Chapter 8
Vitamin D and Ageing

Tom R. Hill, Antoneta Granic, and Terence J. Aspray

Abstract One hundred years has passed since the discovery of vitamin D as the active component of cod-liver oil which cured the bone disease rickets. Since then our knowledge of vitamin D has expanded tremendously and has included recognition of the importance of UV radiation as a source of the vitamin as well as the discovery of the vitamin as a nutrient, a pro-hormone and a potent steroid hormone with a major role in calcium and bone metabolism. In the last 25 years or so, the discovery of the vitamin D receptor in over 30 different body tissues together with the existence of the alpha-1-hydroxylase enzyme in these tissues provided evidence of a pleiotropic role of vitamin D outside its classical role in the skeleton. These important discoveries have provided the basis for the increasing interest in vitamin D in the context of nutritional requirements for health including the prevention of chronic diseases of ageing. The recent publication of the Dietary Reference Intake

T. R. Hill (✉)
Human Nutrition Research Centre, Newcastle University, Newcastle Upon Tyne, UK

Institute of Cellular Medicine, Newcastle University, Newcastle Upon Tyne, UK

Institute of Ageing, Newcastle University, Newcastle Upon Tyne, UK
e-mail: Tom.Hill@newcastle.ac.uk

A. Granic
Institute of Neuroscience, Newcastle University, Newcastle Upon Tyne, UK

Institute of Ageing, Newcastle University, Newcastle Upon Tyne, UK

NIHR Newcastle Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle University, Newcastle Upon Tyne, UK
e-mail: antoneta.granic@ncl.ac.uk

T. J. Aspray
Institute of Cellular Medicine, Newcastle University, Newcastle Upon Tyne, UK

The Bone Clinic, Freeman Hospital, Newcastle Upon Tyne, UK

Institute of Ageing, Newcastle University, Newcastle Upon Tyne, UK

NIHR Newcastle Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle University, Newcastle Upon Tyne, UK
e-mail: terry.aspray@ncl.ac.uk

J. R. Harris, V. I. Korolchuk (eds.), *Biochemistry and Cell Biology of Ageing: Part I Biomedical Science*, Subcellular Biochemistry 90,
https://doi.org/10.1007/978-981-13-2835-0_8

report on vitamin D and calcium by the North American Institute of Medicine (IOM) is the most comprehensive report to date on the basis for setting nutritional requirements for vitamin D. This chapter will summarize the nutritional aspects of vitamin D and discuss the changes in vitamin D metabolism and requirements with ageing. It will summarize key evidence on the relationship between vitamin D status and some of the main ageing related health outcomes including bone, muscle and cognitive health as well as survival focusing on the published literature in very-old adults (those >= 85 years of age).

Keywords Vitamin D · Very-old adults · Metabolism and function · Nutritional requirements · Epidemiology · Musculoskeletal health · Cognitive health · Mortality

Vitamin D Metabolism and Function

The term 'vitamin D' was given during the early 1920's to a group of closely-related secosteroids with antirachitic properties. Two of the most important nutritional forms of vitamin D are cholecalciferol (vitamin D_3, derived from animal origin) and ergocalciferol (vitamin D_2, derived from plant origin). However, natural dietary sources of vitamin D are limited with oily fish, egg yolk and meat contributing up to 90% of vitamin D intake from non-fortified food sources (Hill et al. 2004). Vitamin D_3 and D_2 can also be derived by photoirradiation from their precursors 7-dehydrocholesterol and ergosterol, respectively. In vertebrates, the cholesterol-like precursor, 7-dehydrocholesterol, present in the skin epidermis, undergoes photolysis when exposed to UV-B-light of wavelengths 290–315 nm to yield a variety of photoirradiation products including tachysterol, lumisterol and previtamin D_3. Previtamin D_3 then undergoes spontaneous thermal rearrangement to vitamin D_3. Because of the skin's ability to synthesise the vitamin upon exposure to appropriate sunlight, vitamin D is only an essential nutrient when sunlight is limited.

Vitamin D_3 (obtained from dermal synthesis or from dietary sources), which is biologically inactive, is transported via vitamin D binding protein (DBP) to the liver where it is hydroxylated at the C-25 position by the 25-hydroxylase enzyme [CYP2R1] to yield 25-hydroxyvitamin D_3 [25(OH)D or calcidiol] which is the most commonly used index of vitamin D status (Ross et al. 2010). The CYP2R1 enzyme regulates 25-hydroxylation of vitamin D_3 to produce $25(OH)D_3$, which is dependent on the concentrations of vitamin D_3 in circulating/plasma. From the liver, $25(OH)D_3$ is returned to the circulation, bound to DBP, and transported to the kidney where the enzyme 1-α-hydroxylase [CYP27B1] converts it to 1,25-dihydroxycholecalciferol ($1,25(OH)2D3_3$ or calcitriol), which is the major active metabolite of vitamin D. When $1,25(OH)2D3_3$ is in excess, the enzyme 24-hydroxylase (CYP24) in the kidney converts $25(OH)D_3$ to 24,25-dihydroxycholecalciferol, which is believed to be biologically inactive. Furthermore, $25(OH)D_3$ can be converted to other inactive metabolites such as 23,25-dihydroxycholecalciferol, 25,26-dihydroxycholecalciferol and 1,24,25-trihydroxycholecalciferol and

excreted mainly in faeces, but the biological roles of these metabolites are not well understood [for reviews, *see* Horst and Reinhardt 1997; Holick 2003].

The major biological role of $1,25(OH)2D3_3$ is to promote intestinal calcium absorption. In addition, $1,25(OH)2D3_3$ increases the absorption of other essential minerals across the intestine, such as phosphorus, magnesium, zinc and manganese (Biehl et al. 1995; Krejs et al. 1983), and enhances the net renal reabsorption of calcium and phosphorus (Singh and Dash 1997). Thus, $1,25(OH)_2D3_3$ is a major regulator of calcium homeostasis. The classical target organs for $1,25(OH)_2D_3$ are the intestine, bone, the kidneys and the parathyroid glands however, $1,25(OH)_2D_3$ also acts at several sites in the body in an intracrine or paracrine manner (White 2012). Normal physiological concentrations of calcium are required for proper neuromuscular and cellular functions. Low circulating calcium (hypocalcaemia) stimulates the secretion of parathyroid hormone (PTH) from the parathyroid gland, which, in turn, enhances the conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$. $1,25(OH)_2D_3$ acts on the intestine, kidneys and bone to restore normal circulating calcium concentrations. In addition to PTH, it is also well recognised that other hormones, such as calcitonin, glucocorticoids, growth hormones and sex steroids regulate the production of $1,25(OH)_2D_3$ (Lal et al. 1999). In addition to its classical role in the skeleton, a number of key hydroxylase enzymes together with Vitamin D Receptors (VDR) have been identified in over 30 different extra-skeletal tissues suggesting an important regulatory role of vitamin D in these target tissues (Lal et al. 1999). Furthermore, data from epidemiological and (some) intervention studies have provided fascinating and really exciting hypotheses about relationships between vitamin D status and risk of several chronic conditions [including multiple sclerosis, tuberculosis, rheumatoid arthritis, cardiovascular disease, hypertension, cognitive decline, lung conditions and certain cancers; [for reviews *see* Ross et al. 2010; Wang 2009]. The biological actions of 1,25(OH)2D3 in target tissues are mediated either through:

(i) a nuclear vitamin D receptor (VDR), which, once complexed with $1,25\ (OH)_2\ D_3$ and retinoic acid receptors (RXR), can regulate gene expression (genomic effects),
(ii) intra-cellular signalling pathways activated through putative plasma membrane receptors (non-genomic effects) (Lal et al. 1999).

It is well established that $1,25(OH)_2D_3$ is essential for the normal growth and development of bone. In bone cells, $1,25(OH)_2D_3$ acts on osteoblasts to increase osteoclastogenesis and bone resorption which contribute to mineral homeostasis (Turner et al. 2012). The discovery of the molecular triad of receptor activator of nuclear factor kappa (RANK), RANK–ligand (RANKL) and osteoprotegerin (OPG) [RANK/RANKL/OPG] in the 1990's represented a significant breakthrough in the understanding of the pathophysiology of bone remodelling [for review *see* Theoleyre et al. 2004]. RANK, on the surface of osteoclasts binds to its ligand (RANKL) present on surface of osteoblasts following their stimulation by $1,25(OH)_2D_3$. Binding of RANK to RANKL initiates the maturation of osteoclasts and is enhanced by the antagonistic effect of $1,25(OH)_2D_3$ on the protein OPG. As OPG normally binds RANKL, it prevents binding to RANK therefore inhibiting osteoclast maturation. It should be noted that $1,25(OH)_2D_3$ also regulates the transcription of a number of

key osteoblastic genes such as those coding for the bone proteins osteocalcin, osteopontin, osteonectin and proteoglycan (Martin and Seeman 2008).

Changes in Vitamin D Metabolism with Ageing

Calcium Absorption

Calcium is absorbed from the bowel by an active vitamin D dependent transport mechanism and by passive diffusion. The active transport mechanism plays an important role in calcium homeostasis, as the amount absorbed is inversely related to dietary calcium intake (Ireland and Fordtran 1973). Fractional calcium absorption therefore increases when dietary calcium intake is reduced (Dawson-Hughes et al. 1993). Calcium absorption decreases with advancing age (Bullamore et al. 1970), which has been attributed to a number of mechanisms, including the reduction in circulating 25(OH)D with age (Baker et al. 1980), impaired hydroxylation of 25(OH)D to $1,25(OH)_2D_3$ with declining renal function (Francis et al. 1984), resistance to the action of vitamin D metabolites on the bowel mucosa (Eastell et al. 1991) and low circulating oestrogen concentrations in women after the menopause (Heaney et al. 1989). Increasing circulating 25(OH)D concentrations by oral vitamin D supplementation improves calcium absorption in older women, but this is attenuated by renal impairment (Francis et al. 1983), suggesting that lower levels of substrate circulating 25(OH)D) and impaired hydroxylation of 25(OH)D to $1,25(OH)_2D_3$ both contribute to the decrease in calcium absorption with age. Despite the inverse relationship between dietary calcium intake and calcium absorption, the increase in calcium absorption when dietary calcium is reduced is less marked in older people than younger adults (Ireland and Fordtran 1973). This may be due to reduced production of $1,25(OH)_2D_3$, but it may also reflect resistance to the actions of vitamin D metabolites on the bowel, as some studies have shown an attenuated response in calcium absorption to increases in $1,25(OH)_2D_3$ in older women (Eastell et al. 1991). Although the decline in calcium absorption with advancing age is multifactorial in origin, the improvement in absorption with vitamin D supplementation suggests that vitamin D deficiency is the major cause of malabsorption of calcium in older people (Francis et al. 1983). The positive relationship between circulating 25(OH)D and fractional absorption extends to 25(OH)D concentrations above 100 nmol/L (Francis et al. 1983; Gallagher et al. 2012), leading some experts to advocate that these concentrations are necessary for optimal bone health. Nevertheless, although a recent randomised controlled trial comparing the effect of different doses of vitamin D showed higher calcium absorption in subjects with a circulating 25(OH)D of 75 nmol/L than those with 50 nmol/L, the magnitude of the difference was small (Gallagher et al. 2012).

Renal 1 α Hydroxylase

Renal function declines with advancing age and this is accompanied by a decrease in circulating $1,25(OH)_2D_3$ concentration (Epstein et al. 1986). As mentioned above, the effect of vitamin D supplementation on calcium absorption is attenuated by renal impairment (Francis et al. 1983). An early study showed that as glomerular filtration rate (GFR) falls below 50 ml/min, there is a reduction in circulating $1,25(OH)_2D_3$ and lower fractional absorption of calcium (Francis et al. 1984), together with an increased circulating parathyroid hormone (PTH). Other studies show an inverse relationship between circulating 25(OH)D and PTH across all adult age groups, but that PTH is higher in older people than young adults for any given circulating 25(OH)D concentration (Vieth et al. 2003) possibly due to reduced renal 1 α hydroxylation.

Dermal Vitamin D Production

The dermal capacity to produce vitamin D in persons aged 65 years has been estimated to be about 25% of that in persons aged 20–30 years exposed to the same amount of sunlight (Holick et al. 1989; MacLaughlin and Holick 1985). This reduction cannot be explained by the decrease in mass of the epidermis with ageing, but rather seems to be related to the reduction in the concentration of skin 7-dehydrocholesterol. Other indirect factors which affect exposure to sunlight in older adults include the wearing of more concealing clothing (Matsuoka et al. 1992), an increased use of sunscreen (Holick 1994), and reduced sun exposure, arising from less physical activity and time outdoors compared with younger age groups (Health Survey for England 2008).

Changes in VDR Numbers

Vitamin D deficiency is associated with muscle weakness which potentially increases the risk of falls and fractures, possibly mediated through effects on $1,25(OH)_2D_3$ receptors which have been discovered in muscle (Simpson et al. 1985; Bischoff et al. 2001). Bischoff-Ferrari et al. demonstrated a strong negative correlation between age and VDR expression in muscle as measured by the number of VDR-positive nuclei per 500 counted nuclei (Bischoff-Ferrari et al. 2004). This association was independent of biopsy location and circulating 25(OH)D concentrations. This finding may have significant clinical ramifications in older age owing to the importance of $1,25(OH)_2D_3$ in regulating transcription of muscle related genes. The role of vitamin D in muscle atrophy in older adults has been reviewed by Dawson- Hughes (2012) and will be discussed later in this chapter.

Nutritional Aspects of Vitamin D

Assessment of Vitamin D Status

Circulating 1,25(OH)2D3$_3$ concentrations are under homeostatic control, which limits its value as a nutritional marker of vitamin D status (Ross et al. 2010). However, circulating or plasma total 25(OH)D [i.e. that derived from adding 25(OH)D_2 and 25(OH)D_3] concentration is widely accepted as a good biomarker of vitamin D status, since the concentration of this metabolite closely reflects the amount of vitamin D synthesized in the skin and ingested in the diet (Ross et al. 2010). During winter, in countries of latitudes greater than 40° North or South the skin is incapable of synthesizing vitamin D for 4–5 months of the year as sunlight must pass a much longer distance through the atmosphere and most UV-B-light is absorbed by the atmosphere, preventing any effective UV irradiation of the skin (Webb et al. 1988). Therefore, it is assumed that during winter the circulating 25(OH)D concentration is directly related to late-summer concentrations, oral intake and body stores of its precursor vitamin D_3. While circulating 25(OH)D is generally regarded as a good biomarker of exposure [i.e. that derived from sun and diet], its use as a biomarker of function and outcome is less clear owing to the multitude of factors influencing this prohormone (Prentice et al. 2008). Notwithstanding such difficulties, the concentration of 25(OH)D is widely used to diagnose vitamin D deficiency in both the clinical and non-clinical settings.

Dietary Vitamin D Requirements and Vitamin D Intakes

Using the risk-assessment framework commonly used to set Upper Levels for nutrients, the Institute of Medicine (IOM) in their recent Dietary Reference Intake (DRI) report (Ross et al. 2010) set a 25(OH)D concentration of 30 nmol/L as indicative of vitamin D deficiency based on integrating a number of key bone health outcomes, including rickets, osteomalacia, impaired calcium absorption and lower BMD. The nature of the relationship between 25(OH)D concentration and bone health outcomes will be discussed in detail later in this review. It is noteworthy that the IOM committee concluded that there was insufficient evidence to define vitamin D deficiency based on non-skeletal outcomes. Based on the relationship between 25(OH)D status and those aforementioned bone health outcomes, and using both data from epidemiological and intervention studies, the IOM established a population 25(OH)D concentration of 40 nmol/L and 50 nmol/L as the basis for setting an Estimated Average Requirement (EAR) of 10 μg/day and a Recommended Daily Allowance (RDA) of 15 μg/day, respectively in people aged 1–70 years. The IOM set an RDA of 20 μg/day for individuals aged >70 years, while it could only establish an Adequate Intake (AI) of 5 μg/day for infants <1 year (Ross et al. 2010). The EAR is the amount of a nutrient which meets the needs of half (50%) the population while

the RDA is the amount of a nutrient which will meet the needs of practically all (97.5%) healthy persons in a population. The AI is an estimation of the observed dietary intake of an asymptomatic population. The approach and conclusions of the recent IOM report (Ross et al. 2010) was a significant deviation from those of the previous IOM DRI report of 1997 (Institute of Medicine 1997) in that for the first time an EAR and RDA was established for children and adults. In the past only an AI of 5 μg/day could be derived for persons up to 70 years (Institute of Medicine 1997). Two of the caveats of the IOM report are that the vitamin D recommendations (1) assume an adequate dietary calcium intake and (2) assume a negligible contribution from sunlight to 25(OH)D concentrations. It is also noteworthy that in terms of adverse effects, the Tolerable Upper Intake Level (UL) for vitamin D which is the highest level of daily consumption that current data have shown to cause no side effects is 100 μg/day (Ross et al. 2010) while in the older DRI report (Institute of Medicine 1997) it was set at 50 μg/day. In 1998, the UK Committee on Medical Aspects of Food and Nutrition Policy (COMA) concluded that a prudent public health approach to safeguard against vitamin D deficiency and its adverse effect on bone health would be to retain the Reference Nutrient Intake set in 1991 (10 μg/d for those aged >65 year).

The Scientific Advisory Committee for Nutrition (SACN) in the UK re-evaluated nutritional requirements for vitamin D for the British population in 2016 (SACN 2016). The findings of the report suggests a Reference Nutrient Intake (RNI) of 10 μg/day (400 IU/day), throughout the year, for everyone in the general UK population aged 4 year and above. The approach used in deriving the new RNIs involved determining the dietary input of vitamin D required to keep the circulating 25(OH)D above 25 nmol/L (the population protective cut-off to protect musculoskeletal health) (SACN 2016). The RNI of 10 μg/day (400 IU/day) for the general UK population includes pregnant and lactating women and population groups at increased risk of vitamin D deficiency. Since, there were insufficient data to set RNIs for children aged under 4y, Safe Intakes were recommended for this age group (8.5–10 μg/340–400 IU per day for all infants aged under 1year and 10 μg/400 IU per day for ages 1 up to 4 year). SACN were unable to quantify and take account of sunlight exposure in setting the DRVs because of the number of factors that affect endogenous vitamin D synthesis.

There can be no doubt (and ample evidence exists) that dietary vitamin D intakes are a concern in large proportions of the European population [for review see Kiely and Black 2012]. For example, mean dietary vitamin D intakes (including that from supplements) are between 4 and 5 μg/day among adults from National Diet and Nutrition Surveys in the UK, mostly from meat, fish and eggs, fortified foods and supplements. Therefore, current vitamin D intakes are considerably lower than recommendations and urgent dietary-based strategies are needed to bridge the gap.

Circulating 25(OH)D Concentrations in Older Age

An extensive array of studies including a mix of both representative and convenience sampling frames have reported 25(OH)D concentrations among older adults all over the globe (Wahl et al. 2012; Mithal et al. 2009; Ovesen et al. 2003). Without doubt, the region with the most available data on 25(OH)D concentrations is Europe, followed by North America and Asia. Limited data exist for South America and Africa with very few studies in children and adolescents in these regions (Wahl et al. 2012). Cross sectional data predominate and year round 25(OH)D concentrations are only available in some studies. In addition, comparisons of the prevalence of hypovitaminosis D between studies is compounded by the heterogeneity with regard to circulating 25(OH)D concentrations used to define vitamin D status. Furthermore, the very low calcium intakes seen in some communities complicate the interpretation and subsequent treatment of vitamin D deficiency in these population groups. Data from three multi-centred, standardized studies show that between 17 and 58% of older Europeans are vitamin D deficient (defined as circulating 25(OH)D) less than 30 nmol/L (Van der Wielen et al. 1995; Andersen et al. 2005; Lips et al. 2006). National representative data on 25(OH)D concentrations from the National Diet and Nutrition Surveys in UK adults aged over 64 years show that up to 10% of free-living and 40% of institutionalized adults have plasma 25(OH)D concentrations less than 25 nmol/L throughout the year [reviewed by Lanham-New et al. 2011]. Moreover, if the higher IOM cut point of 40 nmol/L is applied (defining an EAR) the proportion of adults with inadequate 25(OH)D concentrations rises considerably. While older adults are well-established as a 'at risk' group for vitamin D deficiency, it should be noted that ethnic populations residing in less sunnier climates are also particularly at risk of vitamin D deficiency. For example, in a large study of vitamin D status among South Asian (*n* 1105) and Black African and Caribbean adults (*n* 748) >45 years living in the West-Midlands region of the UK (Patel et al. 2013) plasma 25(OH)D concentrations <30 nmol/L were found in 76% of South Asians and 55% of Black African and Caribbean adults throughout the year. Another study involving 35 South Asians living in Surrey (Darling et al. 2013) found that 81% and 79% of the participants had circulating 25(OH)D concentrations <25 nmol/L during winter and autumn, respectively. These studies suggest an extremely high prevalence of vitamin D deficiency in these population groups which require urgent attention. Despite recent concerns about the high prevalence of vitamin D deficiency in much of the British adult and paediatric population [Scientific Advisory Committee for Nutrition 2016] there is a dearth of data on vitamin D status, and its predictors, in very old adults.

Recent data from a large broadly representative cohort of 85 year olds from the Newcastle 85+ study, UK showed that vitamin D deficiency [as defined by a circulating 25(OH)D concentration <30 nmol/L] is alarmingly high at all times of the year but particularly during winter and spring (Hill et al. 2016). Season of the year and use of vitamin D containing preparations (both supplements and medications) were strong predictors of 25(OH)D concentrations in these very old adults. In a cross-sectional investigation of 25(OH)D concentrations among 367 Belgian 80+

year olds, 20% and 66% had circulating 25(OH)D concentrations <25 and 50 nmol/L, respectively (Matheï et al. 2013). In a recent osteoporosis screening trial investigating the anti-fracture efficacy of a new anti-osteoporotic drug, 25(OH)D concentrations were measured at baseline in 1894 individuals aged 80+ years from 9 different European countries (Bruyère et al. 2014). Mean (SD) 25(OH)D concentrations were 53.3 (26.7) nmol/L in the entire cohort while circulating 25(OH)D concentrations showed wide geographical variation with the lowest mean 25(OH)D concentration (45.7 nmol/L) in Belgian participants and the highest mean concentration (81.7 nmol/L) in Spanish participants (Bruyère et al. 2014). The British participants in the Bruyère et al. study (region not specified) had a mean 25(OH)D concentration of 61.8 nmol/L with 22% of the participants having 25(OH)D concentrations <50 nmol/L. These 25(OH)D concentrations are considerably higher than those observed in Newcastle 85+ participants despite the fact that both studies used the same analytical assay for 25(OH)D (DiaSorin RIA).

While no information was available on season from the European study (Bruyère et al. 2014) the use of non-prescribed vitamin D containing supplements was high at >30% among the British participants (Bruyère et al. 2014) and higher than in Newcastle 85+ participants (19%), which agrees with the evidence that vitamin D supplements have a significant effect on circulating 25(OH)D in older adults (Cashman et al. 2009). An extensive array of studies, including both representative and convenience sampling frames have reported 25(OH)D concentrations among the younger old (generally >65 years, but <85 years) all over the globe (Wahl et al. 2012; Mithal et al. 2009). Comparisons of the prevalence of suboptimal D status between studies is compounded by the heterogeneity with regard to circulating 25(OH)D concentrations used to define vitamin D status. For example it has been estimated that between 17 and 58% of older Europeans are vitamin D deficient (circulating 25(OH)D) <25–50 nmol/L (Van Der Wielen et al. 1995; Andersen et al. 2005). Furthermore, the well recognized analytical variability in assays for 25(OH)D compounds further the comparison of vitamin D status measurements between studies (Carter, 2011). In the Newcastle 85+ study, the observation that institutionalized participants had significantly higher circulating 25(OH)D concentrations than their community dwelling counterparts is noteworthy (Hill et al. 2016). These differences are explained primarily by a greater use of prescribed vitamin D containing preparations in institutionalized participants which tend to contain higher amount of vitamin D than over the counter supplements (*see* below). For example, 45% and 14% of institutionalized and community-dwelling participants respectively took prescribed medicines containing vitamin D. Indeed, use of prescribed and non-prescribed vitamin D preparations were strong independent predictors of vitamin D status in the entire cohort. These findings agree with the commonly held view that vitamin D medication and supplement use are strong predictors of 25(OH)D in older adults (Van der Wielen et al. 1995). For example in a large European multicentre study of vitamin D status of older adults >65 years (Van der Wielen et al. 1995) mean circulating 25(OH)D concentrations were significantly higher in Norwegian participants (51 nmol/L) than Spanish participants (34 nmol/L) which was explained in part by high consumption of cod liver oil in Norwegian participants.

Indeed some studies show that 25(OH)D concentrations are inversely associated with risks of death due to cardiovascular disease, cancer, and other causes (reviewed later in the chapter). On the other hand, limited evidence suggests that there may be a U-Shaped association between 25(OH)D and various health outcomes including cognition and all-cause mortality (reviewed later in the chapter). Such findings may lend support to the need to define 'normal' and 'healthy' reference range for 25(OH)D concentrations in very old adults. This is vitally important as a 25(OH)D threshold >70–80 nmol/L across the lifecycle has been regarded by some as 'optimal' for health (Heaney and Holick 2011). Furthermore, there is a need to determine the vitamin D requirements in very old adults specifically since recommendations are generally set for those aged 65+ and the needs of those aged 85+ may not be the same as for those aged >65 but <85 years.

Vitamin D and Bone Health in Older Age

The latest report from the Scientific Advisory Committee on Nutrition (SACN, 2016) defined the threshold of 25 nmol/L as 'population protective level' for musculoskeletal health in the UK population, including older adults, whilst the IOM (Ross et al. 2010) did not support 25(OH)D concentrations >50 nmol/L (i.e. above deficiency threshold) as beneficial for non-skeletal health outcomes, warranting more research. Severe vitamin D deficiency is defined by a circulating 25(OH)D less than 25 nmol/L, which corresponds to the upper end of the range at which vitamin D deficiency osteomalacia and rickets has been observed (Prentice et al. 2008). However, higher levels of circulating 25(OH)D have been associated with secondary hyperparathyroidism, increased bone resorption, bone loss, impaired muscle function and an increased risk of falls and fragility fracture, and there remains contention about the thresholds applied. These outcomes will be reviewed in the next two sections of this chapter.

Osteomalacia

Recommended circulating levels of 25(OH)D in adult life are commonly set against the clinical risk of developing osteomalacia, although falls and fracture risk are important considerations. The gold standard diagnostic test for mineralisation disorder associational with vitamin D deficiency (vitamin D deficiency osteomalacia) is the identification of mineralisation defect with increased osteoid thickness and reduced calcification fronts, which are identified by bone histomorphometry after tetracycline labelling. However, population based studies, using this invasive technique, are impractical. One recent study used bone histomorphometry in post-mortem specimens in Germany, apparently finding that abnormal bone mineralisation was only seen in a proportion of subjects whose circulating 25(OH)D was less than

75 nmol/L (Priemel et al. 2010). The study has been criticised because it uses post mortem bone histomorphometry without tetracycline labelling, so both generalisability is compromised and causes other than vitamin D deficiency may explain histomorphometric changes seen, while the use of such post-mortem data to make dietary recommendations seems bizarre (Aspray and Francis 2013). This theme has been addressed comprehensively in the IOM report (Ross et al. 2010) where, even ignoring the technical limitations in Priemel's study, osteomalacia is sometimes reported at circulating 25(OH)D levels less than 30 nmol/L but rarely observed at 25(OH)D levels greater than 50 nmol/L.

Secondary Hyperparthyroidism

The circulating concentration of 25(OH)D below which parathyroid hormone (PTH) increases outside the normal range may be used to establish a threshold value for vitamin D insufficiency and this is of particular importance for bone metabolism, because an elevated PTH is associated with increased bone loss (Bischoff-Ferrari et al. 2006, 2008; Sahota et al. 2001, 2004; Rejnmark et al. 2011). The relationship of circulating blood levels of 25(OH)D to PTH is contentious. Some studies suggest that PTH reaches a plateau with increasing circulating 25(OH)D concentration (Chapuy et al. 1997; Lappe et al. 2006), while others demonstrate an inverse relationship throughout the physiological range of 25(OH)D concentrations (Vieth et al. 2003; Arabi et al. 2010; Bates et al. 2003; Durazo-Arvizu et al. 2010; Sahota et al. 2006). It is important to consider that the relationship between 25(OH)D and PTH may be influenced by the effects of many other factor including comorbidities. Advancing age, dietary calcium and phosphate intake, renal function, plasma vitamin D binding protein (DBP), magnesium concentration, IGF-1, testosterone, smoking and physical inactivity may all have important roles in the development of secondary hyperparathyroidism (Vieth et al. 2003; Arabi et al. 2010; Durazo-Arvizu et al. 2010; Sahota et al. 2006; Gunnarsson et al. 2009). Moreover, comparisons between studies may be hampered by the use of different assays for 25(OH)D and PTH (Lai et al. 2012; Lips et al. 1999).

Bone Mineral Density

The National Health and Nutrition Examination Survey III (NHANES III) examined the relationship between circulating 25(OH)D and bone mineral density (BMD) at the hip in 4958 women and 5003 men aged 20 years and above (Bischoff-Ferrari et al. 2009a, b). This showed a positive association between circulating 25(OH)D and BMD in both sexes, with the highest BMD found in subjects with a circulating 25(OH)D above 75 nmol/L. Although these results were adjusted for potential confounding variables, the authors acknowledged that one cannot infer a

causal relationship between circulating 25(OH)D and BMD from a cross-sectional study. The evidence based reviews performed for the IOM Report also examined the relationship between vitamin D and BMD (Ross et al. 2010). Among the observational studies reviewed, there was fair evidence to support an association between circulating 25(OH)D levels and BMD or changes in BMD at the femoral neck.

The largest randomised controlled trial (RCT) of the effects of vitamin D supplementation on bone health was the Women's Health Initiative Study (WHI), where 36,282 postmenopausal women aged 50–79 years were randomised to receive calcium (1000 mg) and vitamin D (10 μg) or placebo daily (Jackson et al. 2006). In a sub-set of 2431 women who underwent bone density measurements, there was greater preservation of BMD at the hip with supplementation than with placebo, which comprised 0.59%, 0.86% and 1.06% after 3, 6 and 9 years respectively. The IOM Report highlighted that the combined results of RCTs comparing calcium and vitamin D supplementation with placebo were consistent with a small effect on lumbar spine, femoral neck and total body BMD (Ross et al. 2010). In contrast, in trials comparing combined calcium and vitamin D supplementation with calcium alone, no significant difference in change in BMD was seen, suggesting that vitamin D supplementation may be less beneficial in calcium replete subjects.

Fracture Risk

The IOM Report also examined the relationship between circulating 25(OH)D and fracture risk (Ross et al. 2010). Only one of the three prospective cohort studies reviewed found an inverse relationship between circulating 25(OH)D and fractures, but in contrast nine of the 12 case-control studies observed lower 25(OH)D levels in patients with fractures than in the control subjects. The apparent inconsistency between the results of prospective cohort and case-control studies may reflect a failure to fully adjust for confounding variables in the latter, not least the effect of the fracture, any hospital admission, surgical procedure and associated inflammation on vitamin D production and metabolism (Reid et al. 2011). One of the earliest RCTs investigating the anti-fracture efficacy of vitamin D supplementation compared the effect of combined calcium (1200 mg daily) and vitamin D (20 μg daily) and placebo in 3270 women with an average age of 84 years living in French nursing homes or apartment blocks for the elderly (Chapuy et al. 1992). In a small subset of subject undergoing venepuncture and BMD measurement, there was correction of vitamin D deficiency and secondary hyperparathyroidism with supplementation, together with a small increase in BMD. Intervention also reduced the risk of hip and other non-vertebral fractures. It was unclear from this study if both calcium and vitamin D was required for the beneficial effect of supplementation or if this would be effective in community dwelling older people. The RECORD study sought to address this question, by comparing the effect of placebo or calcium (1000 mg daily) and vitamin D (20 μg daily), either alone or in combination, in 5292 community-dwelling older women or men with a low trauma fracture (Grant et al.

2005). Over the 24–62 month follow-up period there was no difference in the incidence of all clinical fractures or hip fractures. Compliance with supplementation in the RECORD study was relatively poor, especially when this included calcium. Nevertheless, pre-planned analysis showed no difference in outcome in subjects with good compliance with supplementation compared with participants who were less compliant. Although the WHI study showed a small improvement in BMD with calcium (1000 mg) and vitamin D (10 μg) supplementation, there was no overall effect on fracture incidence (Jackson et al. 2006). Among the subjects who remained compliant with supplementation there was a significant reduction in the risk of hip fractures. The results of other RCTs of vitamin D supplementation, with or without additional calcium, on the risk of fracture have yielded inconsistent results.

Meta-analyses indicate that combined calcium and vitamin D supplementation reduces the incidence of hip fractures in older people, but vitamin D alone is ineffective (Boonen et al. 2007; DIPART Group 2010; Chung et al. 2011; Avenell et al. 2009). Nevertheless, much of the beneficial effect of combined supplementation in these meta-analyses is driven by the results of the study in institutionalised French women, where vitamin D deficiency is common. A meta-analysis by Bischoff-Ferrari, which adjusted the dose of vitamin D for compliance, suggested that vitamin D decreased the incidence of non-vertebral fractures independent of additional calcium supplementation (Bischoff-Ferrari et al. 2009a, b). The reduction in fracture risk was more marked in studies where the received vitamin D dose exceeded 10 μg daily, whereas there was no decrease in fractures in studies where the subjects received 10 μg daily or less. An individual patient data meta-analysis by Bischoff-Ferrari, which also adjusted the dose of vitamin D for compliance, showed a trend for reduction in the risk of hip fractures but a small reduction in non-vertebral fractures (Bischoff-Ferrari et al. 2012).

The inconsistency of the results of the anti-fracture trials of vitamin D is likely to reflect heterogeneity in the populations studied, their baseline vitamin D status, dose of vitamin D, frequency and route of administration, compliance with supplementation and the use of additional calcium supplementation Nevertheless, it would appear that vitamin D supplementation is most likely to be beneficial in older people with vitamin D deficiency, such as those who are housebound or living in residential or nursing homes. Although the study in institutionalised French women (Chapuy et al. 1992) and several meta-analyses (Boonen et al. 2007; DIPART Group 2010; Chung et al. 2011; Avenell et al. 2009) suggest that additional calcium supplementation is required, it is unclear if a high dietary calcium intake is sufficient to obtain the benefit of vitamin D supplementation. Although the concept of the annual administration of high dose vitamin D is potentially attractive, either by the intramuscular or oral route, this may be associated with an increase in fracture risk (Sanders et al. 2010; Smith et al. 2007). For example, a study of high dose vitamin D supplementation (12,500 μg once yearly) reported an increased rate of falls and fractures, particularly in the first 3 months (Sanders et al. 2010). Similar findings have been reported in another study which, gave 7500 μg to older people, with a relative risk of hip fracture of 1.49 (1.02–2.18) in older people treated in their own homes for 3 years (Smith et al. 2007) and a non-significant 1% increase in

non-vertebal fractures over 10 months in care home residents (Law et al. 2006). These studies offer a concern with regard to what could be perceived as toxicological doses of vitamin D (i.e. 125 times the IOM UL) and its potential risks. Unfortunately, 25(OH)D and PTH were only measured in a small minority of participants in all of these interventional studies (Francis 2007), limiting the ability to explore the relationship between the circulating 25(OH)D achieved and fracture prevention.

Vitamin D and Muscle Health in Older Age

Finding the likely factors such as circulating 25(OH)D which may help to maintain or improve muscle strength, function, and physical performance well into advanced age to preserve independence bears a great public health importance (Holick 2007). Several lines of evidence have been suggested to support the involvement of 25(OH)D in skeletal muscle strength and function (Bischoff-Ferrari 2012; Ceglia and Harris 2013; Girgis et al. 2013). Firstly, clinical signs of severe 25(OH)D deficiency (<25 nmol/L) (Holick 2007) have been linked to myopathy, muscle pain and impaired gait, and their amelioration by vitamin D supplementation (reviewed by Girgis et al. 2013). Secondly, localisation of vitamin D receptor (VDR) in human muscle cell lines, myoblasts (Olsson et al. 2016), and adult skeletal muscle (Bischoff et al. 2001) although recently challenged (Wang and DeLuca 2011), and functional *in vitro* studies have provided insights into direct biological role of active form of vitamin D, the $1,25(OH)_2D_3$ in regulation of genes and signalling pathways affecting calcium homeostasis, proliferation and differentiation of muscle cells (Ceglia and Harris 2013; Girgis et al. 2013). Thirdly, despite conflicting findings across individual intervention studies, the results of the latest meta-analyses of randomized controlled trials (RCT) of vitamin D supplementation have showed a small but significant improvement in muscle strength and function in older adults who had 25(OH)D concentrations below 30 nmol/L (Beaudart et al. 2014) or 50 nmol/L (Rejnmark 2011), and reduced risk of falls in those with 25(OH)D <25 nmol/L at baseline after vitamin D and calcium co-administration (Murad et al. 2011). Lastly, observational studies (reviewed in; Houston 2015; McCarthy and Kiely 2015), although inconsistent, have suggested that 25(OH)D concentration of <50 nmol/L exerts negative effect on various measures of muscle strength and function and physical performance in older adults aged 60 and over.

Over a dozen prospective studies have examined the role of circulating 25(OH)D in muscle strength and physical performance in older adults (Granic et al. 2017; Houston 2015; Sohl et al. 2013a; Dam et al. 2009; Wicherts et al. 2007; Houston et al. 2011a, b, 2012.

Most have hypothesised a protective effect of higher 25(OH)D concentrations (≥50 or ≥ 75 nmol/L) for muscular health and function. The studies differed, among others, in respect to participants' characteristic, baseline 25(OH)D concentration, muscle strength and functioning measures, and their baseline levels. Only a few

have included the very old (aged ≥85) (Granic et al. 2017; Sohl et al. 2013a; Wicherts et al. 2007; Houston et al. 2011a, b)–the age group at an increased risk of muscle mass and strength loss (Dodds et al. 2017), functional decline (Kempen et al. 2006), and low 25(OH)D (Hill et al. 2016). The Newcastle 85+ study was the first cohort study to test non-linear relationships between 25(OH)D (defined by season-specific quartiles) and decline in grip strength (GS) and timed up and go (TUG) test in the very old (aged ≥85) living in the UK (Granic et al. 2017). The results observed a U-shaped association between 25(OH)D and GS decline in both men and women remained significant only for men in the lowest compared with combined middle quartile. Men in SQ1 [25(OH)D <30 nmol/L] experienced a loss of 1.41 kg/year and accelerated decline of −0.43 kg throughout the 5-year follow-up. Women (but not men) in the lowest and highest 25(OH)D quartile (>47–75 nmol/L) had slower overall TUG times at baseline but not over time. Greater benefits for muscle strength were not observed in participants with 25(OH)D ≥75 nmol/L (Granic et al. 2017). There is only one other study of adults aged ≥80, from Belgium, which has found no association between 25(OH)D concentration and several measures of muscle performance in cross-sectional analysis, although severe vitamin D deficiency (<25 nmol/L) was high in this cohort, especially in winter (Matheï et al. 2013). Therefore, in very old adults it appears that keeping 25(OH)D above 25–30 nmol/L minimum may reduce muscle strength decline, whereas values >50 nmol/L may not confer additional benefits for muscle heath and functioning in the very old.

Several other studies have reported an increased risk of muscle function decline in younger-old participants with low vitamin D status (defined as either <30 or <50 nmol/L or lowest data-driven quartile) (Sohl et al. 2013a, b; Dam et al. 2009; Wicherts et al. 2007; Houston et al. 2011a), others have found no risk (Verreault et al. 2002; Sohl et al. 2013b), and no association with the faster rate of decline in functioning measures (Houston et al. 2011b, 2012). Recently recommended 25(OH)D cut-offs for overall and musculoskeletal health in the UK are much lower (SACN 2016) than the required levels proposed by the IOM (Ross et al. 2010) and The Endocrine Society guidelines (25 vs 50 vs 75 nmol/L, respectively). Despite the differences in hypothesis, definition of exposure (25(OH)D cut-offs), and outcome measures for muscle strength and function, certain parallels between the results in our and the studies that included the very old (Wicherts et al. 2007; Houston et al. 2011a, b, 2012) should be noted. In a sub-group of 979 older adults (aged 65–88 years) from the Longitudinal Aging Study Amsterdam, those with 25(OH)D <25 nmol/L had higher risk of decline in physical performance over 3 years, whilst those in the intermediate group (50–75 nmol/L) did not experience greater rates of decline compared with participants with 25(OH)D >75 nmol/L (Wicherts et al. 2007). In the Cardiovascular Health Study All Stars, participants aged 77–100 with 25(OH)D deficiency (<50 nmol/L) had weaker GS at baseline compared with those in sufficient group (≥75 nmol/L), but did not have an increased risk of GS decline over 3 years (Houston et al. 2011a). The Health, Aging, and Body Composition Study of over 2600 older adults aged 71–80 have determined 25(OH)D threshold

and best performance for physical function and strength at 70–80 nmol/L and 55–70 nmol/L, respectively (Houston et al. 2012). Although participants with 25(OH)D < 50 nmol/L had worse physical performance at baseline and 2- and 4-year follow-up compared with those in sufficient group (≥75 nmol/L), no association was found for GS, and no association with a faster rate of decline in either measures. Increasing 25(OH)D to ≥50 nmol/L was associated with clinically significant improvement in the short physical performance battery over 12 months in older adults aged 70–89 (Houston et al. 2011b). Taken together, the results suggest detrimental effects of low circulating 25(OH)D (<25 nmol/L) and no change (decline) or favourable outcomes for muscle strength and physical performance at both intermediate (>50 nmol/L) and higher (>75 nmol/L) concentrations.

Previous data from the Newcastle 85+ study has identified sex-specific trajectories and baseline determinants of GS decline over 5 years in the very old (Granic et al. 2016). Steeper slopes of GS decline in men compared with women could be partially explained by multi-morbidity (Collerton et al. 2009; Kingston et al. 2014) (a significant predictor of weaker GS in women), body composition (Siervo et al. 2015) (fat mass higher in women despite lower body weight), and survival. Shorter survival time in women in both low and high 25(OH)D groups has also been observed in participants from the Newcastle 85+ study (Granic et al. 2015a). In addition, women's longer life expectancy spend with more diseases and disabilities (Kingston et al. 2014), and selective mortality in men (survival of heathier men), may result in a biased sample, and a lack of power to detect associations in women.

Although recent meta-analyses of RCT have reported a small improvements in muscle strength and function in deficient older adults (25(OH)D <30 or 50 nmol/L), larger scale studies are needed to determine sources and thresholds of 25(OH)D for physical functioning in advanced adulthood. The results of the above studies have several sources of bias related to vitamin D. Most do not report 25(OH)D status prior to baseline or adjust for long-standing vitamin D deficiency which may be corrected by supplementation prior to study commencement (especially in women). Single measures of 25(OH)D may also miss-classify individuals' vitamin D status throughout the year. Other sources of miss-classification in studies may be due to assay variability in measuring 25(OH)D with immunoassays often over estimating 25(OH)D deficiency (<30 nmol/L) (Snellman et al. 2010), particularly in older women (Perna et al. 2012). Loss to follow-up may be another source of bias. As with any cohort of older adults, in particular very old cohorts, mortality is high, thus the results may be influenced by the presence of more robust survivors. There still remains the possibility of residual confounding affecting 25(OH)D status, muscle strength and physical performance relationship.

Vitamin D and Cognitive Health in Older Age

Recent evidence from life sciences and epidemiology points to the role of 25(OH)D in brain function, including cognition, across the life span (Balion et al. 2012; Kesby et al. 2011). Detection of hydroxylases for vitamin D activation and vitamin D receptors in neurons and glia in brain regions essential for cognition and memory implicates their relevance for brain health. Moreover, *in vitro* and *in vivo* studies propose neuroprotective properties of 25(OH)D (Kesby et al. 2011).

Although recent evidence indicates that supplementation improves vitamin D status in older adults without adversely affecting heath and survival (Bjelakovic et al. 2014) there is no consensus on the definition of hypovitaminosis D and upper 25(OH)D thresholds for optimum physical and mental health in old age to prevent problems with under- or over-treatment (Ross et al. 2010; Holick 2008; Sanders et al. 2013; Cranney et al. 2007). Non-optimal concentration of 25(OH)D, variously defined as <25 nmol/L (10 ng/ml) or <50 nmol/L (20 ng/ml), has been implicated as a risk factor for global cognitive impairment (Annweiler et al. 2010; Llewellyn et al. 2011) and weaker performance on domain-specific cognitive tasks (Buell et al. 2009; Hansen et al. 2011; Lee et al. 2009; Seamans et al. 2010) in several, but not all, cross-sectional studies (McGrath et al. 2007) involving adults aged 60+. Only four prospective studies reported an increased risk of cognitive decline in association with lower concentrations of circulating 25(OH)D (≤50 nmol/L) in adults aged 65+ (Slinin et al. 2010, 2012; Llewellyn et al. 2010; Wilson et al. 2014). Studies on 25(OH)D and cognitive decline in those aged 85+ are scarce (Granic et al. 2015b; Formiga et al. 2011; Menant et al. 2012).

The Newcastle 85+ Study tested for the presence of either an inverse or a non-linear association between 25(OH)D concentrations and cognition at baseline and cognitive decline over 3 years, utilizing measures of global and attention-specific cognitive function (Granic et al. 2015b). The investigators found that both low and high season-specific quartiles of 25(OH)D were associated with higher odds of prevalent cognitive impairment (assessed by SMMSE), poorer attention reaction times/processing speed and focused attention/concentration, and greater attention fluctuation (assessed by Cognitive Drug Research battery). Differences remained significant after adjustment for sex, education, lifestyle factors and the presence of several chronic diseases, although effects were small (Granic et al. 2015b). However, the rate of change of all attention measures over 5 years did not vary across 25(OH)D groups, and no association between 25(OH)D and odds of global incident cognitive impairment or decline was found (Granic et al. 2015b). To our knowledge, this is the first prospective study to find evidence for a U-shaped relationship between 25(OH)D and global cognitive function and attention in the very old. Taken together, it could be hypothesized that the neuroprotective effects of vitamin D mediated via expression of proteins that, for example, attenuate the toxicity of reactive oxygen species (Ibi et al. 2001) in very old neurons are attained only at moderate but not at low or high 25(OH)D concentrations.

Thus far, only four prospective studies of older adults aged 65+ have examined the association between 25(OH)D and prevalent and incident global cognitive impairment, and decline in attention and executive function, with inconsistent results. A study of community-dwelling older men (Slinin et al. 2010) found limited evidence of an independent association between lower 25(OH)D concentration (≤19.9 ng/ml) and incident cognitive impairment or decline in global and executive function. A similar study involving community-dwelling older women (Slinin et al. 2012) reported that very low (<25 nmol/L) and low levels (<50 nmol/L) of 25(OH)D were associated with an increased risk of impaired global cognitive function and decline [defined by modified MMSE (3MS)], but not with impaired executive function or decline. Two further studies have also investigated these 25(OH)D cut-points. The InCHIANTI study found that compared with participants with sufficient 25(OH)D (≥75 nmol/L) the deficient group (<25 nmol/L) experienced a substantial global (assessed by MMSE) and executive cognitive decline (assessed by Trails A and B) over 6 years (Llewellyn et al. 2010), whilst the Health, Aging and Body Composition Study confirmed that lower 25(OH)D (<50 nmol/L) was associated with a greater cognitive decline on the 3MS compared with sufficient 25(OH)D (≥75 nmol/L) over 4-year follow-up (Wilson et al. 2014). A similar global cognitive measure as in previous studies was utilized, although different circulating 25(OH)D cut-offs were derived *a posteriori* (Wang et al. 2009), but no association between 25(OH)D and global incident impairment or decline after adjustment for confounders was detected. This lack of association may be due to very old age of study participants, reduced power to detect the association, specific definition of cognitive change at an individual level, and/or changed circulating 25(OH)D status over the 3 years of the study. Increased mortality amongst older women belonging to the lowest and highest season-specific 25(OH)D quartiles as observed in this cohort (Granic et al. 2015a) could be one of the reasons for the loss of analytical power. Nonetheless these findings are in agreement with reports from the NHANES III, a cross-sectional study of the non-institutionalized US population, aged 60–90 years, where the worst performance on learning and memory tasks was associated with the highest quintile of 25(OH)D (McGrath et al. 2007).

There is the possibility of reverse causation (i.e. non-optimal 25(OH)D concentrations being a consequence of prevalent cognitive impairment) (Johansson et al. 2013). To assess change in attention/information processing speed, attention fluctuation and accuracy in relation to 25(OH)D, the CDR system, previously used in dementia studies and clinical trials to discriminate between various types of dementias and to detect change in attention-specific cognitive domains pre and post treatment with millisecond precision, have been employed in previous studies (Wesnes, 2008; Wesnes et al. 2000; Rowan et al. 2007). Future studies should determine whether these attention deficits relate to decline in global cognition and interfere with daily functioning (Bronnick et al. 2006). A small clinical trial of patients aged 65 and over with a history of falls and 25(OH)D insufficiency (≤30 nmol/L) showed an improvement of 0.4 s in CRT, compared with the control group, 6 months after a single intramuscular injection of vitamin D, which increased the average circulating 25(OH)D from 10.4 to 17.5 ng/ml – the latter within the middle quartiles reported

here to be associated with better attention scores (Dhesi et al. 2004). Future prospective studies should test the proposed U-shaped relationship between circulating 25(OH)D and cognition in this age group and determine whether other cognitive domains are affected similarly by 25 (OH)D status.

Vitamin D and Mortality

In the past two decades, accumulated evidence from cellular, animal and population-based studies has indicated the involvement of vitamin D metabolites in immunomodulation, cancer inhibition and cardiovascular, respiratory, brain and muscle function (Christakos et al. 2013; Pludowski et al. 2013; Welsh 2012; IARC 2008; Kesby et al. 2011). These extra-skeletal effects of vitamin D suggest its potential role in overall health and survival (Hossein-Nezhad and Holick 2013). Recent observational studies in the general and older populations (≥65) have shown a non-linear relationship between circulating hydroxyvitamin D [25(OH)D], the major circulatory and storage form of vitamin D, and both disease-specific and all-cause mortality (Michaælsson et al. 2010; Signorello et al. 2013; Amer and Qayyum 2013; Durup et al. 2012; Dror et al. 2013; Melamed et al. 2008). This indicates that moderate rather than low or high concentrations of 25(OH)D may result in more favourable health outcomes and increased survival. Using an evidence-based approach for bone health, the US Institute of Medicine (IOM) has produced its latest report stating that: (i) concentrations of 50 nmol/L 25(OH)D meet the requirements of 97.5% of the North American population; (ii) concentrations of ≥75 nmol/L are not consistently associated with increased health benefits; and (iii) not all persons have inadequate 25(OH)D if concentrations are below 50 nmol/L (Ross et al. 2010). Amongst at-risk groups, older adults are more likely to have lower 25(OH)D levels (Hirani and Primatesta 2005; Ovesen et al. 2003; Shoben et al. 2011) because of reduced skin 7-dehydrocholesterol concentrations (the cutaneous precursor of vitamin D), inefficient renal activation of 25(OH)D and a reduction in outdoor activities with advancing age (Holick 2008). These factors also contribute to greater variability in both circulating 25(OH)D concentrations and in the average requirement for vitamin D supplementation in older adults (Ross et al. 2010; Rosen et al. 2012). The findings of observational studies, randomized control trials (RCTs) and benefit–risk assessments all suggest that vitamin D supplementation in the general and older populations can ameliorate suboptimal 25(OH)D concentrations without adverse effects on disease-specific or all-cause mortality (Neuhouser et al. 2009; Bischoff-Ferrari et al. 2010; Bischoff-Ferrari et al. 2009a, b; LaCroix et al. 2009; Autier and Gandi 2007; Bjelakovic et al. 2014). However, there is no agreement amongst researchers and healthcare professionals about the optimal, beneficial and age-specific 25(OH)D concentrations in relation to extra-skeletal outcomes and mortality [Ross et al. 2010; Holick 2008; Rosen et al. 2012; Brannon 2012; Sanders et al. 2013), especially in older adults. Current evidence supports an inverse or non-linear association between 25(OH) D levels and mortality amongst adults aged 65 years

and older. For example, a meta-analysis including 24,000 participants from nine prospective observational studies demonstrated a 25% increased pooled hazard ratio for all-cause mortality in the lowest compared with the highest 25(OH)D category in those aged ≥65 years (Rush et al. 2013). A similar meta-analysis which included 12 studies (30,000 participants) confirmed an inverse association between 25(OH)D and mortality and a decrease in mortality risk of 8% for an increase in 25(OH)D of 20 nmol/L (SchÖttker et al. 2013). Two recent population-based studies from Denmark (Durup et al. 2012) and Israel (Dror et al. 2013) which both included over 40% of older adults (aged ≥65 years), showed a reversed J- and U-shaped relationship between 25(OH)D concentration and total mortality, respectively, and the best survival for individuals with 25(OH)D levels between 50 and 90 nmol/L. Similarly, an examination of the National Health and Nutrition Examination Survey (NHANES) data (2001–2004) revealed no significant reduction in mortality above a circulating 25(OH)D >52.6 nmol/L (Amer and Qayyum 2013).

To our knowledge, only one prospective cohort study has investigated the relationship between 25(OH)D and mortality in the very old (aged ≥85 years), despite this being the fastest growing segment of many populations worldwide. Furthermore, except for the study conducted amongst members of the Clalit Health Services in Israel (Dror et al. 2013), the numbers of very old adults included in the above-mentioned studies were small. In a prospective cohort study of older adults in the Newcastle 85+ study, we found a dose–response relationship between circulating 25(OH)D and all-cause mortality, with both the lowest and highest season specific 25(OH)D quartiles being associated with higher mortality over 6 years (Granic et al. 2015a). The higher risk of mortality amongst participants with the highest concentrations [a threshold range of ≥47 nmol/L (spring) to ≥69 nmol/L (summer) for the highest season-specific quartile] appeared to be driven largely by women taking vitamin D-containing supplements and/or prescribed medication (Granic et al. 2015a). Furthermore, the greater risk of mortality amongst women with the highest 25(OH)D concentrations (SQ4 or 'sufficient' categories) was independent of their frailty status (Ensrud et al. 2010). To our knowledge, this is the first observational study to suggest a U-shaped relationship between circulating 25(OH)D and all-cause mortality in very old adults. Several recent systematic reviews and meta-analyses of prospective cohort studies investigating the association between 25(OH)D status and risk of mortality [Rush et al. 2013; SchÖttker et al. 2013; Zitterman et al. 2012; Scragg 2011) have demonstrated a shorter survival amongst adults with the lowest (<25 or <50 nmol/L) compared with highest 25(OH)D concentrations, especially in those aged 65 years and older (Rush et al. 2013; Scragg 2011). In other studies, a non-linear relationship was noted with favourable survival outcomes at concentrations between 50 and 90 nmol/L (Amer and Qayyum 2013; Durup et al. 2012; Dror et al. 2013). However, except for the study conducted in Israel (Dror et al. 2013) relatively few participants aged over 85 years were included in these studies.

In a large retrospective study from general practices in Copenhagen (CopD Study) (Durup et al. 2012) an inverse J-shaped relationship between 25(OH)D and mortality was observed, with the longest survival at concentrations of 50–60 nmol/L

during 3 years of follow-up. Similarly, a historical prospective study of more than 420,000 members of the Clalit Health Services in Israel (Dror et al. 2013), which included >20,000 participants aged ≥85 years, found that the lowest risk of mortality and acute coronary syndrome was associated with 25(OH)D in the range of 20–36 ng mL1 (50–90 nmol/L) during 4.5 years of follow-up. A meta-analysis of 14 prospective cohort studies involving the general population (age range 45–80 years and 1.3–27.0 years of follow-up) also suggested a non-linear relationship between 25 (OH)D and mortality, but 25(OH)D levels of ~75–87.5 nmol/L were considered optimal (Zittermann et al. 2012).

The higher mortality rates observed amongst very old women, with higher 25(OH)D concentrations [SQ4 or 'sufficient' (≥75 nmol/L) categories] whether users or nonusers of vitamin D supplements/ medication, respectively, have not been reported previously [Bischoff-Ferrari et al. 2010; Bischoff-Ferrari et al. 2009a, b; LaCroix et al. 2009; Autier and Gandi 2007; Bjelakovic et al. 2014]. The Women's Health Initiative calcium/vitamin D RCT, a 7-year combined therapy intervention (1 g calcium and 400 IU vitamin D daily), reported a trend towards mortality reduction amongst postmenopausal women aged <70 years, but neither a beneficial nor an adverse effect in women aged >70 years (LaCroix et al. 2009). A meta-analysis of 56 RCTs of vitamin D supplementation and survival (Bjelakovic et al. 2014) demonstrated a decrease in all-cause mortality amongst predominantly older adults including women aged ≥70 years, but also found adverse renal outcomes associated with vitamin D3 and calcium combination therapy.

Lower (<37.5 nmol/L) and higher (≥75 nmol/L) concentrations of 25(OH)D have been moderately associated with frailty amongst older women (aged ≥69 years) in the Study of Osteoporotic Fractures (Ensrud et al. 2010), and the risk of death was significantly increased amongst frail NHANES III participants (aged ≥60 years) in the lowest (<49.5 nmol/L) compared with not frail participants in the highest (>84.1 nmol/L) 25(OH)D quartiles (Smit et al. 2012). The results from observational cohort studies exploring sex differences in mortality in relation to 25(OH)D are inconclusive and have not included the very old. The NHANES III showed a U-shaped relationship between 25(OH)D levels and mortality in the general population of women (aged ≥20 years) but not in men at concentrations of <50 and > 125 nmol/L (Melamed et al. 2008). In a study of older men (a birth cohort from 1920 to 1924, aged 71 at baseline) from the Uppsala region, an increased risk of total and cancer mortality was observed at both low (<46 nmol/L) and high (>98 nmol/L) 25(OH)D concentrations over 12.7 years of follow-up (Michaæ lsson et al. 2010). In both these studies, the longest survival was associated with the middle 25(OH)D categories, but the thresholds were much higher than in the present study (NHANES III: 75–100 nmol/L; Uppsala Study of Older Men: 46–98 nmol/L); this difference may be related to the age of participants, habitual diet, supplementation, length of follow-up or other factors/covariates.

Several limitations of the aforementioned studies should be noted. There remains the possibility of residual confounding by additional factors that affect the relationship between circulating 25(OH)D and mortality. Although many of these studies controlled for the number of chronic diseases and for frailty status, increased mor-

tality amongst older women may be mediated by other mechanisms associated with non-optimal 25(OH)D levels such as polypharmacy (Sohl et al. 2012) or an acute inflammatory response (Reid et al. 2011; Waldron et al. 2013). Recent studies have demonstrated a rapid decline in circulating 25 (OH)D after elective hip or knee surgery or after an acute inflammatory insult, thus 25(OH)D may be an unreliable biomarker of vitamin D status up to 3 months after the event (Reid et al. 2011; Waldron et al. 2013). Whilst recognizing that there is seasonal variations in 25(OH)D status, the results of some of the studies above were based on a single measurement, which may misclassify 25(OH)D levels throughout the year. It is also difficult to explore disease-specific mortality in relation to 25(OH)D in very old adults because of high rates of multimorbidity in this age group (Collerton et al. 2009).

Conclusion and Future Direction

The last two decades have seen major advances in our understanding of the metabolism, nutritional requirements and molecular aspects of vitamin D. The upward shift in the target 25(OH)D threshold set by authoritative bodies to define better bone health has been a significant step in recent years and much of the world's elderly population have a vitamin D status below what is considered optimal for bone health. However, the debate surrounding the optimal circulating 25(OH)D concentration for both skeletal and non-skeletal health will continue until significant progress has been made in a number of important areas:

1. The first centres around assay variability for 25(OH)D measurements, which has been addressed somewhat by the recent introduction of the Standard Reference Material (SRM) for vitamin D by the National Institute of Standards and Technology (NIST) in the USA.
2. The second area centres around gaining a better understanding of the production, storage and utilization of 25(OH)D (and it's free form) as biomarkers of effect.

Future intervention studies investigating vitamin D on health outcomes need to carefully choose the dose and form of vitamin D supplementation as well as the appropriate study duration so as to ensure the desired target 25(OH)D concentration is achieved. To date, only limited information is available in studies investigating the relationship between 25(OH)D concentrations and health outcomes in population subgroups, such as infants, adolescents, pregnant and lactating women and in dark-skinned individuals. To address this large research gap, vitamin D researchers need to decide on appropriate endpoints for vitamin D adequacy and insufficiency. The urgent need to undertake more high quality vitamin D intervention studies which quantify the impact on an array of health outcomes (including non-skeletal health) in a broader range of populations needs to be a priority. It is imperative that such studies report all relevant outcomes including adverse events as some recent research suggests (albeit a tentative) a U-shaped relationship between 25(OH)D status and at least some health outcomes. Studies should also give due consideration

to VDR genotype and should control for sun exposure, season, calcium intake, baseline circulating 25(OH)D concentrations and measure potential adverse effects. Studies should take advantage of emerging technology which makes genome-wide analysis possible. Appreciably, genotyping studies will need to be large in study design or analysis, because of the very large sample sizes required to adequately account for genotype effects. The dearth of information in many population subgroups including pregnant women and ethnic minorities should be prioritized in future studies on vitamin D status and health. Finally, in light of the widespread prevalence of dietary and biochemical vitamin D inadequacy in many populations and its negative consequences for bone health, strategies to increase oral vitamin D intake should be a priority.

Acknowledgements This work did not receive external funding.

Declaration of Conflicts of Interest Dr. Tom Hill has received industry funding from Noble Foods Ltd, Nutricia Ltd and the UK Dairy Council.

References

Amer M, Qayyum R (2013) Relationship between 25-hydroxyvitamin D and all-cause and cardiovascular disease mortality. Am J Med 126:509–514

Andersen R, Mølgaard C, Skovgaard LT et al (2005) Teenage girls and elderly women living in northern Europe have low winter vitamin D status. Eur J Clin Nutr 59:533–541

Annweiler C, Schott AM, Allali G et al (2010) Association of vitamin D deficiency with cognitive impairment in older women: cross-sectional study. Neurology 74:27–32

Arabi A, Mahfoud Z, Zahed L et al (2010) Effect of age, gender and calciotropic hormones on the relationship between vitamin D receptor gene polymorphisms and bone mineral density. Eur J Clin Nutr 64(4):383–391

Aspray TJ, Francis RM (2013) What can we learn about vitamin D requirements from post-mortem data? Osteoporos Int 4(5):1769–1770

Autier P, Gandi S (2007) Vitamin D supplementation and total mortality – a meta-analysis of randomized controlled trials. Arch Intern Med 167:1730–1737

Avenell A, Gillespie WJ, Gillespie LD, O'Connell D (2009) Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Re 15(2):CD000227

Baker MR, Peacock M, Nordin BE (1980) The decline in vitamin D status with age. Age Ageing 9:249–252

Balion C, Griffith LE, Strifler L et al (2012) Vitamin D, cognition, and dementia. Neurology 79:1397–1405

Bates CJ, Carter GD, Mishra GD et al (2003) In a population study, can parathyroid hormone aid the definition of adequate vitamin D status? A study of people aged 65 years and over from the British National Diet and Nutrition Survey. Osteoporos Int 14(2):152–159

Beaudart C, Buckinx F, Rabenda V et al (2014) The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. J Clin Endocrinol Metab 99:4336–4345

Biehl RR, Baker DH, DeLuca HF (1995) 1 alpha-hydroxylated cholecalciferol compounds act additively with microbial phytase to improve phosphorus, zinc and manganese utilization in chicks fed soy-based diets. J Nutr 125:2407–2416
Bischoff HA, Borchers M, Gudat F et al (2001) In situ detection of 1,25- dihydroxyvitamin D_3 receptor in human skeletal muscle tissue. Histochem J 33:19–24
Bischoff-Ferrari HA (2012) Relevance of vitamin D in muscle health. Rev Endocr Metab Disord 13:71–77
Bischoff-Ferrari HA, Borchers M et al (2004) Vitamin D receptor expression in human muscle tissue decreases with age. J Bone Miner Res 19(2):265–269
Bischoff-Ferrari HA, Giovannucci E, Willett WC et al (2006) Estimation of optimal circulating concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr 84(1):18–28
Bischoff-Ferrari HA, Orav EJ, Dawson-Hughes B (2008) Additive benefit of higher testosterone levels and vitamin D plus calcium supplementation in regard to fall risk reduction among older men and women. Osteoporos Int 19(9):1307–1314
Bischoff-Ferrari HA, Kiel DP, Dawson-Hughes B et al (2009a) Dietary calcium and circulating 25-hydroxyvitamin D status in relation to BMD among U.S. adults. J Bone Miner Res 24:935–942
Bischoff-Ferrari HA, Willett WC, Wong JB et al (2009b) Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med 169:551–561
Bischoff-Ferrari HA, Shao A, Dawson-Hughes B et al (2010) Benefit-risk assessment of vitamin D supplementation. Osteoporos Int 21:1121–1132
Bischoff-Ferrari HA, Willett WC, Orav EJ et al (2012) A pooled analysis of vitamin D dose requirements for fracture prevention. N Engl J Med 367:40–49
Bjelakovic G, Gluud LL, Nikolova D et al (2014) Vitamin D supplementation for prevention of mortality in adults. Cochrane Database Syst Rev 1:CD007470
Boonen S, Lips P, Bouillon R et al (2007) Need for additional calcium to reduce the risk of hip fracture with vitamin D supplementation: evidence from a comparative metaanalysis of randomized controlled trials. J Clin Endocrinol Metab 92:1415–1423
Brannon PM (2012) Key questions in vitamin D research. Scand J Clin Lab Invest Suppl 243:154–162
Bronnick K, Ehrt U, Emre M et al (2006) Attention deficits affect activities of daily living in dementia associated with Parkinson's disease. J Neurol Neurosurg Psychiatry 77:1136–1142
Bruyère O, Slomian J, Beaudart C et al (2014) Prevalence of vitamin D inadequacy in European women aged over 80 years. Arch Gerontol Geriatr 59(1):78–82
Buell JS, Scott TM, Dawson-Hughes B et al (2009) Vitamin D is associated with cognitive function in elders receiving home health services. J Gerontol A Biol Sci Med Sci 64:888–895
Bullamore JR, Wilkinson R, Gallagher JC et al (1970) Effect of age on calcium absorption. Lancet 2(7672):535–537
Cancer IARC (2008) Vitamin D and cancer/a report of the IARC working group on vitamin D. IARC, Lyon
Carter GD (2011) Accuracy of 25-hydroxyvitamin D assays: confronting the issues. Curr Drug Targets 12(1):19–28
Cashman KD, Wallace JM, Horigan G et al (2009) Estimation of the dietary requirement for vitamin D in free-living adults >=64 y of age. Am J Clin Nutr 89(5):1366–1374
Ceglia L, Harris SS (2013) Vitamin D and its role in skeletal muscle. Calcif Tissue Int 92:151–162
Chapuy MC, Arlot ME, Duboeuf F et al (1992) Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med 327:1637–1642
Chapuy MC, Preziosi P, Maamer M et al (1997) Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int 7(5):439–443
Christakos S, Hewison M, Gardner DG et al (2013) Vitamin D: beyond bone. Ann N Y Acad Sci 1287:45–58

Chung M, Lee J, Terasawa T et al (2011) Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med 155:827–838
Collerton J, Davies K, Jagger C et al (2009) Health and disease in 85 year olds: baseline findings from the Newcastle 85+ cohort study. BMJ 399:b4904
Cranney A, Horsley T, O'Donnell S et al (2007) Effectiveness and safety of vitamin D in relation to bone health. Evid Rep Technol Assess (Full Rep) 158:1–235
Dam TT, von Mühlen D, Barrett-Connor EL (2009) Sex-specific association of circulating vitamin D levels with physical function in older adults. Osteoporos Int 20:751–760
Darling AL, Hart KH, Macdonald HM et al (2013) Vitamin D deficiency in UK South Asian Women of childbearing age: a comparative longitudinal investigation with UK Caucasian women. Osteoporos Int 24(2):477–488
Dawson-Hughes B (2012) Circulating 25-hydroxyvitamin D and muscle atrophy in the elderly. Proc Nutr Soc 71(1):46–49
Dawson-Hughes B, Harris S, Kramich C et al (1993) Calcium retention and hormone levels in black and white women on high- and low-calcium diets. J Bone Miner Res 8:779–787
Dhesi JK, Jackson SH, Bearne LM et al (2004) Vitamin D supplementation improves neuromuscular function in older people who fall. Age Ageing 33:589–595
DIPART (Vitamin D Individual Patient Analysis of Randomized Trials) Group (2010) Patient level pooled analysis of 68,500 patients from seven major vitamin D fracture trials in US and Europe. BMJ 340:b5463
Dodds RM, Granic A, Davies K et al (2017) Prevalence and incidence of sarcopenia in the very old: findings from the Newcastle 85+ study. J Cachexia Sarcopenia Muscle 8(2):229–237
Dror Y, Giveon SM, Hoshen M et al (2013) Vitamin D levels for preventing acute coronary syndrome and mortality: evidence of a nonlinear association. J Clin Endocrinol Metab 98:2160–2167
Durazo-Arvizu RA, Dawson-Hughes B et al (2010) Three-phase model harmonizes estimates of the maximal suppression of parathyroid hormone by 25-hydroxyvitamin D in persons 65 years of age and older. J Nutr 140(3):595–599
Durup D, Jørgensen HL, Christensen J et al (2012) A reverse J-shaped association of all-cause mortality with circulating 25-hydroxyvitamin D in general practice: the CopD study. J Clin Endocrinol Metab 97:2644–2652
Eastell R, Yergey AL, Vieira NE et al (1991) Interrelationship among vitamin D metabolism, true calcium absorption, parathyroid function, and age in women: evidence of an age-related intestinal resistance to 1,25-dihydroxyvitamin D action. J Bone Miner Res 6:125–132
Ensrud KE, Ewing SK, Fredman L et al (2010) Circulating 25- hydroxyvitamin D levels and frailty status in older women. J Clin Endocrinol Metab 95:5266–5273
Epstein S, Bryce G, Hinman JW et al (1986) The influence of age on bone mineral regulating hormones. Bone 7:421–425
Formiga F, Ferrer A, Almeda J et al (2011) Utility of geriatric assessment tools to identify 85- years old subjects with vitamin D deficiency. J Nutr Health Aging 15:110–114
Francis RM (2007) The vitamin D paradox. Rheumatol (Oxf) 46(12):1749–1750
Francis RM, Peacock M, Storer JH et al (1983) Calcium malabsorption in the elderly: the effect of treatment with oral 25-hydroxyvitamin D_3. Eur J Clin Investig 13:391–396
Francis RM, Peacock M, Barkworth SA (1984) Renal impairment and its effects on calcium metabolism in elderly women. Age Ageing 13:14–20
Gallagher JC, Yalamanchili V, Smith LM (2012) The effect of vitamin D on calcium absorption in older women. J Clin Endocrinol Metab 97:3550–3556
Girgis CM, Clifton-Bligh RJ, Hamrick MW et al (2013) The roles of vitamin D in skeletal muscle: form, function, and metabolism. Endocr Rev 34:33–83
Granic A, Aspray T, Hill T et al (2015a) 25-hydroxyvitamin D and increased all-cause mortality in very old women: the Newcastle 85+ study. J Intern Med 277:456–467

Granic A, Hill TR, Kirkwood TB et al (2015b) Circulating 25-hydroxyvitamin D and cognitive decline in the very old: the Newcastle 85+ study. Eur J Neurol 22:106–115
Granic A, Davies K, Jagger C et al (2016) Grip strength decline and its determinants in the very old: longitudinal findings from the Newcastle 85+ study. PLoS One 11:e0163183
Granic A, Hill TR, Davies K et al (2017) Vitamin D status, muscle strength and physical performance decline in very old adults: a prospective study. Nutrients 9(4):379
Grant AM, Avenell A, Campbell MK et al (2005) Oral vitamin D_3 and calcium for secondary prevention of low-trauma fractures in elderly people (randomised evaluation of calcium or vitamin D, RECORD): a randomised placebo-controlled trial. Lancet 365:1621–1628
Gunnarsson O, Indridason OS, Franzson L, Sigurdsson G (2009) Factors associated with elevated or blunted PTH response in vitamin D insufficient adults. J Int Med 265(4):488–495
Hansen AL, Dahl L, Bakke L, Thayer JF (2011) Vitamin D and executive function: a preliminary report. Percept Mot Skills 113:667–685
Health Survey for England (2008) Physical activity and fitness. National Centre for Social Research. Retrieved from http://www.hscic.gov.uk/pubs/hse08physicalactivity
Heaney RP, Holick MF (2011) Why the IOM recommendations for vitamin D are deficient. J Bone Miner Res 26(3):455–457
Heaney RP, Recker RR, Stegman MR, Moy AJ (1989) Calcium absorption in women: relationships to calcium intake, estrogen status, and age. J Bone Miner Res 4:469–475
Hill TR, O'Brien MM, Cashman KD et al (2004) Vitamin D intakes in 18–64 year-old Irish adults. Eur J Clin Nutr 58:1509–1517
Hill TR, Granic A, Davies K et al (2016) Circulating 25-hydroxyvitamin D concentration and its determinants in the very old: the Newcastle 85+ study. Osteoporos Int 27:1199–1208
Hirani V, Primatesta P (2005) Vitamin D concentrations among people aged 65 years and over living in private households and institutions in England: population study. Age Ageing 34:485–491
Holick MF (1994) McCollum award lecture: vitamin D – new horizons for the 21st century. Am J Clin Nutr 60:619–630
Holick MF (2003) Evolution and function of vitamin D. Recent Results Cancer Res 164:3–28
Holick MF (2007) Vitamin D deficiency. N Engl J Med 357:266–281
Holick MF (2008) Vitamin D: a D-lightful health perspective. Nutr Rev 66:S182–S194
Holick MF, Matsuoka LY, Wortsman J (1989) Age, vitamin D, and solar ultraviolet. Lancet 2(8671):1104–1105
Horst RL, Reinhardt TA (1997) Vitamin D metabolism. In: Feldman D, Glorieux FH, Pike JW (eds) Vitamin D. Academic, San Diego, pp 13–31
Hossein-Nezhad A, Holick MF (2013) Vitamin D for health: a global perspective. Mayo Clin Proc 88:720–755
Houston DK (2015) Vitamin D and age-related health outcomes: movement, mood, and memory. Curr Nutr Rep 4:185–200
Houston DK, Tooze JA, Davis CC et al (2011a) Circulating 25-hydroxyvitamin D and physical function in older adults: the cardiovascular health study all stars. J Am Geriatr Soc 59:1793–1801
Houston DK, Tooze JA, Hausman DB et al (2011b) Change in 25-hydroxyvitamin D and physical performance in older adults. J Gerontol A Biol Sci Med Sci 66(4):430–436
Houston DK, Tooze JA, Neiberg RH et al (2012) Health ABC Study. 25-hydroxyvitamin D status and change in physical performance and strength in older adults: the health, aging, and body composition study. Am J Epidemiol 176:1025–1034
Ibi M, Sawada H, Nakanishi M et al (2001) Protective effect of 1 alpha,25-(OH)(2)D-3 against the neurotoxicity of glutamate and reactive oxygen species in mesencephalic culture. Neuropharmacology 40:761–771
Institute of Medicine (1997) Dietary reference intakes. For calcium, phosphorus, magnesium, vitamin D and fluoride. In: Food and nutrition board. National Academy Press, Washington, DC, pp 1–448

International Agency for Research on Cancer (IARC) (2008) Vitamin D and cancer/a report of the IARC working group on Vitamin D. IARC, Lyon
Ireland P, Fordtran JS (1973) Effect of dietary calcium and age on jejunal calcium absorption in humans studied by intestinal perfusion. J Clin Invest 52:2672–2681
Jackson RD, LaCroix AZ, Gass M et al (2006) Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 354:669–683
Johansson P, Almqvist EG, Johansson J-O et al (2013) Cerebrospinal fluid (CSF) 25-hydroxyvitamin D concentration and CSF acetylcholinesterase activity are reduced in patients with Alzheimer's disease. PLoS One 8:e81989
Kempen GI, Ranchor AV, van Sonderen E et al (2006) Risk and protective factors of different functional trajectories in older persons: are these the same? J Gerontol B Psychol Sci Soc Sci 61:95–101
Kesby JP, Eyles DW, Burne THJ et al (2011) The effects of vitamin D on brain development and adult brain function. Mol Cell Endocrinol 347:121–127
Kiely M, Black L (2012) Dietary strategies to maintain adequacy of circulating 25-hydroxyvitamin D concentrations. Scand J Clin Lab Invest 72(Suppl):14–23
Kingston A, Davies K, Collerton J et al (2014) The contribution of diseases to the male-female disability-survival paradox in the very old: results from the Newcastle 85+ study. PLoS One 9:e88016
Krejs GJ, Nicar MJ, Zerwekh JE et al (1983) Effect of 1,25-dihydroxyvitamin D3 on calcium and magnesium absorption in the healthy human jejunum and ileum. Am J Med 75(6):973–976
LaCroix AZ, Kotchen J, Anderson G et al (2009) Calcium plus vitamin D supplementation and mortality in postmeno- pausal women: the Women Health Initiative calcium-vita- min D randomized controlled trial. J Gerontol A Biol Sci Med Sci 64:559–567
Lai JK, Lucas RM, Banks E et al (2012) Variability in vitamin D assays impairs clinical assessment of vitamin D status. Int Med J 42(1):43–50
Lal H, Pandey R, Aggarwal SK (1999) Vitamin D: non-skeletal actions and effects on growth. Nutr Res 19:1683–1718
Lanham-New SA, Buttriss JL, Miles LM et al (2011) Proceedings of the rank forum on vitamin D. Br J Nutr 105(1):144–156
Lappe JM, Davies KM, Travers-Gustafson D, Heaney RP (2006) Vitamin D status in a rural postmenopausal female population. J Am Coll Nutr 25(5):395–402
Law M, Withers H, Morris J, Anderson F (2006) Vitamin D supplementation and the prevention of fractures and falls: results of a randomised trial in elderly people in residential accommodation. Age Ageing 35(5):482–486
Lee DM, Tajar A, Ulubaev A et al (2009) Association between 25-hydroxyvitamin D levels and cognitive performance in middle-aged older European men. J Neurol Neurosurg Psychiatry 80:722–729
Lips P, Chapuy MC, Dawson-Hughes B et al (1999) An international comparison of circulating 25-hydroxyvitamin D measurements. Osteoporos Int 9(5):394–397
Lips P, Hosking D, Lippuner K et al (2006) The prevalence of vitamin D inadequacy amongst women with osteoporosis: an international epidemiological investigation. J Int Med 260:245–254
Llewellyn DJ, Lang IA, Langa KM et al (2010) Vitamin D and risk of cognitive decline in elderly persons. Arch Intern Med 170:1135–1141
Llewellyn DJ, Lang IA, Langa KM, Melzer D (2011) Vitamin D and cognitive impairment in the elderly U.S. population. J Gerontol A Biol Sci Med Sci 66:59–65
MacLaughlin J, Holick MF (1985) Aging decreases the capacity of human skin to produce vitamin D_3. J Clin Invest 76(4):1536–1538
Martin TJ, Seeman E (2008) Bone remodelling: its local regulation and the emergence of bone fragility. Best Pract Res Clin Endocrinol Metab 22(5):701–722
Matheï C, Van Pottelbergh G, Vaes B et al (2013) No relation between vitamin D status and physical performance in the oldest old: results from the Belfrail study. Age Ageing 42(2):186–190

Matsuoka LY, Wortsman J, Dannenberg MJ et al (1992) Clothing prevents ultraviolet-B radiation-dependent photosynthesis of vitamin D_3. J Clin Endocrinol Metab 75:109–103

McCarthy EK, Kiely M (2015) Vitamin D and muscle strength throughout the life course: a review of epidemiological and intervention studies. J Hum Nutr Diet 28:636–645

McGrath J, Scragg R, Chant D et al (2007) No association between circulating 25-hydroxyvitamin D3 levels and performance on psychometric tests in NHANES III. Neuroepidemiology 29:49–54

Melamed ML, Michos ED, Post W, Astor B (2008) 25-hydroxyvitamin D levels and the risk of mortality in the general population. Arch Intern Med 168:1629–1637

Menant JC, Close JC, Delbaere K et al (2012) Relationship between circulating vitamin D levels, neuromuscular and neuropsychological function and falls in older men and women. Osteoporos Int 23:981–989

Michae€lsson K, Baron JA, Snellman G et al (2010) Plasma vitamin D and mortality in older men: a community-based prospective cohort study. Am J Clin Nutr 92:841–848

Mithal A, Wahl DA, Bonjour JP et al (2009) Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int 20(11):1807–1820

Murad MH, Elamin KB, Abu Elnour NO et al (2011) The effect of vitamin D on falls: a systematic review and meta-analysis. J Clin Endocrinol Metab 96:2997–3006

Neuhouser ML, Wassertheil-Smoller S, Thomson C et al (2009) Multivitamin use and risk of cancer and cardiovascular disease in the Women's Health Initiative cohorts. Arch Intern Med 169:294–304

Olsson K, Saini A, Strömberg A et al (2016) Evidence for vitamin D receptor expression and direct effects of 1α,25(OH)2D3 in human skeletal muscle precursor cells. Endocrinology 157:98–111

Ovesen L, Andersen R, Jakobsen J (2003) Geographical differences in vitamin D status, with particular reference to European countries. Proc Nutr Soc 62:813–821

Patel JV, Chackathayil J, Hughes EA et al (2013) Vitamin D deficiency amongst minority ethnic groups in the UK: a cross sectional study. Int J Cardiol 67(5):2172–2176

Perna L, Haug U, Schöttker B et al (2012) Public health implications of standardized 25-hydroxyvitamin D levels: a decrease in the prevalence of vitamin D deficiency among older women in Germany. Prev Med 55:228–232

Pludowski P, Holick MF, Pilz S et al (2013) Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence. Autoimmun Rev 12:976–989

Prentice A, Goldberg G, Schoenmakers I (2008) Vitmain D across the lifecycle: physiology and biomarkers. Am J Clin Nutr 88(2):500S–505S

Priemel M, von Domarus C, Klatte TO et al (2010) Bone mineralization defects and vitamin D deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. J Bone Min Res 25(2):305–312

Reid D, Toole BJ, Knox S et al (2011) The relation between acute changes in the systemic inflammatory response and plasma 25-hydroxyvitamin D concentrations after elective knee arthroplasty. Am J Clin Nutr 93:1006–1011

Rejnmark L (2011) Effects of vitamin d on muscle function and performance: a review of evidence from randomized controlled trials. Ther Adv Chronic Dis 2:25–37

Rejnmark L, Vestergaard P, Heickendorff L, Mosekilde L (2011) Determinants of plasma PTH and their implication for defining a reference interval. Clin Endocrinol 74(1):37–43

Rosen CJ, Abrams SA, Aloia JF et al (2012) IOM Committee members response to Endocrine Society vitamin D guidelines. J Clin Endocrinol Metab 97:1146–1152

Ross C, Abrams S, Aloia JF et al. (2010) Institute of Medicine. Dietary reference intakes for calcium and vitamin D. National Academies Press, Washington, DC

Rowan E, McKeith IG, Saxby BK et al (2007) Effects of donepezil on central processing speed and attentional measures in Parkinson's disease with dementia and dementia with Lewy bodies. Dement Geriatr Cogn Disord 23:161–167

Rush L, McCartney G, Walsh D, MacKay D (2013) Vitamin D and subsequent all-age and premature mortality: a systematic review. BMC Public Health 13:679
Sahota O, Gaynor K, Harwood RH, Hosking DJ (2001) Hypovitaminosis D and 'functional hypoparathyroidism'-the NoNoF (Nottingham Neck of Femur) study. Age Ageing 30(6):467–472
Sahota O, Mundey MK, San P et al (2004) The relationship between vitamin D and parathyroid hormone: calcium homeostasis, bone turnover, and bone mineral density in postmenopausal women with established osteoporosis. Bone 35(1):312–319
Sahota O, Mundey MK, San P et al (2006) Vitamin D insufficiency and the blunted PTH response in established osteoporosis: the role of magnesium deficiency. Osteoporos Int 17(7):1013–1021
Sanders KM, Stuart AL, Williamson EJ et al (2010) Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA 303:1815–1822
Sanders KM, Nicholson GC, Ebeling PR (2013) Is high dose vitamin D harmful? Calcif Tissue Int 92:191–206
SchÖttker B, Ball D, Gellert C, Brenner H (2013) Circulating 25-hydroxyvitamin D levels and overall mortality. A systematic review and meta-analysis of prospective cohort studies. Ageing Res Rev 12:708–718
Scragg R (2011) Vitamin D and public health: an overview of recent research on common diseases and mortality in adulthood. Public Health Nutr 14:1515–1532
Seamans KM, Hill TR, Scully L et al (2010) Vitamin D status and measures of cognitive function in healthy older European adults. Eur J Clin Nutr 64:1172–1178
Shoben AB, Kestenbaum B, Levin G et al (2011) Seasonal variation in 25-hydroxyvitamin D concentrations in the cardiovascular health study. Am J Epidemiol 174:1363–1372
Siervo M, Prado C, Hooper L et al (2015) Circulating osmolarity and haematocrit do not modify the association between the impedance index (Ht2/Z) and total body water in the very old: the Newcastle 85+ study. Arch Gerontol Geriatr 60:227–232
Signorello LB, Han X, Cai Q et al (2013) A prospective study of circulating 25-hydroxyvitamin D levels and mortality among African Americans and non-African Americans. Am J Epidemiol 177:171–179
Simpson RU, Thomas GA, Arnold AJ (1985) Identification of 1,25- dihydroxyvitamin D_3 receptors and activities in muscle. J Biol Chem 260:8882–8891
Singh KP, Dash RJ (1997) Vitamin D endocrine system. J Assoc Phys India 45:559–568
Slinin Y, Paudel ML, Taylor BC et al (2010) 25-Hydroxyvita- min D levels and cognitive performance and decline in elderly men. Neurology 74:33–41
Slinin Y, Paudel M, Taylor BC et al (2012) Association between circulating 25(OH) vitamin D and the risk of cognitive decline in older women. J Gerontol A Biol Sci Med Sci 67:1092–1098
Smit E, Crespo CJ, Michael Y et al (2012) The effect of vitamin D and frailty on mortality among non-institutionalized US older adults. Eur J Clin Nutr 66:1024–1028
Smith H, Anderson F, Raphael H et al (2007) Effect of annual intramuscular vitamin D on fracture risk in elderly men and women – a population-based, randomized, double-blind, placebo-controlled trial. Rheumatology (Oxford) 46:1852–1857
Snellman G, Melhus H, Gedeborg R et al (2010) Determining vitamin D status: a comparison between commercially available assays. PLoS One 5:e11555
Sohl E, van Schoor NM, de Jongh RT et al (2012) The impact of medication on vitamin D status in older individuals. Eur J Endocrinol 166:477–485
Sohl E, van Schoor NM, de Jongh RT et al (2013a) Vitamin D status is associated with functional limitations and functional decline in older individuals. J Clin Endocrinol Metab 98:E1483–E1490
Sohl E, de Jongh RT, Heijboer AC et al (2013b) Vitamin D status is associated with physical performance: the results of three independent cohorts. Osteoporos Int 24:187–196
The Scientific Advisory Committee on Nutrition (2016) Vitamin D and health. https://www.gov.uk/government/groups/scientific-advisory-committee-on-nutrition

Theoleyre S, Wittrant Y, Tat SK et al (2004) The molecular triad OPG/RANK/RANKL: involvement in the orchestration of pathophysiological bone remodeling. Cytokine Growth Factor Rev 15(6):457–475

Turner AG, Anderson PH, Morris HA (2012) Vitamin D and bone health. Scand J Clin Lab Invest Suppl 243:65–72

Van der Wielen RPJ, Lowik MRH, Van Den Berg H et al (1995) Circulating vitamin D concentrations among elderly people in Europe. Lancet 346:207–210

Verreault R, Semba RD, Volpato S et al (2002) Low circulating vitamin d does not predict new disability or loss of muscle strength in older women. J Am Geriatr Soc 50:912–917

Vieth R, Ladak Y, Walfish PG (2003) Age-related changes in the 25-hydroxyvitamin D versus parathyroid hormone relationship suggest a different reason why older adults require more vitamin D. J Clin Endocrinol Metab 88:185–191

Wahl DA, Cooper C, Ebeling PR et al (2012) A global representation of vitamin D status in healthy populations. Arch Osteoporos 7(1–2):155–172

Waldron JL, Ashby HL, Cornes MP et al (2013) Vitamin D: a negative acute phase reactant. J Clin Pathol 66:620–622

Wang S (2009) Epidemiology of vitamin D in health and disease. Nutr Res Rev 22:188–203

Wang Y, DeLuca HF (2011) Is the vitamin D receptor found in muscle? Endocrinology 152:354–363

Wang Y, Jacobs EJ, McCullough ML et al (2009) Comparing methods for accounting for seasonal variability in a bio- marker when only a single sample is available: insights from simulation based on circulating 25-hydroxyvitamin D. Am J Epidemiol 170:88–94

Webb AR, Kline L, Holick MF (1988) Influence of season and latitude on the cutaneous synthesis of vitamin D_3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D_3 synthesis in human skin. J Clin Endocrinol Metab 67:373–378

Welsh J (2012) Cellular and molecular effects of vitamin D on carcinogenesis. Arch Biochem Biophys 523:107–114

Wesnes KA (2008) Assessing change in cognitive function in dementia: the relative utilities of the Alzheimer's disease assessment scale-cognitive subscale and the cognitive drug research system. Neurodegener Dis 5(3–4):261–263

Wesnes KA, Ward T, McGinty A, Petrini O (2000) The memory enhancing effects of a Ginko biloba/Panax ginseng combination in healthy middle-aged volunteers. Psycho-pharmacology 152:353–361

White JH (2012) Vitamin D metabolism and signalling in the immune system. Rev Endocr Metab Disord 13(1):21–29

Wicherts IS, van Schoor NM, Boeke AJ et al (2007) Vitamin D status predicts physical performance and its decline in older persons. J Clin Endocrinol Metab 92:2058–2065

Wilson VK, Houston DK, Kilpatrick L et al (2014) Relationship between 25-hydroxyvitamin D and cognitive function in older adults: the health, aging and body composition study. J Am Geriatr Soc 62:636–641

Zittermann A, Iodice S, Pilz S et al (2012) Vitamin D deficiency and mortality risk in the general population: a meta-analysis of prospective cohort studies. Am J Clin Nutr 95:91–100