vitamin D deficiency are widespread across the world with the highest rates of severe deficiency found in South Asia and the Middle East (van Schoor and Lips, 2011). In Europe, there is much variability in serum 25(OH)D concentrations; a recent systematic review from Hilger *et al.* (2014) reported that the highest concentrations in Europe were in Sweden. Serum 25(OH)D concentration is the most commonly

used, reliable and robust biomarker of vitamin D status (Seamans and Cashman, 2009). Currently, there is no consensus among experts as to the definitive threshold concentration for vitamin D deficiency. The US Institute of Medicine proposed that a serum 25(OH)D concentration of 50 nmol/L would cover the requirements 97.5% of the population for the maintenance of skeletal health and suggested a vitamin D deficiency cut-off value of 30 nmol/L (Institute of Medicine, 2011).

Serum 25(OH)D concentrations are dependent on various factors, mainly cutaneous production in the presence of UVB and dietary intake. There are a limited amount of foods containing naturally occurring vitamin D but some natural sources include oily fish, meat, dairy, egg yolk and mushrooms (Gonzalez-Rodriguez *et al.*, 2013) and depending on legislation, some foods are fortified with vitamin D, including milk, yoghurt, spreads, cheese, juices, breads and breakfast cereals (Kiely and Black, 2012). However it appears that dietary sources alone cannot supply an individual with all their vitamin D needs (Heaney *et al.*, 2003), with variations in vitamin D intakes from dietary sources occurring due to country specific fortification practices, sex, age, and supplement use practices (Cashman and Kiely, 2014). Therefore the cutaneous production of vitamin D is a major determinant of serum 25(OH)D concentrations and vitamin D status. However there are several environmental factors that impede year-round synthesis, such as latitude and prevailing weather conditions. Cutaneous production can also be affected by skin pigmentation, age, attire, sunscreen, working environment, physical activity and sun exposure behaviour (Kiely and Black, 2012).

Muscle Contraction and Muscle Function

To understand how vitamin D can impact on muscle function and strength, the mechanisms of action of muscle cells must be considered. Muscle cells are composed of subunits called myofibrils and each myofibril is composed of smaller structures called myofilaments. There are two main types of myofilament in muscle cells; thick filaments, composed of the protein myosin, and thin filaments, composed of the protein actin (Fox, 2009). Filaments are arranged within subunits known as sarcomeres; the fundamental functional units of muscle. The release of an action potential from the brain spreads into muscle fibres and causes a release of calcium ions (Ca^{2+}) from the sarcoplasmic reticulum into the nearby actin-myosin complex. Ca^{2+} binds to the protein troponin which results in excitation-contraction coupling of the muscle cell (Dulhunty, 2006). Within the myosin filament, an adenosine triphosphate (ATP) molecule is split by myosin ATPase enzymes and the release of a phosphate results in a conformational change in the myosin filament, causing a cross-bridge with actin to produce a power stroke. This power stroke results in the sliding of thick and thin filaments

over each other, also known as muscle contraction. The joining of a second ATP molecule to the myosin head results in the uncoupling of myosin and actin and thus muscle relaxation (Fox, 2009).

Is the vitamin D receptor present in muscle?

The active metabolite of vitamin D, 1,25 dihydroxyvitamin D ($1,25(OH)_2D$) elicits its effects on calcium homeostasis through a vitamin D receptor (VDR); $1,25(OH)_2D$ binds to the VDR on the cell cytosol resulting in a change in gene expression of that cell. VDR have now been located in more than 30 tissues in the body, not just tissues involved in calcium homeostasis (Zittermann, 2003). However, the presence of VDR in muscle tissue is still a debated topic. One of the earliest studies by Simpson *et al.* (1985) in cultured rat muscle cells suggests that $1,25(OH)_2D$ can act directly on muscle through a VDR that is similar to the receptors found in bone and the intestines. Boland *et al.* (1985) demonstrated the presence of VDR in monolayers of chick myoblasts and Costa *et al.* (1986) demonstrated similar results in cloned human skeletal muscle cells. In a study using VDR gene-deleted mice, Endo *et al.* (2003) demonstrated that the absence of VDR in these mice caused muscle abnormalities, supporting the hypothesis of physiological roles of direct VDR actions on skeletal muscle cells. Studies by Bischoff *et al.* (2001), Bischoff-Ferrari *et al.* (2004a) and more recently Ceglia *et al.* (2010) have demonstrated the presence of VDR in skeletal muscle cells using human muscle cell samples. However, Wang and DeLuca (2011) have contradicted earlier findings demonstrating that VDR were not detected in skeletal, smooth or cardiac muscle, using human, mouse and rat muscle tissues. They suggest that the function of vitamin D on muscle does not involve this receptor and may be of an indirect nature. Despite some debate, it is widely thought that VDR are located in muscle cells and that the VDR acts as a mediator for $1,25(OH)_2D$ to elicit its effects on muscle, however this is a point that requires further clarification.

Three adjacent restriction fragment length polymorphisms for *BsmI*, *ApaI*, and *TaqI* at the 3′ end of the VDR gene have been extensively studied (Uitterlinden *et al.*, 2004). Most studies that have looked at musculoskeletal health have focused on the *BsmI* polymorphism. Geusens *et al.* (1997) assessed quadriceps strength in 501 elderly women and those with the *bb* allele had maximal isometric strength 23% higher than those with the *BB* allele and 12% higher than those with the *Bb* allele. However, no such association was found by Windelinckx *et al.* (2007) in 493 adults in Belgium. Other studies have identified the risk of falling as a measure of muscle strength. Results from the ilSIRENTE study of 259 elderly men and women, found an association between the *bb* allele of the *BsmI* polymorphism and a reduced risk of falling compared to those with the *BB* allele (Onder *et al.*, 2008). Similar results

were subsequently reported by Barr *et al.* (2010) in 2374 elderly women. These studies suggest that an association between certain VDR gene polymorphisms and muscle strength may exist. However, further research is required to confirm these findings and to provide further understanding of the role of VDR genetic polymorphisms in muscle function and strength.

Molecular mechanisms of action of vitamin D in muscle tissue

The mechanisms through which vitamin D can influence muscle function and strength are still unclear but it is thought that there are two main pathways through which $1,25(OH)_2D$ functions: the genomic pathway and the non-genomic pathway. Once $1,25(OH)_2D$ has been transported to the nucleus of a muscle cell, it can elicit a slow, genomic transcriptional effect through binding to VDR, causing destabilization of a VDR complex in the VDR response element in the promoter region of a gene. At the same time as this destabilization and in the presence of the retinoic receptor (RXR), the formation of the VDR–RXR heterodimer occurs (Cheskis and Freedman, 1994). This heterodimer can then promote an interaction between the VDR's zinc finger region and DNA, resulting in mRNA transcription and ultimately *de novo* protein synthesis (Freedman, 1999). The synthesis of proteins including the calcium binding proteins calmodulin and calbindin D_{9K} can be altered by the genomic pathway of $1,25(OH)_2D$. These proteins are usually involved in muscle cell calcium uptake, muscle cell proliferation and differentiation and phospholipid metabolism (Ceglia, 2008).

The rapid, non-genomic effects of $1,25(OH)_2D$ are also thought to be mediated by VDR, as the presence of $1,25(OH)_2D$ in muscle cells can induce the translocation of nuclear VDR into the plasma membrane of cells (Capiati *et al.*, 2002). Non-genomic effects of $1,25(OH)_2D$ involve the activation of a number of cell signalling pathways including protein kinase C, calmodulin-dependent kinase and many others. Calcium homeostasis is affected by the non-genomic pathway, as the actions of $1,25(OH)_2D$ can result in a rapid influx of calcium from the sarcoplasmic reticulum which can play a role in regulating muscle cell contractions. Non-genomic effects of $1,25(OH)_2D$ also include the stimulation of proliferation and differentiation of muscle cells, protection of skeletal muscle cells from insulin resistance and induction of the release of arachidonic acid which can alter cell membrane fluidity and permeability (Dirks-Naylor and Lennon-Edwards, 2011). Although many of the non-genomic effects of $1,25(OH)_2D$ have been well described, there is still uncertainty as to how important these pathways are in the body and as to how exactly vitamin D acts in muscle cells.

Effects of vitamin D deficiency on muscle

Vitamin D deficiency (25(OH)D < 30 nmol/L) can have adverse effects in both skeletal and cardiac muscle cells. Dilated cardiomyopathy (DCM), secondary to severe vitamin D deficiency and hypocalcaemia, is a potentially fatal condition affecting cardiac muscle cells. In a review of the prevalence of DCM in paediatric cardiology units in Southeast England, 16 cases of rickets-associated heart failure were seen over a six-year time frame. Of these 16 cases, six of the infants had a cardiac arrest, two were referred for cardiac transplantation and a further three died. Predisposing factors leading to the severe vitamin D deficiency that resulted in DCM were dark skin and exclusive prolonged breastfeeding, with the majority of cases presenting during British wintertime. None of the infants or their mothers took vitamin D or calcium supplements during the pre- or postnatal period, however maternal serum 25(OH)D concentrations were not reported in many cases (Maiya *et al.*, 2008). Subsequent case studies from Brown *et al.* (2009), Al Azkawi and Al Mutair (2012) and Sanyal and Raychaudhuri (2013) reported of infants presenting with DCM; further analysis revealed that they had rickets and severe hypocalcaemia due to vitamin D deficiency. Treatment with calcium and vitamin D resulted in a rapid recovery of cardiac function in most cases.

The focus of this review is vitamin D and skeletal muscle. Muscle weakness and pain are characteristics of rickets and osteomalacia. A detailed review of symptomatic vitamin D deficiency and rickets as well as muscle-related symptoms in affected children and adolescents, including reluctance to bear weight, pain and weakness has been provided by Shaw and Mughal (2013). Likewise in adults, muscle pain and weakness are also symptoms of vitamin D deficiency, which can result in more specific proximal muscle deficits, including an inability to climb stairs, lift objects or rise from a seated/squat position (Girgis *et al.*, 2013). Findings of muscle weakness and pain in the bone diseases rickets and osteomalacia are unsurprising; muscle and bone growth and development are closely connected. Muscle is the main mechanical stimulus for bone tissue growth and development as they cause the largest load and strain on bone and this strain is essential for control of the biological mechanisms determining whole-bone strength (Frost and Schonau, 2000). Much research is still required as little is known about the cellular interactions between muscle and bone, with a need to investigate muscle and bone interactions together as opposed to looking at each tissue separately (Bonewald *et al.*, 2013).

Given the close interaction between muscle and skeletal development, there is a dearth of information on interactions between vitamin D status and bone and muscle development in children. Among older adults, the clinical observational and experimental literature is relatively well developed albeit controversial.

Older Adults

Many of the studies performed in older adults have used lower extremity function tests to assess muscle strength, including walking speed/gait tests, chair stands and tandem tests. Handgrip strength and thigh muscle strength as measured by a dynamometer have also been used. An adverse health consequence of poor muscle strength or muscle weakness in older adults is the increased risk of falling. Lean mass as measured using techniques including dual energy x-ray absorptiometry (DXA) has also been studied, with some studies suggesting a positive association between it and serum 25(OH)D concentrations (Lee, 2013). However, the focus of this review is on vitamin D and its effects on measures of muscle strength and function, not on the size of muscles. In a large sample of 4100 men and women aged ≥60 years, Bischoff-Ferrari *et al.* (2004b) showed better lower extremity functioning in adults with serum 25(OH)D concentrations ≥40 nmol/L compared with those with 25(OH)D concentrations <40 nmol/L. Similarly, Wicherts *et al.* (2007) found in 1234 men and women (mean age 75 years) that 25(OH)D concentrations <50 nmol/L were associated with lower scores for lower extremity functioning and a greater decline in physical performance over the three-year study. While 25(OH)D concentrations of 80 nmol/L or above have been suggested by some investigators (Dawson-Hughes, 2008, Dam *et al.*, 2009) as optimal to promote muscle function in older adults, findings from observational studies have suggested that a serum 25(OH)D concentration of less than 50 nmol/L appears to detrimentally affect muscle function and strength.

Findings from intervention studies in older adults are conflicting despite a multitude of literature in this age group. Flicker *et al.* (2005) randomised 625 adults (mean age 83 years) to receive either placebo or vitamin D_2 (10,000IU [250µg] once weekly initially and then 1,000IU daily) plus 600mg calcium for two years. Those compliant with the vitamin D treatment had a reduced incidence of falls compared to the placebo group, regardless of baseline 25(OH)D concentrations. Pfeifer *et al.* (2009) randomised 242 adults (mean age 77 years) to receive either 1000mg calcium or 1000mg calcium plus 800IU vitamin D_3 daily for 12 months. Vitamin D plus calcium supplementation significantly reduced the number of falls in participants compared to the calcium only treatment group and significant improvements in measures of muscle strength (quadriceps strength, lower extremity

functioning) were also reported in the vitamin D treatment group. Zhu *et al.* (2010) randomised 302 women (aged 70-90 years) to receive either 1000IU vitamin D_2 plus 1000mg calcium or just 1000mg calcium daily for one year. Increased muscle function (maximal contraction of various muscle types) was observed in those in the lowest tertile for baseline muscle strength in this group of women with baseline 25(OH)D concentrations <60 nmol/L.

Conflicting findings were reported in a study of 243 older adults by Latham *et al.* (2003); participants were randomised to receive a single oral dose of 300,000IU vitamin D_3 or placebo and muscle strength (lower extremity functioning) was assessed six months after supplementation. There were no improvements in muscle strength measures after supplementation, even in those with 25(OH)D concentrations <30 nmol/L at baseline. Janssen *et al.* (2010) randomised 70 females aged >65 years with baseline 25(OH)D concentrations <50 nmol/L to receive either 400IU vitamin D_3 plus 500mg calcium or placebo plus 500mg calcium daily for six months. Despite observing significant positive associations between 25(OH)D concentrations and muscle strength at baseline, there were no improvements in muscle strength in either treatment group after six months. Glendenning *et al.* (2012) randomised 686 women (mean age 77 years) to receive 150,000IU vitamin D_3 or placebo every three months for nine months. Vitamin D supplementation was ineffective in reducing the number of falls in these women (mean baseline 25(OH)D of 65.8 nmol/L). The high-dose intermittent supplementation regimen used in this study and by Latham *et al.* (2003) may explain the lack of effect on muscle strength as it has been suggested that high-dose supplementation may alter gene regulation and negate any beneficial effects of vitamin D on muscle metabolism. Similar findings on dose regimen have been reported in a meta-analysis from Muir and Montero-Odasso (2011) where the authors suggest that supplemental daily doses of 800-1000IU of vitamin D demonstrate beneficial effects on muscle strength consistently, with inconsistent findings for high-dose treatments.

The heterogeneity of studies in older adults carried out to date as highlighted here, have made it difficult to draw conclusions from their results, as differences exist in the study populations assessed, treatment durations, muscle strength measures, doses and types of vitamin D used and the use of additional supplementation including calcium. These issues were highlighted in the recent report from the US Institute of Medicine and it declared that there was inconsistent evidence that vitamin D supplementation reduced the risk of falling in older adults (Institute of Medicine, 2011). This finding is in contrast to many earlier studies including a meta-analysis by Bischoff-Ferrari *et al.* (2009) that observed a 19% reduction in falls with daily vitamin D supplementation of 700-1000IU. However,

the Institute of Medicine did claim that this particular meta-analysis was flawed in its choice of studies and its method chosen to explain the heterogeneity of studies. Despite these conflicting arguments, further meta-analyses have suggested that daily vitamin D plus calcium supplementation can improve muscle strength and reduce the risk of falls, especially in individuals with 25(OH)D concentrations <25 nmol/L (Stockton *et al.*, 2011, Murad *et al.*, 2011). Further large randomised controlled trials with standardised muscle strength measures are required to clarify the issues surrounding the role of vitamin D in muscle strength in older adults.

Young Adults

Until recently, much less research had been conducted in younger adults. A recent observational study by Grimaldi *et al.* (2013) in 419 adults (mean age 44 years, 8% had 25(OH)D <50 nmol/L), observed a positive association between 25(OH)D concentrations and muscle strength, most notably for arm muscles. A smaller study of 137 women aged 19 to 29 years (mean 25(OH)D of 54 nmol/L) also found a significant positive association between 25(OH)D concentrations and muscle strength (handgrip strength) (von Hurst *et al.*, 2013). Similar findings were reported in a very small study (*n* 22) of Muslim women living in Canada with mean 25(OH)D concentrations of 36 nmol/L (Ojah and Welch, 2012). Contrastingly, no association between 25(OH)D concentrations and muscle strength was found in a study of 1219 men (mean age 48 years) by Ceglia *et al.* (2011). Reasons for these conflicting findings may be because the study population assessed by Ceglia *et al.* (2011) only consisted of males and the age range of participants was very broad (30-70 years), which is in contrast to the population groups assessed in other studies.

Diamond *et al.* (2013) randomised 30 adults (25(OH)D at baseline <50 nmol/L) to receive either 2000 or 5000IU vitamin D_3 daily for three months; improvements in handgrip strength were observed in both treatment groups. In India, 40 adults (mean age 31 years, 25(OH)D at baseline <50 nmol/L) were randomised to receive either placebo or 60,000IU vitamin D_3 per week for the first eight weeks, followed by 60,000IU vitamin D_3 per month for four months plus 1000mg calcium daily for six months. Muscle strength (handgrip/thigh muscle strength, lower extremity functioning) increased significantly higher in the supplemented group compared to the placebo group (Gupta *et al.*, 2010). However in a similar study performed subsequently by the same research group in 173 females (mean age 22 years), no significant change in muscle strength was observed following vitamin D and calcium supplementation (Goswami *et al.*, 2012). A reason for the lack of an effect may be that vitamin D and calcium supplementation does not improve handgrip strength in young adult females,

as when results from their earlier study were reanalysed by sex, it revealed that improvements in handgrip strength occurred only in males. In a study of non-Western immigrant adults in Norway (mean 25(OH)D at baseline of 27 nmol/L), supplementation of 400 or 1000IU vitamin D_3 daily for 16 weeks did not improve muscle strength (handgrip strength, jump height) (Knutsen *et al.*, 2014). Similar findings were also reported by Wicherts *et al.* (2011) in a study of non-Western immigrant adults in The Netherlands. Contrastingly, a study in male athletes by Close *et al.* (2013) reported significant increases in muscle strength (jump height, endurance tests) after an eight-week intervention of 5000IU vitamin D_3 daily, in the treatment group compared to the placebo group.

Similarly to the findings in older adults, there are conflicting findings regarding younger adults, albeit less research has been conducted in this age group. There is a need for further long-term intervention studies in this age group in both males and females to determine the role of vitamin D in muscle strength during early adult life.

Adolescents and Children

Currently, there are limited data available on the role of vitamin D in muscle strength in adolescents and children and most of the data that are available are in older children or adolescents (Table 1). In an observational study of 99 post-menarchal females (aged 12-14 years), a positive association between 25(OH)D concentrations and muscle strength (jumping mechanography) was observed. Those with lower 25(OH)D concentrations generated less power during jumping and had lower jump height and velocity (Ward *et al.*, 2009). In another study of 301 females aged 15 years in China, participants with 25(OH)D concentrations >50 nmol/L had significantly greater handgrip strength compared to those with lower 25(OH)D concentrations, independent of body size, dietary intakes of vitamin D and calcium and levels of physical activity (Foo *et al.*, 2009).

El-Hajj Fuleihan *et al.* (2006) randomised 179 females aged 10-17 years (mean 25(OH)D at baseline of 35 nmol/L) to receive either 1400IU vitamin D_3 per week (low dose), 14,000IU vitamin D_3 per week (high dose) or a placebo weekly for one year. There were significant increases in lean mass (measured by DXA) in both the low and high dose treatment groups compared to the placebo group, despite no significant change in handgrip strength between the treatment groups. The changes in lean mass observed in this study perhaps suggest a direct effect of vitamin D on muscle size, however the lack of effect on handgrip strength may indicate that this measure is not sensitive enough to detect

slight changes in muscle strength in children and adolescents. Seventy-three 12-14 year old females (25(OH)D at baseline <37.5 nmol/L) were randomised to receive either 150,000IU vitamin D_2 or a placebo every three months for 12 months. Mixed findings for muscle strength (jumping mechanography, handgrip strength) were observed, with improved jumping efficacy observed in the treatment group, but not jump power or force or handgrip strength (Ward *et al.*, 2010). These mixed findings for muscle strength may be explained by the suggestion by Glendenning *et al.* (2012) that intermittant high-dose supplementation may alter gene regulation and negate any beneficial effects of vitamin D on muscle metabolism. The very limited evidence from intervention studies in adolescents and older children have produced conflicting findings. Further research is required in this age group and in younger children to determine if vitamin D can impact on muscle strength in early childhood. The focus of research should be to perform large randomised controlled trials in both males and females, providing daily/weekly vitamin D supplementation at a dose that will not have adverse health effects.

Recently the relationship between intrauterine 25(OH)D exposure and muscle strength in children has been explored. A study from the Southampton Women's Survey reported a significant positive association between maternal 25(OH)D concentrations at 34-weeks' gestation and height adjusted-handgrip strength in their four-year old children (Harvey *et al.*, 2014). Findings from this study suggest that childhood muscle strength may also be influenced by maternal vitamin D status during pregnancy, suggesting the possibility of an early programming effect.

Conclusion

Vitamin D deficiency is now widely recognised as a public health problem of growing concern, particularly for populations at increased risk due to high latitude, prolonged winter season, or other reasons for restricted UVB exposure and low vitamin D intake. Apart from the acknowledged links between muscle myopathy and nutritional rickets and osteomalacia, there is evidence for a biological role for vitamin D in muscle function. Much of the clinical studies have focused on older adults, where an association between serum 25(OH)D concentrations below 50 nmol/L and reduced muscle strength appears to be inconsistent. Data among younger adults and adolescents are few and conflicted. Partly due to the challenges involved in measuring muscle strength in young children, where methods such as jumping mechanography and lower extremity function tests can be difficult to perform and replicate, the data in children are few and far between. New approaches to assess

muscle strength in young children are required. Due to these difficulties and some inconsistent findings, clinical guidelines on vitamin D for muscle strength and function are limited. Current population guidelines regarding vitamin D are to avoid deficiency with the aim to have vitamin D intakes at the level of the Recommended Dietary Allowance (RDA) set by the national governing authority. Despite recommendations, suboptimal serum 25(OH)D concentrations amongst adolescents and children have been reported all around the world, including India (Marwaha *et al.*, 2005), the Middle East (El-Hajj Fuleihan *et al.*, 2006), North America and Canada (Newhook *et al.*, 2009, Sullivan *et al.*, 2005), Ireland (Hill *et al.*, 2008), the UK (Absoud *et al.*, 2011) and throughout Europe (Gonzalez-Gross *et al.*, 2012). Therefore, the potential importance of vitamin D in muscle function and strength throughout life, impacting on normal growth and development, participation in physical activity and concomitant impacts on skeletal and cardio-metabolic health, is an important topic for discussion. The aim of future research should be to further assess the importance of adequate serum 25(OH)D concentrations throughout the life course in the development of muscle and maintenance of physical performance.

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599 **Table 1** Vitamin D and muscle strength in children and adolescents

Study	No. of Subjects	Age	Sex	Muscle Strength Measure	Treatment Regimen	Main Outcomes
Cross-sectional						
Ward *et al.*, 2009	99	12-14y	Female	Jumping Mechanography	Not Applicable	Significant positive association between 25(OH)D concentrations and muscle power, force, velocity and jump height.
Foo *et al.*, 2009	301	15y	Female	Handgrip strength	Not Applicable	Participants with 25(OH)D concentrations >50 nmol/L had significantly greater handgrip strength compared to those with lower 25(OH)D concentrations.
Harvey *et al.*, 2014	678	4y	Male Female	Handgrip strength	Not Applicable	Significant positive association between maternal 25(OH)D concentrations at 34-weeks' gestation and handgrip strength in their four-year old children.
Intervention						
El-Hajj Fuleihan *et al.*, 2006	179	10-17y	Female	Handgrip strength	1400IU vitamin D_3 or 14,000IU vitamin D_3 or placebo weekly for 1 year	No significant improvements in handgrip strength in either of the vitamin D treatment groups.
Ward *et al.*, 2010	73	12-14y	Female	Jumping Mechanography, Handgrip strength	150,000IU vitamin D_2 or placebo every 3 months for 12 months	Improved jumping efficacy in the vitamin D treatment group, but no improvements in jump power, force or handgrip strength.

600 25(OH)D, serum 25-hydroxyvitamin D; IU, international units