Update on Vitamin D

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Position statement by the Scientific Advisory Committee on Nutrition

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1. Summary

1. The main source of vitamin D in man is usually considered to be skin photosynthesis following irradiation with short wavelength ultra violet light (290-310 nm). Vitamin D is also found in a few foods, such as oily fish, fortified margarines and some breakfast cereals and there are smaller amounts in red meat and egg yolk.

2. 25-hydroxyvitamin D (25(OH)D) is the major circulating metabolite of vitamin D and plasma levels of this metabolite serve as an indicator of vitamin D status. Traditionally a plasma 25(OH)D concentration less than 25nmol/l (10ng/ml)[1] has been regarded an index of suboptimal vitamin D status. Recently higher thresholds have been proposed though the functional outcomes associated with them are currently unclear. Moreover, laboratory methodology for plasma 25(OH)D measurement is not well standardized.

3. Several factors potentially affect vitamin D status. These include genetic factors, adiposity and factors affecting the cutaneous synthesis of vitamin D such as skin pigmentation, age, season, latitude, melanin concentration, clothing and use of sunscreens. Seasonal variations in vitamin D status are observed in the UK where the 2000/1 National Diet and Nutrition Survey (NDNS) reported average plasma 25(OH)D concentrations to be highest in July-September and lowest in January-March. During winter, the UK population relies on body stores and dietary vitamin D to maintain vitamin D status. Solar UV radiation varies with latitude, and in winter months at latitudes of about 52° and above[2], there is no ultraviolet light of the appropriate wavelength for the cutaneous synthesis of vitamin D. For the remaining months, more than half the effective UV radiation occurs between certain times (1100 and 1500 hours) and is lower in the north than the south. Skin exposure to UV irradiation of the appropriate wavelength is essential for maintaining adequate vitamin D status and a clear recommendation on length and intensity of exposure is required.

1 1 2.5 nmol/l = 1 ng/ml

2 Mainland United Kingdom lies between 50°-60°N

4. The NDNS provides evidence of low vitamin D status, as defined by a plasma 25(OH)D concentration less than 25nmol/l, in most age groups in the UK population, especially older children and young adults, and in older people living in institutions. Young women of childbearing age also have low vitamin D status and are likely to begin their pregnancies with low stores. Other evidence highlights a greater risk of vitamin D deficiency in population subgroups, particularly infants from black and ethnic minority groups. Cases of rickets and hypocalcaemia in UK children, predominantly of Afro-Caribbean or South Asian origin, are widely reported but there are no NDNS data for these population subgroups.

5. The Dietary Reference Values (DRVs) as defined in the 1991 COMA report do not set a Reference Nutrient Intake for vitamin D for adults or children over four years of age who receive adequate sunlight exposure. The current Reference Nutrient Intake (RNI) for pregnant and breastfeeding women is 10µg (400 IU)[3] vitamin D per day. For children under the age of four years it is 7-8.5µg (280-340 IU) per day and for those in the population aged over 65 years or confined indoors is 10µg vitamin D per day.

Table 1. Reference Nutrient Intakes (RNI) for vitamin D (µg/d) (Department of Health, 1998)

Age	Males	Females
0-6 months	8.5	8.5
7 months to 3 years	7	7
4 years to 65 years	–	–
65+ years	10	10
Pregnancy		10
Lactation, 0-4 months		10
Lactation, 4+ months		10

Note: The above RNIs apply to healthy populations. Those at risk of inadequate sunlight exposure may require supplementation.

3 1µg = 40 international units (IU)

6. In most instances, these intakes cannot be met from the diet and at the present time can only be guaranteed by supplementation. A recommendation of 10μg (400 IU) a day has been made for pregnant and lactating women and for people over the age of 65 years. Although this has been in place for sometime, there is concern that it is overlooked or not implemented by health professionals and the general public.

7. Deficiency of vitamin D results in rickets and osteomalacia. The incidence of rickets in the UK declined from the 1920s onwards, which can partly be attributed to better living conditions, a reduction in atmospheric pollution, changes in diet, mandatory fortification of margarine with vitamin D and replacement of cow's milk by infant formula during the first year of life. Rickets and osteomalacia are now reported rarely among the white UK population although there is evidence of significant incidence in UK South Asian and Afro-Caribbean groups. There is also recognition of a high prevalence of low vitamin D status among older people, particularly those living in institutions. However, there are no population-based estimates of incidence and it is likely that many cases do not reach clinical attention. This has implications for long-term health and well-being.

8. A low vitamin D status has been implicated in a range of diseases including osteoporosis, several forms of cancer, cardiovascular disease, tuberculosis, multiple sclerosis and type I diabetes. Osteomalacia and osteoporosis both increase the risk of fracture. Research in these areas is developing, but evidence is inconclusive at present, and further work is needed before any definitive conclusions can be drawn.

2. Introduction

9. This paper highlights the re-emergence of rickets in population subgroups and the high prevalence of low vitamin D status throughout the UK population. The 1991 UK Dietary Reference Values (DRV) recommended that certain at-risk individuals or groups receive 7-10μg daily vitamin D (Table 1). A Reference Nutrient Intake of

10μg/d was set for pregnant and lactating women, for the majority of whom supplementation will be required. Recent antenatal guidance from the National Institute for Health and Clinical Excellence (NICE), however, stated that there was insufficient evidence to evaluate the effectiveness of vitamin D supplementation in pregnancy and that, in the absence of evidence of benefit, vitamin D supplementation should not be offered routinely to pregnant women (National Institute for Health and Clinical Excellence, 2003). Discrepancy between these recommendations has led to a lack of clarity, which requires resolution to ensure clear guidance to health professionals and the general public.

10. This report is not a systematic review of the relationship between vitamin D status and health but provides an update on vitamin D status and other related issues including a synopsis of evidence about the relationship between vitamin D status and chronic disease, to assess the need for full risk assessment.

3. Background

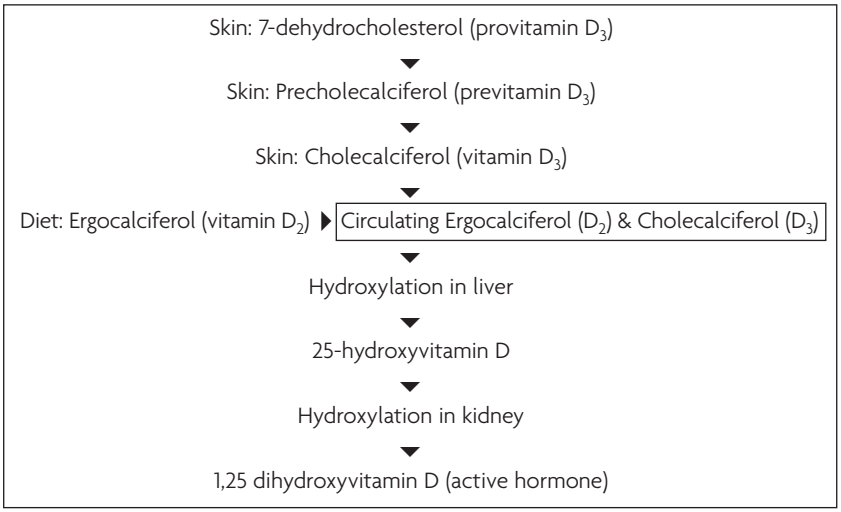
Vitamin D metabolism

11. Vitamin D is a pro-hormone that is produced photochemically in the skin from 7-dehydrocholesterol; however, if there is insufficient endogenous synthesis, generally caused by limited exposure of the skin to sunlight, then a dietary supply becomes essential. The action of sunlight (ultraviolet (UV) radiation of wavelength 290-310nm) on the skin converts 7-dehydrocholesterol to previtamin D3, which is then metabolized to vitamin D_3 by isomerization. Vitamin D_3 is transported by vitamin D-binding protein to the liver. Dietary vitamin D exists as either ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3), is fat-soluble and once ingested is incorporated into the chylomicron fraction, absorbed through the lymphatic system and transported to the liver. The liver enzyme 25-hydroxylase converts dietary and endogenously synthesized vitamin D_2 and D_3 to 25 hydroxyvitamin D (25(OH)D). Further conversion to the active form, 1,25-dihydroxyvitamin D (1,25 $(OH)_2D$), by 25(OH)D 1α-hydroxylase (1α-OHase) occurs under the influence of PTH in the kidney (DeLuca, 2004) (see Figure 1).

12. The only difference between ergocalciferol and cholecalciferol is the structure of the side chain to the sterol skeleton. Ergocalciferol is derived from the UV irradiation of the plant sterol ergosterol, which is widely distributed in plants and fungi, whereas, cholecalciferol is formed from the action of UV irradiation on skin. The widespread assumption that ergocalciferol and cholecalciferol are equipotent medicinally has recently been questioned (Houghton and Vieth, 2006).

13. The main circulating vitamin D metabolite is 25(OH)D and its concentration in plasma or serum is used as an indication of body status. The plasma concentration of $1,25(OH)_2D$, the active form of the vitamin involved in calcium metabolism, is homeostatically regulated (Holick, 2004). The plasma 25(OH)D concentration is about a thousand-fold higher than $1,25(OH)_2D$ concentration, and provides a substrate reservoir for 1α-OHase. The appearance in plasma of the parent compound, vitamin D, is short-lived since it is either taken up by adipose tissues or metabolized in the liver (Mawer *et al*., 1972). The half-life of plasma 25(OH)D is about 2-3 weeks (Lund *et al*., 1980); whereas, the half-life of plasma $1,25(OH)_2D$ is less than four hours (Holick, 2004).

Figure 1 The chemical conversion of vitamin D to the active hormone.



14. Vitamin D binding protein is a multi-functional plasma protein that transports vitamin D and its metabolites in the blood. It is a member of a gene family that includes albumin and alpha-fetoprotein and is identical to the group specific component (Gc-globulin) of serum. Vitamin D binding protein is synthesized in the liver and circulates at a concentration which is in excess of normal circulating vitamin D metabolite concentrations (Haddad, 1995). Like other fat-soluble compounds, only a small fraction of any vitamin D metabolite is freely dissolved in plasma. Vitamin D binding protein has a higher affinity for 25(OH)D than $1,25(OH)_2D$ (Bikle *et al*., 1985; Bikle *et al*., 1986; Teegarden *et al*., 1991) and it is the free fraction of $1,25(OH)_2D$ that is functional *in vivo* (Vieth, 1990).

Vitamin D function

15. $1,25(OH)_2D$ acts in concert with parathyroid hormone and calcitonin to maintain plasma calcium concentration within the normal range. This is achieved by regulating the efficiency of the small intestine to absorb calcium from the diet, by promoting the mobilization of calcium from the skeleton and by increasing the tubular reabsorption of calcium within the kidney (DeLuca, 2004). PTH and 1,25(OH)2D together stimulate osteoblasts to induce the maturation of preosteoclasts to osteoclasts, thereby increasing bone resorption.

16. The synthesis of $1,25(OH)_2D$ in the kidney is tightly regulated, principally through the action of PTH. Calcium-sensing proteins in the parathyroid gland stimulate PTH secretion in response to a fall in plasma calcium concentration. PTH promotes the renal synthesis of $1,25(OH)_2D$, which, in turn regulates the synthesis of PTH by negative feedback (DeLuca, 2004). This hydroxylation step may be impaired in the presence of renal disease.

17. An increase in plasma 25(OH)D concentration, when plasma $1,25(OH)_2D$ concentration remain unchanged, has been associated with suppression of plasma PTH concentration and an increased efficiency of calcium absorption (Heaney, 2004). It has been suggested that the local production of $1,25(OH)_2D$ (acting in an autocrine or paracrine fashion), as well as the endocrine function attributable to renal production, is important in many physiological processes (Fleet, 2004).

18. The active form of vitamin D, $1,25(OH)_2D$, interacts with a specific receptor (VDR) similar to other steroid hormones. This receptor acts through nuclear vitamin D-responsive elements, which are usually found within 1 kilobase of the start site of the target gene and are involved in the regulation of gene transcription. VDR is expressed in cells involved in calcium homeostasis, e.g. enterocytes, osteoblasts, parathyroid and distal renal tubule cells, but is also expressed in cells unrelated to calcium homeostasis. VDR is present in the small intestine, colon, osteoblasts, activated T and B lymphocytes, pancreatic ß-islet cells, and most organs in the body, including brain, heart, skin, gonads, prostate, breast, and mononuclear cells (DeLuca, 2004).

19. The 1α-OHase, which catalyses the conversion of 25(OH)D to $1,25(OH)_2D$, has been shown to be expressed in many extrarenal tissues, including osteoclasts, skin, macrophages, placenta, colon, brain, prostate, endothelium and parathyroid glands (Zehnder *et al*., 2001; Zehnder *et al*., 2002; Segersten *et al*., 2002; Schwartz *et al*., 2004; van Driel *et al*., 2006). Extrarenal production of $1,25(OH)_2D$ appears to play an important role in cell differentiation, proliferation and immune function. Vitamin D may therefore, be involved in other physiological processes, independently of calcium metabolism. In contrast to renal 1α-OHase, extrarenal 1α-OHase is known to be unresponsive to stimulation by PTH; there is a lack of feedback inhibition by $1,25(OH)_2D$ and relatively low levels of $1,25(OH)_2D$-directed catabolic 24-hydroxylase activity (Ren *et al*., 2005; van Driel *et al*., 2006).

4. Assessment of vitamin D status

20. Plasma 25(OH)D concentration is used to assess vitamin D status. Plasma or serum concentration of $1,25(OH)_2D$, and particularly free $1,25(OH)_2D$, is a measure of vitamin D hormone activity, but, because of tight physiological regulation and levels that are much lower than that of its precursor metabolite, it does not reflect vitamin D nutritional status.

21. Several units of measurement are used to describe vitamin D intake and plasma 25(OH)D concentration. For vitamin D intake, 1μg of dietary vitamin D is equivalent to 40 international units (IU). For plasma 25(OH)D concentration, 2.5nmol/l is equivalent to 1ng/ml.

22. Different methods may be used to measure serum or plasma 25(OH)D concentration but comparisons are complicated by a lack of standardization. Different laboratories and different methods, have been shown to yield different results from the same sample (Heaney, 2004; Binkley *et al*., 2004). The international Vitamin D Quality Assessment Scheme (DEQAS) was established in 1989 to monitor the performance of 25(OH)D assays and now has over 100 registered participants in 18 countries, including the UK. For samples containing only $25(OH)D_3$, DEQAS has found that most commercial 25(OH)D methods available in 2004 were capable of giving results close to the target value, but that the results were highly operator- and laboratory-dependent (Carter *et al*., 2004). To complicate further the interpretation of results, some assay methods failed to detect $25(OH)D_2$ with the same efficiency as $25(OH)D_3$ (Carter *et al*., 2004; Leventis *et al*., 2005). New high performance liquid chromatographic methods and mass spectrometric methods may offer more robust and reliable measurements (Lensmeyer *et al*., 2006).

23. Plasma 25(OH)D concentration in rickets and osteomalacia ranges from the undetectable to around 20nmol/l (Department of Health, 1998). A plasma 25(OH)D concentration of 25nmol/l has been used as a conventional cut-off for defining the lower limit of adequacy of vitamin D status (Department of Health, 1998); however, this approach has been questioned and higher thresholds have been proposed (e.g. Bischoff-Ferrari, 2006). This is reflected in the different thresholds adopted by studies cited later.

24. It has been suggested, for example, that vitamin D insufficiency or hypovitaminosis D, without clinical signs or symptoms, occurs at a plasma 25(OH)D concentration of less then 40nmol/l (Hanley & Davison, 2005), but there is no agreed definition. Based on associations between plasma 25(OH)D concentration and plasma PTH concentration, calcium absorption, bone turnover markers, and

bone mineral density, others have argued that a plasma 25(OH)D concentration of greater than 75nmol/l is more appropriate to define vitamin D sufficiency or physiologically optimal concentrations (Hollis, 2005; Bischoff-Ferrari *et al*., 2006).

25. The concept of establishing a reference range for plasma 25(OH)D concentration based on a threshold at which plasma PTH concentration starts to rise, is complicated by the large variation between individuals, the observation that this threshold varied between 30 and 78nmol/l in several studies, and the fact that that no threshold could be identified in some studies (Department of Health 1998; Bates *et al* 2003.) Dietary calcium intake and renal function influence plasma PTH concentration, and plasma PTH may also influence the turnover of Vitamin D metabolites (Lips, 2004). Inter-laboratory variation in determining plasma 25(OH)D concentration may also influence the definition of a reference range.

26. The inverse relationship between plasma 25(OH)D and PTH concentrations appears to be more pronounced with increasing age. Secondary hyperparathyroidism, associated with diminishing renal function, is observed in older people with poor vitamin D status (Vieth *et al*., 2003). In a study of 1741 adults, those aged over 70 years had a higher mean PTH concentration than those aged less than 50 years and the plasma 25(OH)D concentration associated with a minimal PTH concentration was higher in the older subjects (Vieth *et al*., 2003). The relationship between plasma 25(OH)D and PTH concentrations was investigated in the National Diet and Nutrition Survey (NDNS) of people aged 65 years and over (Bates *et al*., 2003). An inverse association was observed between plasma 25(OH)D and PTH concentrations, but there was no evidence of a threshold for plasma 25(OH)D concentration above which an irreducible minimum plasma PTH concentration was achieved.

27. Thresholds of plasma 25(OH)D concentration have been suggested, based on associations with chronic disease end-points in older adults, e.g. osteoporosis and colorectal cancer (Dawson-Hughes *et al*., 2005; Bischoff-Ferrari *et al*., 2006). The relevance of these thresholds in other age groups is unknown.

5. Dietary Reference Values for the UK

28. The Dietary Reference |Values (DRV) for vitamin D set in 1991 were based on the dietary amount required to maintain plasma 25(OH)D concentration in winter to prevent vitamin D deficiency (Department of Health, 1991a). A subsequent review examined the evidence on the relationship between bone health and vitamin D status and recommended no change to the DRV (Department of Health, 1998).

Table 1. Reference Nutrient Intakes (RNI) for vitamin D (µg/d) (Department of Health, 1998)

Age	Males	Females
0-6 months	8.5	8.5
7 months to 3 years	7	7
4 years to 65 years	–	–
65+ years	10	10
Pregnancy		10
Lactation, 0-4 months		10
Lactation, 4+ months		10

Note: The above RNIs apply to healthy populations. Those at risk of inadequate sunlight exposure may require supplementation.

29. For 4 to 65 year olds it is assumed that the action of summer sunlight will provide adequate vitamin D status, except for specific at risk groups who are not exposed to sufficient sunlight, e.g. women whose clothing conceals them fully, those who are confined indoors. The RNI for these at risk groups is 10µg/d. For the majority of people in this group, as well as the majority of pregnant and lactating women, people aged 65 years or more, infants and children aged up to 3 years, vitamin D supplementation will be needed to achieve the RNI (Department of Health, 1998).

6. Safe upper intake levels for vitamin D

30. The cutaneous conversion of 7-dehydrocholesterol to previtamin D_3, which spontaneously isomerizes to cholecalciferol, is regulated so that prolonged sunlight exposure does not lead to excess production; both precholecalciferol and cholecalciferol can be photolysed to inert compounds. High doses of oral vitamin D supplements, however, have been shown to have toxic effects (Vieth, 2006).

31. The toxic effects of vitamin D excess are primarily related to the role of the biologically active free form, $1,25(OH)_2D$, in the regulation of plasma calcium (Pettifor *et al*., 1995). Excessive production of $1,25(OH)_2D$ or greatly increased plasma 25(OH)D (which may displace $1,25(OH)_2D$ from its binding protein and/or stimulate paracrine/autocrine $1,25(OH)_2D$ production) can lead to an elevated plasma concentration of calcium (hypercalcaemia), due partly to over-stimulated intestinal absorption and partly to excessive calcium mobilization from bone. Hypercalcaemia could also lead to an increased calcium excretion into urine (hypercalciuria) (Vieth, 1990). Patients with sarcoidosis are abnormally sensitive to vitamin D, due to uncontrolled conversion of the vitamin to its active form in the granulomatous tissue. Although the condition is uncommon, it would be a potential hazard if affected individuals were to take supplementary vitamin D (Expert Group on Vitamins and Minerals, 2003) and would be the same for those with primary hyperparathyroidism. Increased risk of hypercalcaemia has also been associated with combined treatment with vitamin D and thiazide related diuretics (Mehta, 2006).

32. In the UK, the Expert Group on Vitamins and Minerals report on safe upper levels for vitamins and minerals concluded that, for guidance purposes only, a level of 25µg/d supplementary vitamin D would not be expected to cause adverse effects in the general population when consumed regularly over a long period.

33. The EU Scientific Committee on Food Opinion from 2002, published as part of the European Food Safety Authority tolerable upper intake levels for vitamins and minerals report (Scientific Committee on Food & Scientific Panel on Dietetic Products, 2006) could not establish a no observed adverse effect level (NOAEL) or a lowest observed adverse effect level (LOAEL), due to uncertainty in the data. A tolerable upper intake level (UL) was established at 25μg/d for infants and children aged 10 years or less and 50μg/d for children aged over 11 years and adults.

34. The US Standing Committee on the Scientific Evaluation of Dietary Reference Intakes set a UL for infants aged up to 12 months of 25μg/d and for children aged 1 to 18 years and adults a UL of 50μg/d (Institute of Medicine, 1997).

35. There is some controversy over the recommended safe upper limits in Europe and the USA. It has been argued that published cases of vitamin D toxicity with hypercalcaemia, for which the plasma 25(OH)D concentration and vitamin D dose are known, all involved an intake of ≥1000μg/d and that the UL of 50 μg/d, in the US, is too low by at least 5-fold (Vieth, 1999; Vieth, 2006). However, these studies involved no more than four weeks of supplementation, which may not be enough time for a steady state to be achieved (Scientific Committee on Food & Scientific Panel on Dietetic Products, 2006).

36. A risk assessment by Hathcock *et al* (2007) based on well designed clinical trials of vitamin D in which doses in a range of 50-2500μg/day were used, suggested that vitamin D is not toxic at intakes well above current upper safe limits (Hathcock *et al*, 2007).

7. Sources of Vitamin D

Dietary sources

37. There are few dietary sources of vitamin D. In the UK, rich sources are oily fish (5-10µg/100g), e.g. salmon, mackerel, sardines and fortified foods, e.g. margarines (~7µg/100g) and some breakfast cereals (3-8µg/100g) (see *Vitamin D Food Fortification section below*). Red meat (~1µg/100g) and egg yolk (~5µg/100g) also provide vitamin D.

38. Supplemental vitamin D contains either ergocalciferol or cholecalciferol. Studies in the 1930s did not show any differences in antirachitic activity between the two forms, but more recent studies have suggested that cholecalciferol increases plasma 25(OH)D concentrations more efficiently than does ergocalciferol (Tjellesen *et al*., 1986; Trang *et al*., 1998; Armas *et al*., 2004). A lower binding affinity of ergocalciferol metabolites to the vitamin D binding protein in plasma may be a factor in these differences (Houghton & Vieth, 2006).

39. A nationwide cohort study of dietary and lifestyle predictors of hypovitaminosis D in British adults aged 45 years found circulating 25(OH)D concentrations significantly higher in participants who used vitamin D supplements (200 IU) or oily fish than in those who did not ($P<0.0001$ for both) (Hypponen & Power, 2007).

40. A supplement is recommended for breastfed infants from 6 months of age. Infant formula sold in the UK is fortified with vitamin D (Infant Formula and Follow-on Formula Regulations, 1995) and so the recommendation is to commence supplementation if average consumption of infant formula or follow-on formula falls below 500ml/day. In both instances this may need to be commenced earlier in the absence of sun exposure at the appropriate wavelength, or if the mother was at suboptimal status during pregnancy (Ahmed *et al*., 1995; Mughal *et al*., 1999; Ziegler *et al*., 2006).

41. A reformed scheme for provision of welfare foods, Healthy Start, was launched in November, 2006; this provides for beneficiaries licensed supplements containing vitamins A, C and D for children and vitamins C, D and folic acid for pregnant and breastfeeding mothers.

42. Most commercial multivitamin preparations contain vitamin D but are deemed unsuitable for pregnant women because of their vitamin A content. No licensed single component vitamin D supplement currently supplies the recommended dose of 10μg/day, although this dose is combined with calcium in some. More recently, single food supplements containing 10μg of vitamin D are available.

Vitamin D food fortification

43. In the UK, manufacturers have practised voluntary fortification of margarine with vitamins since 1925. In 1940, with the advent of war, the Government mandated addition of vitamins A and D to all margarine sold for domestic use. This mandatory fortification was justified by evidence that a large proportion of the population, particularly children, were at risk of deficiency. Levels of added vitamin A were chosen to equate to the levels found in butter, but it was felt that vitamin D levels should be higher since margarine in the diet was considered to be the easiest, and possibly the only, means of ensuring an adequate supply of this vitamin to children in some sections of the community. Fat spreads, which have a fat content of less then 80%, are not subject to specific legislation, but some brands are fortified voluntarily to the same levels as margarine (Department of Health, 1991b). This policy of fortification, together with other factors such as the later Clean Air Acts, improved housing, increasing affluence and longer and more frequent holidays, appeared to have been effective. Enquiries by the Ministry of Health between 1963 and 1966 confirmed a low prevalence of rickets in some industrial cities, notably Glasgow (Department of Health, 1991b).

44. In 1952 an outbreak of failure to thrive and hypercalcaemia, occasionally fatal, was described amongst infants and young children. Excessive intakes of vitamin D were suggested as a causative factor. At that time, cod liver oil compounds, infant milks and cereals were all fortified with vitamin D. The Ministry of Health and the Department of Health for Scotland concluded in 1957 that infants had unnecessarily high intakes of vitamin D and the levels in cod liver oil compound, infant milks and cereals, were reduced (British Paediatric Association, 1956; Ministry of Health and Department of Health for Scotland, 1957). In 1960, the incidence of idiopathic hypercalcaemia was believed by many British paediatricians to have decreased since reduction of the vitamin D content of various infant foods and supplements. Although it was generally inferred that a causal relation between vitamin D and infantile hypercalcaemia had been established, rigorous epidemiological evidence of a reduction in incidence was not available (Fraser, 1967).

45. Early in the 1970s there were reports of vitamin D deficiency rickets and osteomalacia in the UK, particularly in South Asian immigrants. COMA, therefore, convened a Working Party on Fortification of Food with Vitamin D which reported in 1980 (Department of Health and Social Security, 1980) confirming that rickets and osteomalacia did occur in South Asian children and women. It recommended that appropriate dietary supplements should be used and, that the mandatory fortification of margarine with vitamin A and D should continue. However it did not recommend that fortification with vitamins A and D be extended to any other foods.

46. In the US and a number of other countries, milk is fortified with vitamin D. In Finland in February 2003, the vitamin D fortification of liquid milk products (0.5µg/dl milk) and margarines (10µg/100g) was introduced. A study of 196 young Finnish men (aged 18-28 years) observed that the prevalence of a serum 25(OH)D concentration <40nmol/l decreased by 50%, from 78% in January 2003, before fortification to 35% in January 2004 (Laaksi *et al*., 2006). A study of Finnish children indicated that national fortification of fluid milks and margarines with vitamin D safely improved the vitamin D status of the children, where mean intakes and mean serum 25(OH)D concentrations were both higher after fortification (Piirainen *et al*., 2007).

47. However, another study (Valimaki *et al*., 2007) observed that vitamin D fortification in Finland improved the vitamin D status of 65 young Finnish men only marginally during winter: 33.8% of men had a serum 25(OH)D concentration ≤20nmol/l prefortification compared to 29.2% postfortification. The median serum 25(OH)D concentration prefortification was 24nmol/l compared to 27nmol/l postfortification.

48. Reports of hypervitaminosis D in the US caused by the inadvertent over-fortification of milk (Jacobus *et al*., 1992; Blank *et al*., 1995) have highlighted the need for careful monitoring of the effects of fortification programmes.

200,000 IU of vitamin D was a bit excessive

Exposure to sunshine

49. It is thought that most people in the UK obtain the majority of their vitamin D by exposure of skin to sunlight (Department of Health, 1998). The skin has a large capacity to produce vitamin D and exposure of about 20% of the body's surface to either direct sunlight or equivalent tanning bed radiation was effective in increasing the plasma concentration of 25(OH)D in both young adults and older adults (Holick, 2004).

50. The exact relationship between skin exposure to sunlight of the necessary wavelength and subcutaneous vitamin D synthesis is not well defined. For example, in Cincinnati (latitude 38° N) during the spring, summer, and autumn, exclusively breastfed infants aged less than six months spending 20 minutes a day out of doors with exposed hand and face maintained 25(OH)D concentration above 27.5nmol/l (Specker *et al*., 1985). It is suggested that exposure to sunlight for 5-15 min between the hours of 10:00 and 15:00 during the spring, summer, and autumn at latitudes above 37° may be adequate for individuals with lighter skin (Holick, 2004).

51. The WHO/Euroskin Workshop on Vitamin D and UVR met in 2005, to discuss the growing controversy around how best to optimize vitamin D status while minimizing the risk of diseases associated with sunshine exposure. The Workshop concluded that sun exposure is responsible for a substantial burden of skin and eye disease, and may

play a role in reactivating some viral diseases. They also recognized that inadequate vitamin D status is a serious health issue but that more research is needed to establish optimal vitamin D status for different groups within the general population. The solar UV index is an international standard measurement of how strong the ultraviolet radiation from the sun is at a particular place on a particular day. The group suggested that use of the solar UV index might be beneficial, where reference to location (latitude) and the likely UV sensitivity (skin type) of the recipient in articulating the need for varying levels of protection. It was agreed that the index should be actively promoted and form part of a sun protection programme, but presented in such a way as to enable individuals to relate the index to their own skin in interpreting what protective actions might be appropriate. There was general agreement that moderation of sun exposure is an important goal and that the key message is to ensure that people protect themselves when Solar UV Index is greater than 3 (McKinlay, 2006).

Exposure to sunshine and skin cancer

52. Most cases of skin cancer are caused by damage from UV rays in sunlight. As part of its SunSmart campaign, Cancer Research UK (CRUK) advises avoidance of the summer sun between 11am and 3pm by covering up with suitable clothing and by using a high-factor sunscreen when shade or clothing are not practical options (CRUK, 2007). Fairer skinned people, those with a family history of skin cancer and people with many moles are at greater risk of skin cancer and need to take more care in the sun.

53. CRUK recognizes that a balance must be found to reduce further increases in skin cancer rates while also allowing enough sun exposure for optimal concentrations of vitamin D. A meeting to discuss the amount of sunlight needed for optimum health in European populations was convened in October 2005. CRUK, together with its advisory group of experts, is currently working on a collaborative position statement (CRUK, 2006).

8. Dietary intakes and vitamin D status in the UK

54. The 1998 COMA report on Bone Health concluded that British children aged 0-3 years, pregnant and lactating women and people aged 65 years or older, all of whom are vulnerable to vitamin D deficiency, had low dietary intakes even when provision from supplements was included. The contribution of supplements appears to be minimal except for infants and young children.

55. The DRV committee (Department of Health, 1998) assumed that most people aged 4-64 years of age will receive enough vitamin D from exposure of their skin to sunlight. Within this group, however, there may be individuals who are at risk of vitamin D deficiency and require dietary vitamin D to maintain adequate status. For these 'at risk' groups, e.g. where sunlight exposure is restricted, the RNI is 10μg/d and supplements may be necessary.

Infants and young children

56. The NDNS of 1.5-4.5 year olds (Gregory *et al*., 1995) found that mean intake of vitamin D from all sources was 1.9μg/d (median 1.1μg). Vitamin D intake from dietary supplements increased average intake by about half for all children. There were no significant differences between boys and girls or between age cohorts in intakes from food or from all sources. Children aged 1.5-2.5 obtained 17% of their mean vitamin D intake from "other milk and products", which included infant formula (fortified with vitamin D); children aged 2.5-4.5 obtained only 2-5% from these sources. Vitamin D fortified spreads (26%) and breakfast cereals (17%) were the other main food sources of vitamin D for all children.

57. Mean plasma 25(OH)D concentration for children 1.5-4.5 years was 68.1nmol/l and there was no apparent association with age or sex. There was seasonal variability in concentrations – highest among children assessed between July and September and lowest among children assessed between January to March. Plasma 25(OH)D concentration was below 25nmol/l in 1% of children. The relation between vitamin D intake and status was also seasonally dependent,

being strong in the winter and negligible in the summer (Davies *et al*., 1999).

58. A population survey in 1996 of children aged 2 years (n=618) of Bangladeshi, Indian, or Pakistani origin living in England showed that 20-34% had a plasma 25(OH)D concentration (measured during October-November 1996) less than 25 nmol/l; 3-18% had a value below 20nmol/l (Lawson & Thomas, 1999). A significant association was found between failure to take a vitamin supplement, chapatti consumption and low plasma 25(OH)D concentration (Lawson *et al*., 1999).

59. The 1998 COMA report on Bone Health concluded that *"vitamin D status, assessed from plasma 25(OH)D, of the majority of the population of children under 4 years appears to be satisfactory"*. Some minority groups of children remain at risk due to factors associated with lifestyle. The current programme of vitamin D supplementation for this section of the population should continue. Education programmes to reinforce this policy appear to be needed.

Older children

60. The NDNS of 4-18 year olds (Gregory *et al*., 2000) showed that mean daily intake of vitamin D from food sources for boys was 2.6µg, significantly higher than that for girls at 2.1µg (medians 2.4 and 1.9µg/d, respectively). Mean intake increased with age. The main dietary sources of vitamin D were cereal and cereal products (37% boys and 35% girls), fat spreads (20% both sexes), meat and meat products (20% both sexes) and oily fish (7% boys and 9% girls). Supplements of vitamin D increased mean intake from food sources by 8% for boys and 5% for girls. Predominantly the younger children took supplements; in the 4 to 6 age group, supplements increased mean intake by 19% for boys and 22% for girls.

61. Correlation between plasma 25(OH)D concentration and dietary intake of vitamin D was very weak and did not reach the level of statistical significance at any age or sex group. The mean plasma 25(OH)D concentration was 62.0nmol/l for boys and 60.6nmol/l for girls. Three percent of boys and 2% of girls aged 11 to 18 years had a

plasma 25(OH)D concentration less than 12nmol/l. The proportion below 25nmol/l increased with age for both boys and girls from 3% for boys and 2% for girls aged 4 to 6 years to 10-16% for boys aged 11 to 18 and 10-11% for girls aged 11-18. Plasma concentration was influenced by season of sample collection, as for younger children. Boys aged 11 to 18 years were the most likely to have low vitamin D status. From January to March there were 19% of boys in the age group with low status, 15% from April to June, 6% from July to September and 10% from October to December. The functional consequences of low status at this age are uncertain and the possibility that low plasma 25(OH)D concentration reflects physiological change at puberty cannot be excluded.

62. A study in Manchester showed that of 51 adolescent girls (aged 14.7 to 16.6 years; 14 white; 37 non-white) 73% (n=37) had a plasma 25(OH)D concentration below 30nmol/l and 17% (n=9) below 12.5nmol/l (Das *et al*., 2006). Non-white girls (21 South Asian; 5 Middle Eastern; 1 black) were more severely vitamin D deficient. Reduced sunlight exposure, rather then diet, accounted for the differences in vitamin D status.

Pregnant and lactating women

63. Vitamin D deficiency in infancy is associated with poor maternal vitamin D status. Vitamin D deficiency in pregnant mothers is associated with congenital rickets and craniotabes in the newborn (Specker, 1994) and with rickets in infancy, especially when the child is exclusively breastfed (Mughal *et al*., 1999; Kreiter *et al*., 2000). Poor maternal vitamin D status can adversely affect fetal and infant skeletal growth and ossification, tooth enamel formation and calcium handling (Specker, 1994) even in the absence of clinical rickets in the child. The vitamin D status of the infant appears to be more influenced by the vitamin D status of the mother during pregnancy, and by the infant's sunshine exposure, than by maternal vitamin D status during lactation (Specker, 1994).

64. Both maternal vitamin D status in pregnant women and infant exposure to UV radiation, are major factors affecting infant vitamin D status. However, infant plasma 25(OH)D concentration does not correlate with milk 25(OH)D concentration of the mother's milk,

unless the mother receives high doses of supplemental vitamin D (Specker, 1994; Hollis & Wagner, 2004). A dose of 50μg/d given to lactating mothers increased infant plasma 25(OH)D concentration, yet a dose of 25μg/d did not do so (Ala-Houhala, 1985; Ala-Houhala *et al*., 1986); supplementation of infants with 10μg/d vitamin D raised plasma 25(OH)D concentration to a similar extent to maternal supplementation with 50μg/d. In breastfeeding women a dose of 50μg/d, and more so 100μg/d, of vitamin D_2 and vitamin D_3 was shown to raise breast milk concentrations of vitamin D and 25(OH)D, and infant plasma 25(OH)D concentration (Hollis & Wagner, 2004). Maternal exposure in pregnancy and lactation to UV radiation of appropriate wavelengths has been shown to increase the anti-rachitic activity of human milk (Greer *et al*., 1984). Under normal circumstances, the sunshine exposure of breastfed infants is the major factor affecting their vitamin D status (Specker, 1994).

65. There is no national information on the vitamin D status of pregnant and lactating women. A study of 160 pregnant women from non European ethnic minorities living in South Wales found that 50% of women had a plasma 25(OH)D concentration below 20 nmol/l on their first antenatal visit (Datta *et al*., 2002). The study found that fluency in English, dressing habits and religion did not appear to influence status, but a higher proportion of women who had lived in Britain for longer than three years had a low 25(OH)D concentration. A relatively high number of South Asian mothers in Leicester have also been reported to have vitamin D deficiency at the end of pregnancy (Shenoy *et al*., 2005), although the authors do not indicate how this was assessed.

66. A study of white women and their offspring (n=198) in Southampton (latitude 50° N) (Javaid *et al*., 2006), observed 31% of mothers had a serum 25(OH)D concentration between 27.5-50nmol/l and 18% had a serum 25(OH)D concentration less than 27.5nmol/l during late pregnancy. Mothers who had a serum 25(OH)D concentration of less than 27.5nmol/l in pregnancy had an offspring whose whole-body bone mineral content at 9 year's of age was lower than those born to mothers with a higher plasma 25(OH)D concentration. Both the estimated exposure to UVB radiation during late pregnancy and the maternal use of vitamin D supplements predicted maternal 25(OH)D concentration and childhood bone mass. A low concentration of

umbilical-venous calcium also predicted lower childhood bone mass. In addition, 25(OH)D concentrations in excess of 75nmol/l in mothers during pregnancy did not appear to influence the child's intelligence, psychological health or cardiovascular system but the authors reported an increased risk in atopic disorders which needs further confirmation (Gale *et al*., 2007).

Adults aged 19-64 years

67. Mean daily intake of vitamin D from food sources was 3.7µg for men and 2.8µg for women. Inclusion of supplements containing vitamin D increased mean intake by 14% in men, to 4.2µg, and by 32% for women, to 3.7µg. For women aged 50-64 years supplements increased mean daily vitamin D intake by 46%, from 3.5µg to 5.1µg. Median daily intake from all sources, was 2.1µg for women (aged 19-64 years) living in a household receiving certain benefits, compared with 2.9µg for women not receiving benefits (Henderson *et al*, 2003).

68. The NDNS of 19-64 year olds (Ruston *et al*., 2004) showed that the mean concentration of plasma 25(OH)D was 48.3nmol/l for men and 49.6 nmol/l for women. A plasma 25(OH)D concentration below 25 nmol/l was found in around 15% of the adult population overall and a quarter of the 19-24 age group. This proportion was higher during the winter months.

69. A study in Birmingham of 240 adults compared plasma 25(OH)D concentration in South Asians with non-Asians (white and Afro-Caribbean) (Pal *et al*., 2003). South Asians had a lower plasma 25(OH)D concentration than non-Asians in both summer and winter; the majority of South Asians had a concentration below 30nmol/l (94% in winter; 82% in summer). Again, the functional outcome of low vitamin D status for this age group is unknown.

Adults aged over 65 years

70. Mean vitamin D intake was below the RNI (10µg) in all groups: mean daily intake from all sources was 3.47µg for institutionalized and 3.92µg for free-living subjects. Overall, 6% of men and 10% of women in the free-living group had a plasma 25(OH)D concentration below 25nmol/l; this increased in the winter months (Finch *et al*, 1998).

71. Vitamin D status was significantly worse in the institution group than in the free-living group. Over a third of men and women had a plasma 25(OH)D concentration below 25nmol/l and there was no evidence of seasonal variation. Vitamin D intake from food sources was below the RNI (10µg/day) with mean daily intakes of 3.42µg for institutionalized and 3.40µg for free-living subjects, and the contribution from supplements was low (Finch *et al*, 1998). The relationship between plasma 25(OH)D concentration and vitamin D intake in free-living subjects was seasonal: 25(OH)D concentration was associated with vitamin D intake in the winter, but not in the summer (Bates *et al*., 2003).

72. In the Health Survey for England 2000, serum 25(OH)D concentration was measured in 1,766 people aged 65 years and over living in private households and institutions (Hirani & Primatesta, 2005). The mean serum 25(OH)D concentration was lower for both men (38.1nmol/l) and women (36.7nmol/l) in institutions than among men (56.2nmol/l) and women (48.4nmol/l) in private households. In institutions, the prevalence of serum 25(OH)D concentration below 25nmol/l was 30.2% for men and 32.5% for women, while in private households women (15.0%) had a higher prevalence of low 25OHD concentration than men (9.6%).

Summary

73. The NDNS provides evidence of low vitamin D status in most population age groups, especially older children and young adults, and in older people living in institutions. Figure 2 below shows the percentage of people from different age groups with a plasma concentration of 25-hydroxy D below 25nmol/l. Almost a third of young women of childbearing age (19-24 years) appear to have low status and are likely to start pregnancy with low maternal stores. Routine supplementation of this group of women will be necessary, as recommended by COMA, in order to ensure adequate fetal supply and stores in the newborn.

74. Other studies also highlight population subgroups, e.g. those of South Asian origin, that have an even higher high prevalence of low vitamin D status and in whom rickets is increasingly common.

Figure 2 Percentage in NDNS with a plasma 25(OH)D concentration <25 nmol /l. F, free living; I, institutionalized.

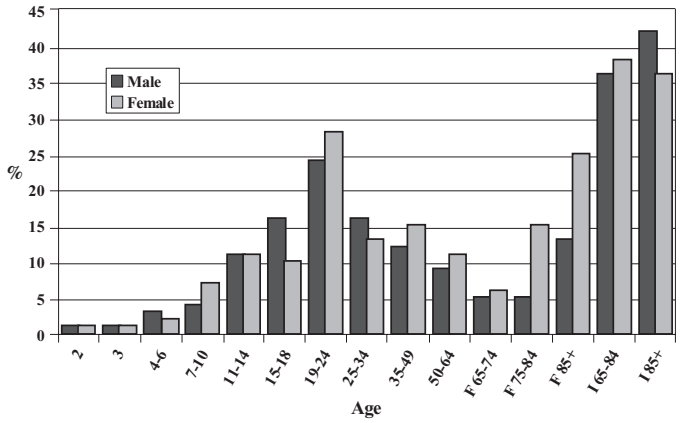
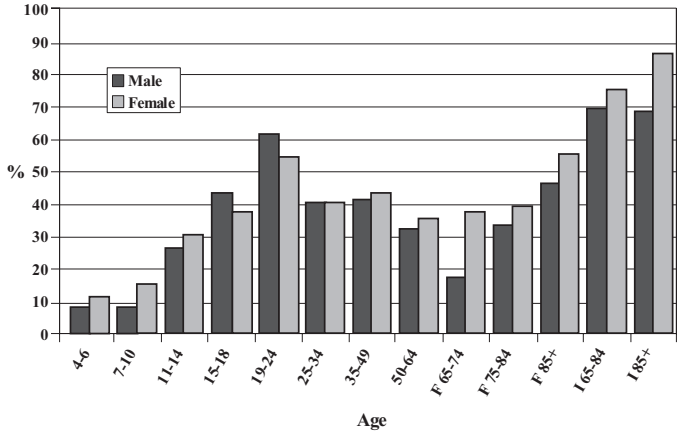


Figure 3. Percentage in NDNS with a plasma 25(OH)D concentration <40 nmol /l. F, free living; I, institutionalized. Data for 1.5-4.5 year olds not available.



9. Factors affecting the cutaneous synthesis of vitamin D

Season and latitude

75. Solar UV radiation varies with latitude, time of year and time of day. From mid-October to the beginning of April at latitudes of about 52° and above (the UK is at latitude 50-60°N) there is no UV radiation of appropriate wavelength for the cutaneous production of previtamin D3 (Webb & Holick, 1988). For the remaining months of the year 60% of the effective UV radiation occurs between 11:00 and 15:00 hours, but is lower in the north than the south (CRUK, 2007).

76. Seasonal variations in plasma 25(OH)D concentration are observed in the UK. The 2000/1 National Diet and Nutrition Survey (NDNS) of adults aged 19 to 64 years reported average plasma 25(OH)D concentration to be highest in July-September (64.5nmol/l for women; 64.9nmol/l for men) and lowest in January to March (38.7nmol/l for women; 40.8nmol/l for men) (Ruston *et al*., 2004). Summer plasma 25(OH)D concentration correlates with exposure to UV radiation and is largely a result of time spent outdoors as well as the amount of skin exposed (which can be subject to cultural influences) (Holick, 2004). A nationwide cohort in British adults aged 45 years (Hypponen & Power, 2007) found the prevalence of hypovitaminosis D in the general population was higher during the winter and spring months and authors suggested action at a population level rather than at a risk group level.

77. During winter, the UK population relies on body stores and dietary vitamin D to maintain vitamin D status. The relative contribution of body stores and dietary intake is not well defined. In the UK, two studies of data from the NDNS of children and adults aged 65 years and over (Davies *et al*., 1999; Bates *et al*., 2003), observed the relationship between vitamin D intake and status to be seasonally dependent, being stronger in the winter and negligible in the summer. A study in healthy subjects in the US (Omaha; latitude 41.2° N) suggested that greater than 80% of the requirement for vitamin D

in the winter months was met from body stores (Heaney *et al*., 2003). A study in those aged over 65 years and over in the UK estimated that the plasma concentration during the summer months needed to be greater than 40nmol/l to maintain plasma 25(OH)D concentration above 20nmol/l during winter (Lawson *et al*., 1979).

Age

78. The amount of 7-dehydrocholesterol in the epidermis is relatively constant until later in life, when it begins to decline; a person 70 years of age exposed to the same amount of sunlight as a 20-year-old person makes about 25% of the vitamin D_3 that the younger person can make (Holick, 2004).

Skin pigmentation and ethnicity

79. Skin pigmentation can also affect vitamin D_3 production, because melanin absorbs UV radiation in the 290-320nm range and functions as a light filter determining the amount of incident UV radiation available for the cutaneous production of previtamin D_3 (Norman, 1998). A study in Boston, USA (latitude: 42°N), observed mean plasma 25(OH)D concentration in young black women (n=51) to be less then half that in young white women (n=31) (Harris & Dawson-Hughes, 1998). Equally, whole body exposure to UV radiation resulted in a higher plasma 25(OH) D concentration in white and East Asian subjects than in South Asian or black subjects (Matsuoka *et al*., 1991). Another study observed that a higher dose of UV radiation was required to increase plasma 25(OH)D concentration in South Asian subjects than white subjects, but the capacity to produce vitamin D was no different in Asian than in white skin (Lo *et al*., 1986). It has also been suggested that altered vitamin D metabolism (increased 25(OH)D-24 hydroxylase activity) may be responsible for the high prevalence of low 25(OH)D concentration observed in South Asians (Awumey *et al*., 1998).

Skin covering, and the avoidance of direct sun exposure

80. Laboratory studies have shown that clothing prevents or significantly impairs the formation of vitamin D_3 after photostimulation (Matsuoka *et al*., 1992). A study in Lebanon measured serum 25(OH)D concentration in 316 young adults (99 men and 217 women) from rural and urban areas. Almost three quarters of the study population had a concentration below 25nmol/l, which was more common in women than in men, particularly in veiled women. In a multiple regression analysis; vitamin D intake, dwelling, veiling, and parity were independent predictors of hypovitaminosis D (Gannage-Yared *et al*., 2000).

81. A study in 321 healthy Saudi Arabian females showed that 52% had a 25(OH)D concentration ≤20nmol/l (Ghannam *et al*., 1999). This study did not specify the type of clothing, but a study in Kuwait showed that veiled women had lower 25(OH)D concentration than non-veiled women (el Sonbaty & Abdul-Ghaffar, 1996).

Sunscreen use

82. Sunscreens are designed to prevent the entry of UV radiation through the skin. Sunscreen with a sun protection factor (SPF) of 8 was shown to reduce the capacity of the skin to photoisomerize 7-dehydrocholesterol to previtamin D_3 by more than 95% in one laboratory based study (Matsuoka *et al*., 1987) and, in a preliminary study, long-term users of sun screening agents were observed to have a lower serum 25(OH)D concentration than non-users (Matsuoka *et al*., 1988).

83. It has been suggested that the regular use of sunscreens might impair vitamin D status (Holick *et al*., 1995; Ness *et al*., 1999). A prospective study of 24 sunscreen users and 19 controls over 2 years, observed seasonal variation in serum 25(OH)D concentration in all subjects with slightly lower winter concentration in the sunscreen users (Farrerons *et al*., 1998). However, a recent study of British 45 year old adults found that the use of sun protection was associated with slightly higher (rather than lower) 25(OH)D concentrations, which

suggests that the use of sunscreen partly reflects levels of sun exposure (Hypponen & Power, 2007).

84. A randomized controlled trial of the daily use of sunscreen (SPF 17) versus placebo cream over a summer period in Melbourne, Australia (latitude 37°S) was conducted in 113 people aged 40 years (Marks *et al*., 1995). No differences by age, sex, and skin type were observed in the change in serum concentrations of 25(OH)D and 1,25(OH_2)D over the study period. The authors suggest that over an Australian summer sufficient skin exposure to sunlight was received, probably through both the sunscreen itself and the lack of total skin cover at all times, to allow a similar level of vitamin D production between people who are recommended to use sunscreens regularly and those who are not. No person using sunscreen developed serum vitamin D levels below the reference range over the period of the study.

Atmospheric pollution

85. The first evidence of the importance of sunlight for human health began with the industrial revolution in northern Europe, where people congregated in cities and lived in dwellings that were built in close proximity to each other. The burning of coal and wood polluted the atmosphere reducing direct exposure to sunlight and, as a result, many children living in these industrialized cities developed rickets (Holick, 2004).

86. A study in India, compared serum 25(OH)D concentration in children 9-24 months old, from two regions of Delhi: one renowned for high levels of atmospheric pollution, the other less polluted (Agarwal *et al*., 2002). Children living in areas of high atmospheric pollution had a mean serum 25(OH)D concentration of 31nmol/l, less than half that of those living in the less polluted area.

10. Other factors affecting vitamin D status

Vitamin D and adiposity

87. Vitamin D is fat-soluble and can be stored in the body fat. Adipose tissue was found to be the major site where vitamin D accumulated in human tissues after injection of radioactive vitamin D_3 (Mawer *et al*., 1972). It is thought that excess vitamin D_3 produced during exposure to sunlight, and that what is not broken down in the skin, is deposited in body fat.

88. A lower serum 25(OH)D concentration and a higher serum PTH concentration were observed in obese subjects compared with non-obese subjects (Compston *et al*., 1981; Hey *et al*., 1982; Bell *et al*., 1985; Liel *et al*., 1988; Zamboni *et al*., 1988; Buffington *et al*., 1993; Hyldstrup *et al*., 1993; Need *et al*., 1993; Wortsman *et al*., 2000; Parikh *et al*., 2004; Snijder *et al*., 2005; Hypponen & Power, 2006), suggesting that the larger body fat compartments in the obese individuals sequester vitamin D. In obese subjects exposure to the same amount of UV radiation raised plasma 25(OH)D concentration by only 50% compared with non-obese subjects (Wortsman *et al*., 2000). The content of the vitamin D_3 precursor 7-dehydrocholesterol in the skin was not significantly different between obese and non-obese subjects and the percentage conversion to previtamin D_3 and vitamin D_3 was similar in both groups. Obesity did not, therefore, affect the capacity of the skin to produce vitamin D_3, but may have altered the release of vitamin D_3 into the circulation, due to more being deposited in subcutaneous fat in obese subjects.

89. Total body fat, as determined by whole body dual energy x-ray absorptiometry scan (Arunabh *et al*., 2003; Snijder *et al*., 2005) and bioelectrical impedance analysis (Looker, 2005), has been shown to be inversely associated with plasma 25(OH)D concentration in healthy subjects. Amount of leg fat was more strongly inversely related to 25(OH)D concentration compared with abdominal fat, which might support the concept that endogenously produced

vitamin D is deposited particularly in the subcutaneous fat depot (Snijder *et al*., 2005).

90. Several small studies have reported morbidly obese individuals to have a higher $1,25(OH)_2D$ serum concentration than non-obese individuals (Hey *et al*., 1982; Bell *et al*., 1985; Liel *et al*., 1988; Zamboni *et al*., 1988). However, a more recent study in 302 healthy adults (152 obese) reported $1,25(OH)_2D$ serum concentration to be lower in obese subjects and to be inversely associated with percent total body fat, as determined by whole body dual energy x-ray absorptiometry scan (Parikh *et al*., 2004). Methodological differences may be a factor in the apparent discrepancy with the earlier studies.

Genetics

91. Several polymorphisms in the *VDR* gene have been investigated with regard to vitamin D status. A UK study of 143 healthy British South Asians, aged 31-65 years old, found serum 25(OH)D concentration did not vary with VDR genotype (*Apa*I, *Bsm*I, *Fok*I and *Taq*I polymorphisms) (Ogunkolade *et al*., 2002); however, a study in Finnish women (n=93) observed that BB homozygotes *Bsm*I polymorphism of the *VDR* gene had a higher winter serum 25(OH)D concentration than other genotypes (Laaksonen *et al*., 2002). In a study of 185 adolescent French girls, homozygotes for two polymorphisms in the promoter region of *VDR* had a lower serum 25(OH)D concentration than other genotypes (d'Alesio *et al*., 2005). Phenotypes of the vitamin D-binding protein (Gc-globulin) were associated with plasma $1,25(OH)_2D$ and 25(OH)D concentrations in 595 Danish postmenopausal women, being highest in Gc1-1, intermediate in Gc1-2, and lowest in Gc2-2 phenotype (Lauridsen *et al*., 2005).

92. In a study of 33 subjects, duodenal expression of the calcium channel/transporter gene *TRPV6* was strongly positively associated with plasma $1,25(OH)_2D$ concentration in men, but not in women, suggesting that *TRPV6* expression was vitamin D dependent in men (Walters *et al*., 2006). An analysis of the *CDX2*-site polymorphism in the *VDR* promoter region, showed that in the *GG* genotype, but not the *AG* genotype, duodenal *TRPV6* expression was positively associated with plasma $1,25(OH)_2D_3$ concentration (Walters *et al*., 2004).

11. Vitamin D deficiency

93. Vitamin D deficiency impairs the absorption of dietary calcium and phosphorus, which results in poor mineralization of the skeleton (Holick, 2006). Severe vitamin D deficiency generally presents as rickets and osteomalacia in children and osteomalacia in adults. Rickets and osteomalacia are conditions characterized by pathological defects in growth plate and bone matrix mineralization. Histologically, the end result is an increased quantity of unmineralized bone matrix (osteoid).

94. In children, failure of bone mineralization gives rise to bone deformities; bones are painful and linear growth is reduced. In adults, bone pain and tenderness are the most prominent features of osteomalacia and proximal myopathy may also develop. Rickets can be precipitated by dietary calcium or phosphorus deficiency and calcipenic and hypophosphataemic rickets have been observed in children who are vitamin D sufficient (Thacher *et al*., 1999) – the use of the term 'rickets' below refers to vitamin D deficiency rickets only.

95. Rickets is the commonest presentation of vitamin D deficiency in children, but vitamin D deficiency may also present with hypocalcaemic symptoms – usually seizures, but occasionally more serious manifestations such as cardiomyopathy (Ladhani *et al*., 2004).

96. In children with vitamin D deficient rickets, plasma 25(OH)D concentrations below 20nmol/l have been observed, and in adults with osteomalacia concentrations below 10nmol/l have been observed (Department of Health, 1998).

97. Antagonistic interaction between retinol and vitamin D may have implications for bone health. Recent epidemiological evidence suggests that post-menopausal women with long-term high intakes of preformed retinol have an increased risk of hip-bone fracture. These findings are supported by animal data, which have indicated that retinol has a direct effect on bone, possibly via an interaction with vitamin D, and an effect on parathyroid hormone and therefore

calcium metabolism (Expert Group on Vitamins and Minerals, 2003). The vitamin D status of certain population subgroups, e.g. older people confined indoors and people from ethnic communities wearing enveloping clothing, may be poor and high intakes of retinol might be of greater concern in these populations (Scientific Advisory Committee on Nutrition, 2005).

Reports of clinically apparent vitamin D deficiency among children in the UK

98. Prior to 1900, rickets affected about two-thirds of infants in the UK with the incidence of rickets peaking at the end of the 1800s. The incidence of rickets declined dramatically from the 1920s onwards, which may be partly attributed to better living conditions and changes in diet. In the period 1926-1942, studies in the UK indicated a prevalence of radiological signs of rickets among young children of 2% to 8%. A survey of 23 areas in the UK in 1943, showed on average, around 2% of infants had radiological signs of rickets (Department of Health and Social Security, 1980). Margarine was compulsorily fortified with vitamin D in the 1940s and cod liver oil, originally given as part of the Welfare Food Scheme (WFS), was substituted with vitamin supplements in 1975 (Department of Health, 2002). National Dried Milk was also fortified and manufacturers soon followed suit by adding vitamin A and D to infant milks, rusks and cereals. In the 1970s targeted campaigns of vitamin D supplementation, predominantly in Asian communities, helped further reduce the incidence of rickets in the UK (Dunnigan *et al*., 1985).

99. The sporadic incidence of rickets has continued; however, there is no information on the national prevalence of clinically apparent vitamin D deficiency in the UK. An unpublished review undertaken by Kings College, London in the 1990s (at the request of DH) confirmed that the problem of vitamin D deficiency and rickets, when occurring, still remained predominantly a problem in Asian populations. Where rickets was identified it was associated with strict vegetarian diets and breastfeeding exclusively without vitamin D supplementation for periods longer than 6-months. Inadequate maternal status during pregnancy is likely to have been the important antecedent factor in such circumstances.

100. Over the past few years there have been several reports of clinically apparent vitamin D deficiency in UK children (infants and adolescents) (Pal & Shaw, 2001; Shaw & Pal, 2002; Ashraf & Mughal, 2002; Crocombe *et al*., 2004; Odeka & Tan, 2005; Shenoy *et al*., 2005; Callaghan *et al*., 2006; Zipitis *et al*., 2006). Most, though not all, of the cases that occur in the UK are seen in patients of Afro-Caribbean or South Asian origin. Although skin pigmentation is a factor, other factors, such as diet and low exposure to sunlight (either by staying indoors or covering the skin) are also important. An increase in clinically apparent vitamin D deficiency has been reported even in countries where sunlight is plentiful (Robinson *et al*., 2006), underlining the importance of these lifestyle factors. Breastfeeding exclusively without vitamin D supplementation for periods longer than 6 months also appears to be important (Ahmed *et al*., 1995; Mughal *et al*., 1999) particularly when associated with inadequate maternal status during pregnancy. It should be noted, however, that there is the possibility of a detection bias in reporting the link between ethnic group and South Asian children, as most of the reports come from areas with high South Asian populations; furthermore, national data are available for South Asian but not black children.

101. A study in Glasgow, compared dietary intakes of 62 cases of rickets and osteomalacia and 113 normal women and children (Dunnigan *et al*., 2005). An inverse association was observed between meat consumption and risk of rickets and osteomalacia; the relationship was curvilinear and relative risk did not fall further at meat intakes above 60g daily. Daylight outdoor exposure was also inversely associated, and dietary fibre intake positively associated, with risk of rickets and osteomalacia.

102. In a child health clinic in Manchester, six cases of florid rickets were described in infants of Asian ethnicity aged 10 to 28 months between 1995 and 1997 (Mughal *et al*., 1999). The clinic subsequently reported that a further 8-10 non-white children with florid rickets were identified at their unit each year between 2001 and 2002 (Ashraf & Mughal, 2002). In a study of 124 ethnic minority children aged 6 to 36 months, two were identified with rickets, giving a prevalence of 1.6% (Ashraf & Mughal, 2002).

103. A prospective survey conducted from May 2000 to April 2001 in the West Midlands reported 24 cases of clinically apparent vitamin D deficiency among children aged 0-4 years (Callaghan *et al*., 2006); only one child was of white ethnic origin, the rest were either of South Asian or Afro-Caribbean origin. It was estimated from census data that the overall incidence was 7.5 per 100,000 children, with children of South Asian origin having an incidence of 38 per 100,000 and of Afro-Caribbean origin children having an incidence of 95 per 100,000. A separate survey of children under the age of 16 years presenting to three Birmingham hospitals between June 2001 and June 2003 identified 65 cases.

104. A study in three London hospitals examined 65 children who presented with either rickets or hypocalcaemia and a plasma 25(OH)D concentration below 25 nmol/l; 39 children were of Asian origin, 24 Afro-Caribbean, and two were Eastern European. Forty five percent (n=29) had hypocalcaemic symptoms, of whom 55% (n=17) had no radiological evidence of rickets; 48 children had radiological evidence of rickets, with or without other clinical signs (Ladhani *et al*., 2004). Children who presented with hypocalcaemia were either under the age of 2 years or in adolescence. The authors speculated that during rapid bone growth hypocalcaemia develops before rickets can ensue.

105. A study at Leicester hospital observed significant numbers of south Asian mothers having vitamin D deficiency at the end of pregnancy, and substantial numbers of children having infantile and adolescent rickets, some of whom have extremely severe bony deformities (Shenoy *et al*., 2005). Increasing numbers of hypocalcaemic newborns, presenting predominantly with seizures, were also reported.

106. A survey conducted at the Burnley Health Care NHS Trust between 1994 and 2004 identified 14 cases of children presenting with clinically apparent (hypocalcaemia, rickets) vitamin D deficiency (Zipitis *et al*., 2006). Thirteen of the 14 patients were of South Asian origin. From 1994 to 2001 there were 3 cases, but from 2002 to 2004 11 cases were reported, highlighting the rising incidence of clinically

apparent vitamin D deficiency in the British Asian child community. The incidence of clinically recognized vitamin D deficiency was 1 in 117 for the Trust's Asian population compared to 1 in 923 in the general population. The rise in incidence of rickets, especially in British Asian children, observed in the study was attributed to the lack of maternal vitamin D supplementation (Zipitis *et al*., 2006).

107. In the US, an assessment of women participating in the WIC programme (Special Supplemental Food Programme for Women, Infants and Children) suggested that factors that may have contributed to the increase in referrals of children with nutritional rickets included more African American women breastfeeding, fewer infants receiving vitamin D supplements and mothers and children exposed to less sunlight (Kreiter *et al*., 2000).

Prevention of deficiency

108. Many countries have attempted to prevent such problems by ensuring that vulnerable groups receive dietary supplements of vitamin D during critical periods, such as pregnancy, lactation and infancy. In the UK, there is a specific recommendation for pregnant and lactating women, infants, the elderly and black and ethnic minority groups.

109. The UK RNI for vitamin D for all pregnant and breastfeeding women is 10µg of vitamin D daily, and for breastfed babies is 7-8.5µg daily from the age of six months or earlier if there is increased risk of deficiency by virtue of low maternal status. It is essential that pregnant women receive sufficient vitamin D to build up their own stores and fetal stores to ensure adequate supply to infants during the first six months of life. Vitamin drops for children under 5 years of age (included in Healthy Start) contain 7.5µg of vitamin D and supplements for pregnant and nursing mothers contain a daily dose of 10µg.

110. There is concern that these recommendations are overlooked by health professionals (Callaghan *et al*, 2006; Department of Health, 1998), as well as by the general public. The Review of the Welfare Food Scheme identified that uptake of vitamin drops in the UK is very low even amongst those entitled to receive free supplies. The Review concluded that the provision of free vitamin supplements offers a simple and potentially effective means of preventing adverse nutritional outcomes, particularly rickets. Rickets remains evident in the UK and it is likely that the prevalence would increase among high risk groups if the Scheme were withdrawn (Department of Health, 2002).

111. It has been questioned whether relying on vitamin D supplements given to infants or vitamin D supplementation of formula feeds is adequate to overcome the impact of maternal vitamin D deficiency (Shaw & Pal, 2002). This is also reinforced in a recent survey by Callaghan *et al* (2006), which highlighted that recommendations for vitamin D supplementation were being ignored and that 50% of those presenting with hypocalcaemic convulsions were formula-fed, implying that these infants had low stores of vitamin D at birth (Callaghan *et al*, 2006).

112. There appears to be lack of awareness in high risk groups of the recommendations to take vitamin D supplements (Allgrove, 2004; Shenoy *et al*., 2005; Callaghan *et al*., 2006); furthermore, an audit in the Leicester area reported that while health professionals were aware of the issue there was no clear policy to resolve it (Iqbal *et al*., 2001).

113. Although antenatal guidance from NICE stated that vitamin D supplementation should not be offered routinely to pregnant women (National Institute for Health and Clinical Excellence, 2003), the Chief Medical Officer subsequently endorsed the COMA vitamin D recommendations for vulnerable groups including (Department of Health, 1998) pregnant and nursing mothers, young children and older people (Chief Medical Officer, 2005).

12. Vitamin D and chronic disease

114. New data continue to emerge regarding the health benefits of vitamin D. Although a full systematic review was not undertaken, much evidence suggests that vitamin D may be implicated in a range of other diseases including osteoporosis, several forms of cancer, cardiovascular disease, tuberculosis, multiple sclerosis and type I diabetes (Appendix 1). Both osteoporosis and osteomalacia increase the risk of fractures. Research in these areas is developing, but evidence is inconclusive at present and further work is needed before any definitive conclusions can be drawn.

115. In addition, there is no clear relationship between biochemical measures of vitamin D status and clinical outcomes, which may have implications for setting the Reference Nutrient Intakes. At present there is insufficient evidence to warrant a full review of the DRVs.

13. Conclusions

116. A significant proportion of the UK population have low vitamin D status based on the current COMA definition (a plasma 25-hydroxy vitamin D concentration below 25nmol/L). This increases their risk of vitamin D deficiency. This is a particular concern for pregnant and breastfeeding women, infants, the elderly and black and ethnic minority groups.

117. A lack of national data, for certain population subgroups, particularly South Asian and Afro-Caribbean; pregnant and breastfeeding women; infants, makes it difficult to estimate precisely the prevalence of low vitamin D status in the UK population. The Committee suggests the need for further national surveys of vitamin D status, particularly in black and minority ethnic groups, in order to fully quantify the problem in the UK and to monitor prevalence into the future.

118. Accumulating evidence suggests that vitamin D may be important for health outcomes other than rickets and osteomalacia, and that plasma concentrations of 25(OH)D several fold higher than 25nmol/l may be required for optimal health. Current data is insufficient to clarify relationships between intake, biochemical status and chronic disease outcomes.

119. Sufficient skin exposure to solar UV radiation of the appropriate wavelength is essential for maintaining adequate vitamin D status in the UK. There is a need to state clearly the length and intensity of exposure necessary to balance maintenance of vitamin D status with the risk of developing skin cancer.

120. The Committee reiterates the current Dietary Reference Values for vitamin D set by COMA for pregnant and breastfeeding women, young children, people aged 65 years and over, and individuals who are at risk of inadequate sunshine exposure, including recommendations on the use of dietary supplements to achieve these.

121. The Committee also explicitly reiterates that all pregnant and breastfeeding women should consider taking a daily supplement of vitamin D in order to ensure their own requirement for vitamin D is met and to build adequate fetal stores for early infancy. A supplement suitable for this group has recently become available[4]. A clear public health strategy and guidance on vitamin D supplementation is necessary to overcome poor understanding and advice among health professionals and at risk groups of the population.

122. There is an urgent need to standardize laboratory methodologies for the measurement of plasma 25(OH)D concentration. There is also a need to identify markers of functional outcome in different age and vulnerable groups to refine the interpretation of plasma 25(OH)D measurements. This will allow more robust assessment of the

4 Under the Healthy Start scheme, free vitamins containing 70mg vitamin C, 10µg vitamin D and 400µg folic acid, are available for women who receive Healthy Start vouchers while they are pregnant and for one year after the birth of their child.

relationships between plasma 25(OH)D concentration and health outcomes in order to define threshold concentrations indicative of adequate population status.

123. There is a need to understand better the effects of adiposity on circulating 25-hydroxyvitamin D concentration and its implications for vitamin D requirements.

124. Further risk assessment and consideration of existing Dietary Reference Values will only be warranted when definitive evidence becomes available. Completion of ongoing research by the Food Standards Agency within the next 3-4 years will be contributory.

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Appendix 1

Vitamin D and diseases other than rickets and osteomalacia

125. Evidence suggests that low vitamin D status is implicated in a range of diseases including osteoporosis, several forms of cancer, cardiovascular disease, tuberculosis, multiple sclerosis and type I diabetes. Although the following section is not a systematic review of published studies, the following review highlights evidence for a relationship between low vitamin D status and disease.

Osteoporosis and fracture risk

126. Osteoporosis is a condition resulting from reduced bone mass and disruption of the micro-architecture of bone giving decreased bone strength and increased risk of fracture. Two meta-analyses of primary prevention supplementation trials (5 trials for hip fracture risk (n=9,294), 7 trials for non-vertebral fracture risk (n=9,820), and 5 trials for falls (n=1,237)) concluded that vitamin D supplements may have a beneficial effect on bone mineral density, fracture risk (Bischoff-Ferrari *et al*., 2005) and falls (Bischoff-Ferrari *et al*., 2004). The beneficial effects were observed in trials of older adults where the dose of vitamin D was between 17.5 and 20μg/d, but not at 10μg/d, and when serum 25(OH)D concentration was about 75 nmol/l or more.

127. Several trials have been published since these meta-analyses were conducted. A secondary prevention trial in people aged 70 years (n=5,292) or more who had had a low-trauma, osteoporotic fracture in the previous 10 years, found no evidence of a beneficial effect of 20μg/d vitamin D_3 over 2 years on fracture prevention (Grant *et al*., 2005). Based on the observed rise in serum 25(OH)D concentration in a subset of subjects, and the recorded compliance rate, it has been suggested that a lack of subject compliance and low baseline concentrations resulted in serum 25(OH)D concentration being too low for an effect on fracture rate (Bischoff-Ferrari *et al*., 2006).

128. In another trial conducted in the UK (Porthouse *et al*., 2005) 3,314 women, aged 70 years and over with one or more risk factors for hip fracture, received either daily supplements of 1000 mg of elemental calcium with 20μg of vitamin D_3 and an information leaflet on dietary calcium intake and prevention of falls, or leaflet only for 25 months. No effect of supplementation on fracture rates was observed; although, the odds ratio for hip fracture was 0.75 the 95% confidence intervals were large (0.31 to 1.78). Serum 25(OH)D concentration was not measured in this trial. It has been suggested that the open design of the trial and instruction to the control group to ensure adequate calcium and vitamin D intakes may have biased the result towards the null hypothesis (Bischoff-Ferrari *et al*., 2006).

129. A prospective study in the US (McAlindon *et al*., 1996), reported low intake and low serum concentration of 25(OH)D to be associated with an increased risk for progression of osteoarthritis of the knee. Another prospective study in the US, reported that subjects with serum 25(OH)D concentration in the highest tertile had a reduced risk of incident changes of radiographic hip osteoarthritis, but not with incident hip osteoarthritis defined as the development of definite osteophytes or new disease (Lane *et al*., 1999).

130. In a US trial among healthy postmenopausal women (n=36,282) involving supplementation with calcium and vitamin D (1000 mg/d of elemental calcium and 10μg/d of vitamin D_3) did not significantly reduce hip fracture rate, although hip bone mineral density was slightly improved. However, a detrimental effect of supplementation (increased risk of kidney stones) was observed in this study (Jackson *et al*., 2006). Again, based on the observed rise in serum 25(OH)D concentration in a subset of subjects, it has been suggested that a higher dose of vitamin D_3 would have been required to see an effect on fracture rates (Bischoff-Ferrari *et al*., 2006).

131. A recent review of the effects of vitamin D or analogues in the prevention of fractures in older people (Avenell *et al*, 2006), indicated that frail older people confined to institutions may sustain fewer hip and other non-vertebral fractures if given vitamin D (17-20μg/d) with calcium supplements. However, there was no evidence

of effect of vitamin D with calcium on vertebral fractures and effectiveness of vitamin D alone in fracture prevention was unclear.

Colorectal cancer

132. Vitamin D insufficiency has been implicated in the development of cancer (Garland *et al*., 2006), especially colorectal cancer (Gorham *et al*., 2005; Giovannucci, 2006). The evidence from prospective cohort studies that have investigated dietary vitamin D intake and colorectal cancer risk are mixed. Several studies found an inverse association (Garland *et al*., 1985; Martinez *et al*., 1996; McCullough *et al*., 2003), whilst others either showed no association (Jarvinen *et al*., 2001; Lin *et al*., 2005) or an inverse association which was not significant after adjustment for confounding variables (Bostick *et al*., 1993; Kearney *et al*., 1996).

133. A small nested case-control prospective study (34 cases) in the US (Garland *et al*., 1989), observed a serum 25(OH)D concentration of 50nmol/l or more to be associated with a reduced risk of colon cancer.

134. In a prospective nested case-control study in the US (Feskanich *et al*., 2004), higher plasma concentration of 25(OH)D was associated with a lower risk of colorectal cancer in women aged 46 to 78 years (193 colorectal cancer cases), particularly for cancers at the distal colon and rectum. Several case-control studies determining the risk of colorectal adenoma in relation to serum 25(OH)D concentration have also reported an inverse association and based on the available epidemiological evidence it has been argued that a serum 25(OH)D concentration of ≥90nmol/l would be optimal (Bischoff-Ferrari *et al*., 2006).

135. A prospective study in the US (Giovannucci *et al*., 2006) considered multiple determinants of vitamin D exposure (dietary and supplementary vitamin D, skin pigmentation, adiposity, geographic residence and leisure-time physical activity - to estimate sunlight exposure) in relation to cancer risk. Based on measurements in 1,095 men of this cohort, Giovannucci *et al* quantified the relation of these six predictors to plasma 25(OH)D level and used results from the

multiple linear regression model to predict 25(OH)D levels for each of 47,000 men and prospectively examined this variable in relation to cancer risk. A predicted low plasma 25(OH)D concentration was associated with increased cancer incidence and mortality, particularly for digestive-system cancers. This study used an indirect assessment of plasma 25(OH)D concentration that could be influenced by established surrogates such as race and geographic residence.

136. A trial among healthy postmenopausal women (n=36,282), calcium with vitamin D supplementation (1000 mg/d of elemental calcium and 10μg/d of vitamin D_3) for 7 years did not reduce the risk of colorectal cancer (Wactawski-Wende *et al*., 2006). It has been suggested, however, that, based on the epidemiological evidence, the supplementation period was not long enough, nor the dose of vitamin D sufficient, for an effect to become apparent (Bischoff-Ferrari *et al*., 2006).

Other cancers

137. Some epidemiological evidence also suggests associations between low vitamin D status and risk of prostate and breast cancers, but the evidence is weak (Giovannucci, 2005). A review of case-control and cohort studies (Cui & Rohan, 2006) found no association between dietary vitamin D intake and breast cancer risk, but plasma 25(OH)D concentration was inversely associated with breast cancer risk in a case-control study (Lowe *et al*., 2005), but not significantly in a prospective nested case-control study (Bertone-Johnson *et al*., 2005).

138. Pre-diagnostic serum 25(OH)D concentration has been assessed in relation to prostate cancer risk in several prospective nested-case control studies. A 3-fold increased risk was observed in Finnish men aged less then 50 years with serum 25(OH)D concentration of <40nmol/l (Ahonen *et al*., 2000). A study in Swedish and Norwegian men observed both high (≥80nmol/l) and low (≤19nmol/l) serum 25(OH)D concentrations to be associated with a higher prostate cancer risk (Tuohimaa *et al*., 2004). Several prospective nested case-control studies conducted in the US have,

however, observed no association between serum 25(OH)D concentration and prostate cancer risk (Corder *et al*., 1993; Braun *et al*., 1995; Gann *et al*., 1996; Nomura *et al*., 1998; Platz *et al*., 2004). It has been suggested that the subjects in the US studies may have a higher mean vitamin D status than the subjects in the Nordic studies; subsequently, the increased risk associated with a low 25(OH)D concentration in the Nordic studies may be difficult to detect in the US studies (John *et al*., 2005).

139. A prospective study in the US, in cohorts of 46,771 men ages 40 to 75 years and 75,427 women ages 38 to 65 years, examined the relation between dietary vitamin D intake and pancreatic cancer risk (Skinner *et al*., 2006). Compared with participants in the lowest category of total vitamin D intake (<3.75μg/d), pooled adjusted relative risks for pancreatic cancer were 0.78 (95% CI, 0.59-1.01) for 3.75-7.47μg/d, 0.57 (95% CI, 0.40-0.83) for 7.50 to 11.22μg/d, 0.56 (95% CI, 0.36-0.87) for 11.25-14.97μg/d, and 0.59 (95% CI, 0.40-0.88) for ≥15μg/d (P_{trend} = 0.01).

140. In a prospective nested case-control study in male Finnish smokers, those in the highest quintile of serum 25(OH)D concentration (>65.5nmol/l) had a 3-fold increased risk for pancreatic cancer relative to those in the lowest quintile (<32.0nmol/l) (Stolzenberg-Solomon *et al*., 2006).

Cardiovascular disease

141. Low vitamin D status has also been implicated in cardiovascular disease risk (Zittermann *et al*., 2005), although the evidence is relatively weak (Bischoff-Ferrari *et al*., 2006).

142. A trial, conducted in men with congestive heart failure who were randomly assigned to receive a placebo or vitamin D (50μg/d), found no effect of vitamin D on either left ventricular function or 15-mo survival rates (Schleithoff *et al*., 2006); however, the serum concentration of tumor necrosis factor-α, an inflammatory cytokine, decreased with vitamin D treatment; in contrast, the concentration of interleukin 10, an anti-inflammatory cytokine, increased.

143. One trial observed a beneficial effect of vitamin D_3 supplementation (33µg/d for one month) on insulin sensitively in type 2 diabetics (Borissova *et al*., 2003) and a study, in normoglycemic subjects, observed insulin sensitivity to be positively correlated with 25(OH)D concentration. A concentration below 50nmol/l was associated with reduced pancreatic ß cell function (Chiu *et al*., 2004). An association between type II diabetes and a low serum 25(OH)D concentration in British South Asians has also been observed (Boucher, 2006).

144. Two trials have reported a lowering effect of the active form of vitamin D on blood pressure in normocalcaemic (Lind *et al*., 1988b) and hypercalcaemic individuals (Lind *et al*., 1988a). A trial giving either a single oral dose of 2.5 mg vitamin D_3 or placebo to 189 elderly individuals in the winter observed no effect on blood pressure nor serum cholesterol concentrations after 5 weeks (Scragg *et al*., 1995). A trial in 148 elderly women, with a serum 25(OH)D concentration below 50nmol/l, who received either supplemental calcium (1200 mg/d) or supplemental calcium (same dose) and vitamin D (20µg/d) for 8 weeks, observed that the group receiving calcium and vitamin D had a 9.3% decrease in systolic blood pressure relative to those receiving calcium alone (Pfeifer *et al*., 2001). A large prospective study on over 200,000 subjects in the US, however, found no association between vitamin D intakes and hypertension (Forman *et al*., 2005).

145. In 146 healthy, non-diabetic British South Asians both soluble C-reactive protein concentration and plasma metalloproteinase 9 concentration were inversely related to vitamin D status (Timms *et al*., 2002). A higher plasma concentration of C-reactive protein metalloproteinase 9 has been associated with an increased risk of cardiovascular disease.

Tuberculosis

146. Vitamin D deficiency has been associated with susceptibility to tuberculosis (Ustianowski *et al*., 2005), but paradoxically, tuberculosis has been associated with increased production of the active vitamin D metabolite, $1,25(OH)_2D_3$ (Barnes *et al*., 1989). TB-

activated monocytes and macrophages account for increased $1,25(OH)_2D_3$ production in and the increased vulnerability of subjects with vitamin D deficiency to tuberculosis was explained by the requirement for sufficient 25(OH)D as substrate for $1,25(OH)_2D_3$ production by the activated monocytes/macrophages (Liu *et al*., 2006). Activation of Toll-like receptors (TLRs) during infection triggers direct antimicrobial activity against intracellular bacteria which up-regulates expression of the VDR and 1α-OHase, leading to induction of the antimicrobial peptide cathelicidin and subsequent killing of intracellular Mycobacterium tuberculosis. This suggests that there may be a higher requirement for vitamin D in tuberculosis.

Other diseases

147. A prospective study in Finland observed that dietary vitamin D supplementation was associated with a reduced risk of type I diabetes (Hypponen *et al*., 2001). Another study observed an association between supplementation in infancy and an increased risk of atopy and allergic rhinitis in later life (Hypponen *et al*., 2004). A multi-centre study in the EU, also observed that vitamin D supplementation in infancy was associated with a decreased risk of type I diabetes (EURODIAB Substudy 2 Study Group, 1999).

148. A prospective study in the US (Munger *et al*., 2004), observed vitamin D intake from supplements, but not foods, to be inversely associated with risk of multiple sclerosis. A subsequent prospective, nested case-control study observed the risk of multiple sclerosis to be inversely associated with serum 25(OH)D concentration (Munger *et al*., 2006). Those in the lowest quintile of serum 25(OH)D concentration (<63.3nmol/l) had a higher associated risk of multiple sclerosis than those in the highest quintile (>99.1nmol/l).