Review

Emphasizing the Health Benefits of Vitamin D for Those with Neurodevelopmental Disorders and Intellectual Disabilities

William B. Grant 1,*, Sunil J. Wimalawansa 2, Michael F. Holick 3, John J. Cannell 4, Pawel Pludowski 5, Joan M. Lappe 6, Mary Pittaway 7 and Philip May 8

1 Sunlight, Nutrition, and Health Research Center, PO Box 641603, San Francisco, CA 94164-1603, USA
2 Department of Medicine & Endocrinology, Cardio Metabolic Institute, Somerset, NJ 08873, USA; E-Mail: suniljw@hotmail.com
3 Department of Medicine, Section of Endocrinology, Nutrition, and Diabetes, and the Vitamin D, Skin, and Bone Research Laboratory, Boston University Medical Center, Boston, MA 02118, USA; E-Mail: mfholick@bu.edu
4 Vitamin D Council and San Luis Obispo Integrative Medicine, San Luis Obispo, CA 93401, USA; E-Mail: jjcannell@vitamindcouncil.org
5 Department of Biochemistry, Radioimmunology, and Experimental Medicine, The Children’s Memorial Health Institute, 04-730 Warsaw, Poland; E-Mail: pludowski@yahoo.com
6 Creighton University School of Medicine, Omaha, NE 68131, USA; E-Mail: joanlappe@creighton.edu
7 Global Clinical Advisor-Health Promotion, Special Olympics International and Affiliate Faculty, College of Education and Human Sciences, University of Montana, Missoula, MT 59812, USA; E-Mail: mpitt59802@aol.com
8 International Foundation for Chronic Disabilities, Inc., PO Box 166, Oxford, NJ 07863, USA; E-Mail: pmay1@mindspring.com

* Author to whom correspondence should be addressed; E-Mail: wbgrant@infionline.net; Tel.: +1-415-409-1980.

Received: 23 October 2014 / Accepted: 5 February 2015 / Published: 27 February 2015

Abstract: People with neurodevelopmental disorders and intellectual disabilities have much greater health care needs. Mainly staying indoors, such people generally have low 25-hydroxyvitamin D (25(OH)D) concentrations. The Vitamin D Task Force of the American Academy of Developmental Medicine and Dentistry (AADMD) reviewed the evidence of 25(OH)D concentrations that benefit the health of persons with developmental disabilities. Maintaining recommended optimal serum 25(OH)D concentrations year long will benefit skeletal development in infants, children, and adolescents, and benefit musculoskeletal...
health and neuromuscular coordination in adult patients, and decrease risk of falls. Maintaining optimal concentrations decreases risks and severities of autoimmune diseases, cardiovascular disease, many types of cancer, dementia, types 1 and 2 diabetes mellitus, and respiratory tract infections. Other benefits include improved dental and oral health and improved physical performance. The Task Force recommends that 25(OH)D concentrations for optimal health to be in the range of 75 to 125 nmol/L, which can be achieved using between 800 and 4000 IU/day vitamin D3 and sensible exposure to solar UVB radiation. The paper also discusses the potential risks of higher 25(OH)D concentrations, the evidence from and limitations of randomized controlled trials, and the recommendations by various groups and agencies.

**Keywords:** autism; bone health; cancer; cardiovascular disease; developmental disabilities; down syndrome; fractures; intellectual disabilities; vitamin D; 25-hydroxyvitamin D

---

1. Introduction

People with neurodevelopmental disorders and intellectual developmental disabilities (IDD), or medically complex developmental disabilities (MCDD), require much greater health care than other patient populations. According to the American Academy of Developmental Medicine and Dentistry (AADMD), the most commonly diagnosed neurodevelopmental disorders are Down syndrome, fetal alcohol spectrum disorder, fragile X syndrome, cerebral palsy, autism, and intellectual disability of unknown origin [1]. The Canadian consensus guidelines for adults with developmental disabilities [2] summarize these and related issues for such people in Canada.

People with MCDD are prone to having low blood concentrations of 25-hydroxyvitamin D (25(OH)D) for several reasons, including generally staying indoors or excessive use of sunscreens, propensity to obesity, and taking various medications [3]. These people therefore have higher rates of osteopenia and osteoporosis [4], chronic diseases, [5–8], respiratory infections [9], and poorer oral health [10] than community-dwelling individuals. Evidence suggests that vitamin D offers several health benefits, including reduced risk of falls and fractures, several types of cancer, cardiovascular disease, cognitive decline, dementia, diabetes mellitus, respiratory and other types of infections, and many other conditions and diseases [11].

In light of the rapidly advancing understanding of vitamin D’s importance for optimal health, AADMD commissioned its Vitamin D Task Force to review evidence of vitamin D’s health benefits and recommend strategies to manage vitamin D deficiency among the MCDD community. Since those in the MCDD community are living longer now [12], the task force considered the effects of vitamin D for all age groups.

2. Approach and Rationale

In carrying out this charter, task force members used PubMed.gov and other databases to review the literature on the health conditions of people with MCDD as well as on vitamin D’s health benefits.
Members used the following search terms: vitamin D and intellectual disabilities, developmental disabilities, many diseases; developmental disabilities or intellectual disabilities and health outcomes. Many findings supporting vitamin D’s role in reducing risk of disease come from observational studies that determined health outcomes from studies measuring blood 25(OH)D concentrations at time of enrollment or diagnosis. One can raise 25(OH)D concentrations by either UVB exposure or oral vitamin D intake. Thus, it is possible that 25(OH)D concentrations are, in part, an index of solar UVB exposure that includes effects other than vitamin D production.

Concern has been raised that 25(OH)D concentration-health outcome relations could be due to reverse causation, that is, that having disease affects 25(OH)D concentrations, since few randomized controlled trials (RCTs) have supported the findings of observational studies in general. The reason for this is thought to be largely because of trial design. Most vitamin D RCTs were based on the pharmaceutical drug model and assume that the only source of the agent is through the trial and that a linear dose-response relation exists; neither assumption is valid for vitamin D [13]. In addition, many trials used little vitamin D (400–1000 IU/day), did not measure 25(OH)D concentrations at time of enrollment or end, and enrolled mostly people with 25(OH)D concentrations near or above 50 nmol/L. Thus, one would not expect such studies to find significant benefits. Thus, for now, observational studies—especially in the form of meta-analyses—appear to offer the best information on the link between vitamin D and many health outcomes [11,14].

We intend these guidelines to prevent chronic and infectious diseases, not treat them, and several papers discussed here based their vitamin D guidelines and recommendations largely on observational studies.

3. Findings

The first task was to determine what conditions and diseases are more common among those with MCDD. Table 1 shows representative findings for several vitamin D-sensitive diseases. Rates for many chronic diseases are approximately twice those for community-dwelling, non-MCDD individuals. Table 2 gives the definitions of the acronyms regarding disabilities.

| Disease                  | Population                                      | Finding                                         | Reference |
|--------------------------|-------------------------------------------------|------------------------------------------------|-----------|
| Cancer                   | US 2006–2012 National Health Interview Survey  | OR = 1.61 (95% CI, 1.34, 1.94)                 | [8]       |
| Chronic kidney disease   | Adults older than 50 years with ID in The Netherlands | Prevalence = 15.3%                            | [15]      |
| Coronary heart disease   | US 2006–2012 National Health Interview Survey  | OR = 2.92 (95% CI, 2.33, 3.66)                 | [8]       |
| Diabetes mellitus        | US 2006–2012 National Health Interview Survey  | OR = 2.57 (95% CI, 2.10, 3.15)                 | [8]       |
| Fractures                | Adults with Down syndrome or DD, Wisconsin     | 32% (30/93) of charts contained history of an adult-onset fracture | [16]      |
| Hypertension             | US 2006–2012 National Health Interview Survey  | OR = 2.18 (95% CI, 1.94, 2.45)                 | [8]       |
Table 1. Cont.

| Table 1. Cont. | Table 1. Cont. |
| -------------- | -------------- |
| Obesity        | US 2006–2012 National Health Interview Survey | OR = 1.81 (95% CI, 1.63, 2.01) [8] |
| Oral health    | Adults with IDDs dental care from state-supported dental clinics | Untreated caries, 32.2%; periodontitis, 80.3%; edentulism, 10.9% [17] |
| Osteopenia, osteoporosis | Community-dwelling individuals with DD and/or ID in Tennessee | Osteopenia, 51%; osteoporosis of femur bone, 17.1% [18] |
| Respiratory infections | 6-month-long observational cohort study with 63 persons with IDD | (35% of participants): 12 pneumonias, 7 sinusitis, 1 bronchitis, and 1 upper respiratory tract infection [19] |
| Sarcopenia     | Adults older than 50 years with ID in The Netherlands | Prevalence = 14.3% [21] |

DD, developmental disabilities; ID, intellectual disability; IDD, intellectual and developmental disabilities; OR, odds ratio.

Table 2. Definitions.

| DD | Developmental disability (DD) is a diverse group of severe chronic conditions due to mental and/or physical impairments. Developmental disabilities cause individuals living with them many difficulties in certain areas of life, especially in “language, mobility, learning, self-help, and independent living” [22]. |
| ID | Intellectual disability is a disability characterized by significant limitations in both intellectual functioning and adaptive behavior, which covers many everyday social and practical skills. This disability originates before the age of 18 [23]. |
| IDD | Intellectual and developmental disability is a combination of ID and DD. |
| MCDD | Multiple complex developmental disorder is a category proposed to involve several neurological and psychological symptoms where at least some symptoms are first noticed during early childhood and persist throughout life, including both pervasive developmental disorder and psychosis. |

Respiratory tract infections (RTIs) are common among those with developmental disabilities [19,24] because they: (1) often live together in group homes or institutions, where RTIs can spread rapidly; and (2) generally have low serum 25(OH)D concentrations due partly to staying largely indoors. Also, some medicines given to this population, such as anticonvulsant drugs, glucocorticoids, and AIDS medications, reduce serum 25(OH)D concentrations [25].

Similarly, the MCDD community has low serum 25(OH)D concentrations for several reasons. They stay mostly indoors and so produce little vitamin D from solar ultraviolet-B (UVB), are often obese, and take medications that lower 25(OH)D concentrations [26]. They also are unlikely to take vitamin supplements. Table 3 presents findings regarding serum 25(OH)D concentrations for those with ID or primarily older people living in nursing homes.
Table 3. Blood 25(OH)D concentrations among those with ID.

| Population                                      | Serum 25(OH)D Concentration | Reference |
|------------------------------------------------|-------------------------------|-----------|
| People with ID in Australia—clinical study      | 43% had <50 nmol/L            | [27]      |
| People with ID in Australia—institution study   | 57% had <50 nmol/L            | [28]      |
| Adults with ID living in nursing homes, Finland | Mean value, 40 nmol/L         | [3]       |
| ID patients aged 18–70 years living in Oxfordshire, England | Mean value, 28.8 nmol/L (36.8 nmol/L in summer, 20.3 nmol/L in winter) | [29]       |

ID, intellectual disability.

3.1. Conditions and Diseases That Vitamin D Might Prevent and Treat

3.1.1. Bone Metabolism, Falls and Fractures

Vitamin D was first known as the substance that prevented rickets. Although doctors in the 19th century knew that lack of sunlight was a risk factor for rickets, research did not identify vitamin D as the compound that prevented rickets until the early 20th century [30]. Vitamin D prevents rickets by mediating calcium absorption in the intestines as well as calcium metabolism.

A 2010 study regarding vitamin D deficiency and bone mineralization involved examining bones from vehicular accident victims in Germany. Both blood and bone samples were obtained at autopsy. That study defined osteomalacia as a pathologic increase in osteoid volume per bone volume greater than 2%. People with serum 25(OH)D concentration <75 nmol/L met that criterion, but no one with serum 25(OH)D concentrations >75 nmol/L did [31].

Avoiding falls and fractures involves both strong bones and good neuromuscular control. Postural sway is linked to increased risk of falls, and sway was more prevalent in those with serum 25(OH)D concentrations below 30 nmol/L [32]. A study in The Netherlands found that weekly treatment with 8400 IU of vitamin D3 reduced postural sway in those with elevated sway at enrollment [33]. A meta-analysis of vitamin D supplements showing reduced risk of falls for elderly people suggested that vitamin D’s effect may be due to improved neuromuscular function with vitamin D supplementation [34]. A pooled analysis of fractures with respect to vitamin D supplementation among those older than 65 years found that “By quartiles of actual intake, reduction in the risk of fracture was shown only at the highest intake concentration (median, 800 IU daily; range, 792 to 2000), with a 30% reduction in the risk of hip fracture (hazard ratio (HR), 0.70; 95% CI, 0.58, 0.86) and a 14% reduction in the risk of any nonvertebral fracture (HR, 0.86; 95% CI, 0.76, 0.96)” [35].

The Endocrine Society recommends serum 25(OH)D concentrations above 75 nmol/L to reduce risk of falls and fractures [36]. People with MCDD often have osteomalacia [37] and osteopenia [38], which has been treated with bisphosphonates [38]. However, a DXA machine, which measures bone mineral density, cannot distinguish low bone mineral density caused by osteoporosis from that caused by osteomalacia. Treating osteomalacia with a bisphosphonate could precipitate severe or even lethal hypocalcemia. In an observational study of patients associated with two U.S. hospitals, favorable response to bisphosphonates was better at higher 25(OH)D concentrations: nonresponder rates were 79% for those with 25(OH)D concentrations <75 nmol/L, 50% for those with 25(OH)D concentrations of 75–100 nmol/L, and only 33% for those with 25(OH)D concentrations >100 nmol/L [39].
To maintain calcium concentration in the blood, the body takes calcium from the intestines or bones according to the balance between parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D [40]. The 25(OH)D concentration–PTH relation has an inverse relation out to at least a serum 25(OH)D concentration of 150 nmol/L [41]. Increased PTH concentrations are associated with increased mortality rates, vascular and valvular calcification, renal failure, heart failure, and cardiovascular disease [40].

However, other factors—such as intake of vitamins C and K as well as calcium and magnesium [42], protein intake [43], and exercise [44,45]—also affect bone strength.

### 3.1.2. Physical Functioning

Since 25(OH)D concentrations affect muscles and neuromuscular control [32], we can reasonably expect concentrations to also affect physical functioning. A study of two cohorts of elderly people living in Amsterdam examined the relation between serum 25(OH)D concentrations and functional limitations. The study included six functions: walking up and down staircases, dressing and undressing oneself, sitting down and standing up from a chair, cutting one’s toenails, walking outside for 5 minutes without resting, and using one’s own or public transportation. After 3 years of follow-up, those aged at least 65 years at enrollment and with serum 25(OH)D concentrations <75 nmol/L showed more functional limitations (at least two more), whereas those aged 55–65 years at enrollment had more functional limitations after 6 years of follow-up than those with concentrations ≥75 nmol/L [46].

### 3.1.3. Infectious Diseases

Vitamin D fights bacterial and viral infectious diseases in at least two ways. One is by inducing cathelicidin (also known as LL-37), a polypeptide with antimicrobial and antiendotoxin properties, and defensins [47]. The other is by shifting cytokine production toward diseases less prone to cause inflammation [48,49].

### 3.1.4. Type A Influenza

The seasonal variation of influenza formed the basis of Cannell’s UVB–vitamin D–influenza hypothesis [50]. Two RCTs supported this hypothesis, one involving black postmenopausal women with a baseline mean 25(OH)D concentration of 48 nmol/L [51], the other involving schoolchildren in Japan [52]. In the black postmenopausal women study, for 312 person-years of taking a placebo with baseline 25(OH)D concentrations 47 ± 21 nmol, 30 colds or influenza cases occurred; for 208 person-years of taking 800 IU/day vitamin D3, 8 colds or influenza cases occurred; for 104 person-years of taking 2000 IU/day vitamin D3, one cold or influenza case occurred. In the Japan study, supplementation with 1000 IU of vitamin D3 per day reduced risk of type A influenza by 67% but did not affect that of type B influenza.

### 3.1.5. Acute Respiratory Tract Infections, Asthma, and Chronic Obstructive Pulmonary Disease

A June 2013 meta-analysis of the 11 RCTs on vitamin D and RTIs associated vitamin D supplementation with an OR of 0.64 (95% CI, 0.49, 0.84). That analysis also noted that once-daily dosing yielded better effects than bolus dosing (odds ratio = 0.51 vs. 0.86; p = 0.01) [53]. This study supports
daily rather than weekly or monthly dosing. Studies have also associated higher 25(OH)D concentrations and vitamin D supplementation with reduced effects of asthma [54–56] and chronic obstructive pulmonary disease [57,58]. A meta-analysis of results of vitamin D trials found a statistically significant reduction (relative risk (RR) 0.41, 95% CI, 0.27, 0.63) in asthma exacerbation with vitamin D therapy [59].

3.1.6. Insulin Resistance

In insulin resistance, cells do not respond to insulin, causing high blood sugar. A vitamin D RCT involving insulin-resistant South Asian women living in New Zealand with baseline 25(OH)D concentrations below 50 nmol/L gave half the women 4000 IU of vitamin D3 per day and placebos to the other half. Participants reaching serum 25(OH)D concentrations of 80–120 nmol/L showed significantly improved insulin sensitivity [60].

3.1.7. Type 2 Diabetes Mellitus

Mounting evidence indicates that vitamin D reduces risk of developing type 2 diabetes mellitus (T2DM), for which insulin resistance is a risk factor. Several observational studies found that people with higher serum 25(OH)D concentrations had reduced risk of developing T2DM. A meta-analysis of 18 studies found that the RR dropped from 1.0 (95% CI, 0.9, 1.1) at 33 nmol/L to 0.67 (95% CI, 0.45, 0.73) at 100 nmol/L [61]. Some caution regarding this finding is in order because a recent study found that after adjustment for body mass index, the inverse correlation between incidence of T2DM and baseline 25(OH)D concentration was no longer significant [62]. An open-label prospective study in India involving prediabetic individuals with mean age of 48 years followed for a mean of 28 ± 9 months found that having mean baseline 25(OH)D concentration of 95 nmol/L or being supplemented with sufficient vitamin D to raise the final 25(OH)D concentration to 89 nmol/L significantly reduced the conversion to diabetes mellitus compared with baseline or final 25(OH)D concentration of 45 nmol/L [63]. A study in Israel found a beneficial effect of supplementation with 1000 IU of vitamin D per day for patients with T2DM for 12 months in improving the central aortic augmentation index, thereby alleviating some cardiovascular damage [64].

3.1.8. Cardiovascular Disease

Strong evidence from prospective observational studies indicates that serum 25(OH)D concentrations are inversely correlated with cardiovascular disease (CVD). A meta-analysis of 16 studies found that the RR of CVD was 2.2 (95% CI, 1.7, 2.8) for 20 nmol/L, dropping to 1.0 (95% CI, 0.8, 1.2) at 75 nmol/L [65]. The RR for low vs. high serum 25(OH)D concentration from these studies was 1.52 (95% CI, 1.30, 1.77). RCTs on those with low 25(OH)D concentrations at enrollment found beneficial effects of vitamin D supplementation. In the Women’s Health Initiative Study, 400 IU of vitamin D3 plus 1500 mg of calcium supplementation per day was associated with increased high-density lipoprotein cholesterol and lower low-density lipoprotein cholesterol and triglycerides [66]. The improvements in lipid profiles were most pronounced for those with 25(OH)D concentrations above 100 nmol/L. However, vitamin D RCTs conducted on healthy community-dwelling populations found no beneficial effect of vitamin D
supplementation on risk of CVD [67]. Respiratory infections such as influenza can trigger CVD events such as acute myocardial infarction [68], suggesting another way vitamin D might reduce risk of CVD.

3.1.9. Alzheimer’s Disease

Evidence is mounting that vitamin D deficiency is an important risk factor for Alzheimer’s disease (AD). A prospective study in Denmark associated low 25(OH)D concentrations with about a 20% increased risk of both AD and vascular dementia over a 30-year follow-up [69]. Cardiovascular risk factors contribute to risk of AD [70]. As just discussed, vitamin D deficiency is a risk factor for CVD. In early 2014, Gezen-Ak and colleagues reviewed evidence that vitamin D deficiency is an important risk factor for AD. The evidence includes that vitamin D plays roles in protecting the central nervous system, regulating calcium homeostasis, attenuating oxidative stress, and enhancing immune response [71]. Another recent paper suggested that vitamin D supplements could be used in therapy for those with AD [72]. A recent cohort study in the U.S. involving 658 elderly people monitored for a mean of 5.6 years found a multivariate-adjusted HR for incident AD of 2.22 (95% CI, 1.02, 4.83) for those with 25(OH)D <25 nmol/L compared with those with 25(OH)D >50 nmol/L [73].

3.1.10. Autism Spectrum Disorder

Evidence increasingly indicates that vitamin D deficiency plays an important role in risk for and progress of autism spectrum disorder. Cannell proposed the vitamin D–autism hypothesis in 2008 [74]. An ecological study of autism prevalence rates for those aged 6–17 years in the United States found significant inverse correlations with solar UVB doses, a proxy for vitamin D production [75]. Researchers in 2014 proposed that a mechanism linking vitamin D deficiency to risk of autism was that vitamin D regulates serotonin synthesis both inside and outside the brain [76]. They also indicated that increasing 25(OH)D concentrations might ameliorate some symptoms of autism. A recent paper reviewed the evidence that vitamin D reduces risk of autism spectrum disorder [77]. Treating those with autism spectrum disorder with vitamin D may reduce symptoms of autism [78,79].

3.1.11. Attention Deficit–Hyperactivity Disorder

People with ID have an increased risk of attention deficit hyperactivity disorder (ADHD) [80]. Two recent papers reported that people with ADHD have lower 25(OH)D concentrations than control subjects [54,81]. Preliminary evidence indicates that increasing 25(OH)D concentrations can reduce symptoms of ADHD [82].

3.1.12. Cancer

Evidence that vitamin D reduces cancer risk comes from several study types. Ecological studies based on geographical variations of solar UVB and cancer incidence or mortality rates furnish good evidence for about 15 cancers [83,84]. Observational studies based on serum 25(OH)D concentrations offer good evidence that vitamin D reduces risk of colorectal and breast cancer [85,86] and aggressive prostate cancer [87]. RCTs offer some evidence that vitamin D reduces risk of cancer [88–90], although vitamin D RCTs to date have not been well designed or conducted [13]. As Ref. [13] outlines, vitamin D RCTs
should start with an understanding of the 25(OH)D concentration–health outcome relation, measure the 25(OH)D concentration of the prospective participants, include only those whose 25(OH)D concentration is near the lower end of the relation, supplement them with enough vitamin D to raise the concentration to the upper end of the relation, and then remeasure 25(OH)D concentrations. Most vitamin D RCTs to date did not measure baseline 25(OH)D concentrations; those doing so did not reject those with higher 25(OH)D concentrations. Also, until recently, the vitamin D₃ supplementation was 400 IU/day, although it is rising to 1000–4000 IU/day. Also, for those diagnosed with breast cancer, colon cancer, lung cancer, and lymphoma and who have higher 25(OH)D concentrations, survival rates are much higher [91].

3.1.13. Oral Health

Vitamin D’s role in reducing risk of dental caries has been known since 1928 with a study of vitamin D supplementation in boys in Sheffield, England [92]. The effect was originally thought to be due to better calcium metabolism but has now been linked more strongly to antimicrobial properties through vitamin D’s induction of cathelicidin [93]. Several geographical ecological studies in the mid-20th century inversely correlated solar UVB doses and dental caries [93]. Further evidence comes from controlled trials of vitamin D supplementation and observation of caries incidence. A 2012 review of 24 controlled clinical trials encompassing 2827 participants found a pooled relative-rate estimate of supplemental vitamin D of 0.53 (95% CI, 0.43, 0.65) [94]. Although many of these trials were not modern RCTs, results among them were consistent, giving crediblity to the findings. Studies have also linked vitamin D deficiency to periodontal disease [95–97]. A recent study in Saudi Arabia found that for older men, “total vitamin D intake ≥ 800 IU was associated with lower odds of severe periodontal disease (OR = 0.67, 95% CI, 0.55, 0.81) and moderate-to-severe ABL (OR = 0.54, 95% CI, 0.30, 0.96) relative to intake <400 IU/day” [98].

3.1.14. Other Health Outcomes

Evidence also indicates that vitamin D reduces risk of cognitive decline [99], hypertension [100], and nonspecific pain [101,102]. These associations are still the subject of ongoing research, but they do offer additional reasons to recommend higher 25(OH)D concentrations for people with MCDD.

3.1.15. All-Cause Mortality Rate

A recent meta-analysis of 32 observational studies found increased HR for 25(OH)D concentrations below 90 nmol/L [103]. The HR for <25 nmol/L was 1.90 (95% CI, 1.63, 2.23), that for 25–48 nmol/L was 1.58 (95% CI, 1.36, 1.84), and that for 50–73 nmol/L was 1.23 (95% CI, 1.06, 1.24). Another meta-analysis found significant RRs for low vs. high 25(OH)D concentration in observational studies ranging from 1.14 (95% CI, 1.01, 1.29) to 1.60 (95% CI, 1.32, 1.94), with the exception of secondary prevention cohorts for noncardiovascular, noncancer death, for cancer, cardiovascular, other, and all-cause mortality rates [104].
3.1.16. Health Outcomes in Relation to 25(OH)D Concentrations

Table 4 presents 25(OH)D concentrations above which little additional benefit is found. Several values are based on meta-analyses of 25(OH)D concentration–health outcome relations from observational studies such as those for breast cancer [85], cardiovascular disease [65], T2DM [61], and all-cause mortality rate [103]. Others are based on a variety of studies, including clinical, cohort, and prospective studies, and guidelines by organizations. These results are in line with those reported by Spedding, generally 75–100 nmol/L [105].

Table 4. Findings regarding 25(OH)D concentrations related to health conditions from observational studies.

| Outcome                        | Study                     | Findings with Respect to 25(OH)D | Reference |
|--------------------------------|---------------------------|----------------------------------|-----------|
| Athletic performance           | Review                    | 100–125 nmol/L                   | [106]     |
| Bisphosphonate therapy         | Clinical study            | >100 nmol/L                      | [39]      |
| Bone quality (poor)            | Analysis of people killed in road accidents | 75 nmol/L                  | [31]      |
| Cancer, breast                 | Meta-analysis             | Little change >100 nmol/L        | [107]     |
| Cardiovascular disease         | Meta-analysis             | No change >75 nmol/L             | [65]      |
| Dementia                       | Cohort study              | 50 nmol/L                        | [73]      |
| T2DM                           | Meta-analysis             | Little change >75 nmol/L         | [61]      |
| Fractures, hip                 | Prospective study         | >63 nmol/L                       | [108]     |
| Fractures, stress              | Prospective study         | >75 nmol/L                       | [109]     |
| Mortality, all-cause           | Meta-analysis             | No change >90 nmol/L             | [103]     |
| Pain, chronic                  | Clinical study            | >75 nmol/L                       | [111]     |
| Respiratory infections         | Cohort study              | >95 nmol/L                       | [112]     |

The U.S. Department of Health and Human Services is developing more coordinated and comprehensive approaches to prevent and treat disease in persons with multiple chronic conditions [113]. We hope that these approaches will include increasing 25(OH)D concentrations.

From the relationships between health outcomes and 25(OH)D concentrations, one can estimate the beneficial effects of increasing 25(OH)D concentrations. Table 5 presents findings from several studies, primarily meta-analyses of observational studies. Increasing from 38 to 75 nmol/L reduces average adverse health outcomes by 27%, whereas increasing to 100 nmol/L reduces outcomes by 36%.

Table 5. Estimated reductions in disease rates by increasing 25(OH)D concentrations.

| Outcome                                   | 75 vs. 38 nmol/L | 100 vs. 38 nmol/L | Reference |
|-------------------------------------------|------------------|-------------------|-----------|
| Cancer, breast                            | 0.59             | 0.48              | [107]     |
| Cardiovascular disease                    | 0.71             | 0.71              | [65]      |
| T2DM                                      | 0.76             | 0.62              | [61]      |
| Fractures, nonvertebral                   | 0.81             |                   | [114]     |
| Mortality, all-cause                      | 0.72             | 0.64              | [103]     |
| Periodontal disease                       | 0.67             |                   | [115]     |
| Respiratory infections, upper respiratory | 0.85             | 0.76              | [116]     |
| Mean values                               | 0.73             | 0.64              |           |

Mean values for those with data for 75 and 100 nmol/L:

| Mean values for those with data for 75 and 100 nmol/L | 0.73 | 0.64 |
A few reports found adverse health effects for higher 25(OH)D concentrations, the most important being hypercalcemia, which generally does not occur for 25(OH)D concentrations below 500 nmol/L [117]. Achieving this concentration is highly unlikely unless someone takes more than 50,000 IU of vitamin D daily for a prolonged period or mistakenly overdoses with high-concentration vitamin D supplements with 1 million IU of vitamin D [118]. We discuss findings of J- or U-shaped 25(OH)D concentration–health outcomes later.

3.2. Reviews of Vitamin D Benefits, Requirements, Recommendations

Several health organizations and vitamin D working groups have reviewed the evidence of health benefits of vitamin D and recommended desirable serum 25(OH)D concentrations and vitamin D₃ supplementation. Many molecular mechanisms of vitamin D’s action are well known [119]. Table 6 summarizes recommendations for those likely to be vitamin D deficient. The general consensus of these recommendations is that serum 25(OH)D concentrations should be at least 75 nmol/L and up to 125 nmol/L and that reaching these concentrations takes about 1000–2000 IU of vitamin D₃ per day. A recent paper also analyzed optimal concentration on the basis of three diverse findings (zero correlation between 25(OH)D and PTH above a threshold, support of lactation, and ancestral values), concluding that 100–130 nmol/L was optimal and could be achieved with all-source inputs of 4000–6000 IU per day [13]. The task force considered input from these organizations and working groups in making recommendations for people with MCDD.

Table 6. Vitamin D recommendations by organizations and groups.

| Organization                          | Intended Group                                   | Serum 25(OH)D Concentration (nmol/L) | Vitamin D₃ (IU/day) | Vitamin D₃ UL (IU/day) | Reference |
|---------------------------------------|-------------------------------------------------|--------------------------------------|---------------------|------------------------|-----------|
| Vitamin D experts                     | Elderly and institutionalized individuals       | 75–100                               | 800                 |                        | [120]     |
| Endocrine Society                     | Patients at risk of vitamin D deficiency, 1–18 years | 75                                   | 600–1000            | 4000                   | [36]      |
|                                       | Patients at risk of vitamin D deficiency, ≥19 years | 75                                   | 1500–2000           | 4000                   | [121]     |
| European Menopause and Andropause Society | Women with vitamin D deficiency related to osteoporosis | >75                                  | 800–1200            |                        | [25]      |
| French Group of Geriatrics and Nutrition | Elderly nursing home residents                  | 75–100                               | 1000                |                        | [122]     |
| Central European Guidelines           | Obese children and adolescents                  | 75–125                               | 1200–2000           | [123]                  |
|                                       | Obese adults and the elderly                    | 75–125                               | 1600–4000           |                        | [123]     |
| ESCEO                                 | Adults                                          | >50                                  | 800–1000            | [124]                  |
|                                       | Elderly at risk                                 | >75                                  |                      |                        | [124]     |
| American Geriatrics Society           | Adults ≥70 years                                 | >75                                  | 4000                |                        | [125]     |

ESCEO, European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis; UL, upper limit.
3.2.1. Institute of Medicine Report

The Institute of Medicine (IOM) issued a report in 2010 on dietary requirements for calcium and vitamin D for people living in North America. Its recommendations for vitamin D intake to achieve a serum 25(OH)D concentration of 50 nmol/L were 400 IU/day for infants younger than 1 year, 600 IU/day for those aged 1–70 years, and 800 IU/day for those aged ≥71 years [126]. The abstract of that paper stated, “The Committee concluded that available scientific evidence supports a key role of calcium and vitamin D in skeletal health, consistent with a cause-and-effect relationship and providing a sound basis for determination of intake requirements. For extraskeletal outcomes, including cancer, cardiovascular disease, diabetes, and autoimmune disorders, the evidence was inconsistent, inconclusive as to causality, and insufficient to inform nutritional requirements. Randomized clinical trial evidence for extraskeletal outcomes was limited and generally uninformative”. The vitamin D research community severely criticized the IOM report. For example, “The IOM recommendations for vitamin D fail in a major way on logic, on science, and on effective public health guidance. Moreover, by failing to use a physiological referent, the IOM approach constitutes precisely the wrong model for development of nutritional policy” [127]. The only evidence that the IOM committee found acceptable as a basis for policy recommendations was from RCTs and observational studies regarding bone health. Among other things, IOM misinterpreted the observational study it used to set the 25(OH)D concentration to 50 nmol/L; the authors of the study concluded from the data that 75 nmol/L was the appropriate concentration [31].

The levels of evidence for evidence-based medicine place systematic reviews of RCTs at the top but permit observational studies and mechanism-based reasoning in the absence of RCTs [128]. The recommendations in Table 6 were based largely on observational studies and mechanisms. As noted, vitamin D RCTs have in general been poorly designed. A recent paper argued that absence of supportive vitamin D RCTs should not undermine the observational studies finding beneficial effects [129]. The IOM report also noted that “Guidelines regarding the use of serum markers of vitamin D status for medical management of individual patients and for screening were beyond the scope of the Committee’s charge, and evidence-based consensus guidelines are not available. However, these issues should be addressed by appropriate federal agencies and professional organizations in light of the findings in this report.” Most of the recommendations in Table 6 were done by professional organizations for the benefit of those they serve. For example, one stated, “The objective was to provide guidelines to clinicians for the evaluation, treatment, and prevention of vitamin D deficiency with an emphasis on the care of patients who are at risk for deficiency” [36].

Finally, since the IOM report was published (29 November, 2010), 13,535 publications with vitamin D in the title or abstract have been published at PubMed.gov as of 23 February, 2015, compared with 27,775 published before that date. This paper cites many of these publications. Until about 2000, most papers published on the use of vitamin D in clinical trials was related to musculoskeletal effects; now, however, the evidence of benefits for nonskeletal effects is still accruing. The IOM listed 4000 IU/day vitamin D as the upper limit of supplementation. However, they noted that no adverse effects had been reported for less than 10,000 IU/day (see [130]). A recent paper studied the dose–response relation for 25(OH)D and serum calcium as a function of vitamin D supplementation. For daily doses of 10,000 IU/day, the mean 25(OH)D concentration was above 150 nmol/L (155 nmol/L)
only for the underweight group; for the obese group, the mean concentration was 110 nmol/L [131]. Serum calcium was nearly unchanged for up to 20,000 IU/day.

3.2.2. U- and J-Shaped 25(OH)D Concentration–Health Outcome Relations

Several observational studies reported a J- or U-shaped 25(OH)D concentration–health outcome relation with the following factors: all-cause mortality [132,133]; adverse cardiac and cerebrovascular events in cardiac surgery [134]; frailty [135]; hospital mortality [136]; and immunoglobulin E [137]. The mortality rate findings are not supported in a meta-analysis of 32 studies [103]. Such studies have been cited to warn against supplementing with too much vitamin D or raising 25(OH)D concentrations too high. However, most of these studies are on elderly people and the highest 25(OH)D quintile was generally above 100 nmol/L, a value generally reached in the U.S. and Europe through vitamin D supplementation. None of those studies seems to have asked participants when they started taking supplements. For frailty, although a U-shaped relation emerged for older women, a nearly linear inverse 25(OH)D concentration-frailty relation was present for men [138]. The difference between men and women is consistent with the fact that women are often advised to start taking vitamin D supplements after menopause, and that taking vitamin D late in life cannot overcome all the adverse effects of low 25(OH)D concentrations earlier in life. No mechanisms have been proposed to explain most of the J- or U-shaped relations.

A recent paper reporting an observational study of inflammation with respect to 25(OH)D concentration stated, “On the other hand, the U-shaped association may be an artifact, determined by the small proportion of subjects with 25(OH)D in the target range (25(OH)D ≥30 ng/mL: 13.1% of subjects; 25(OH)D ≥40ng/mL: 3.0% of subjects). The majority of our study population (76.3%) had 25(OH)D concentrations <25 ng/mL, a range in which hs-CRP decreased with increasing 25(OH)D. Additionally, we cannot exclude that subjects with high 25(OH)D concentrations had not acknowledged taking vitamin D supplements in the SHIP examination, which might have biased the analyses. Overall, there is no final explanation for the U-shaped association between 25(OH)D and hs-CRP in our study population and we suggest assessing it in future studies” [139].

Another recent paper examined whether 25(OH)D concentrations >100 nmol/L reduced 1,25-dihydroxyvitamin D concentrations to account for the U-shaped relation for postoperative recovery after cardiac surgery; the answer was no [140]. However, that paper noted that impaired kidney function as measured by estimated glomerular filtration rate is associated with lower conversion of 25(OH)D to 1,25(OH)2D, which could account for some adverse effects associated with higher 25(OH)D concentrations. Reports that seem most credible—both for 25(OH)D >125 nmol/L—revealed increased immunoglobulin E, a marker of allergic responses [137], as well as reduced cognitive performance [141]. Men had increased risk of hypogonadism for 25(OH)D concentrations >100 nmol/L [142]. However, these reports need further confirmation.

3.2.3. Reports of Adverse Events Associated with High dose Vitamin D

One of the dangers of vitamin D supplementation is risk of hypercalcemia or blood calcium levels that are too high. Vitamin D intoxication can result in an elevated serum calcium and serum phosphorus level. Constitutional symptoms include confusion, nausea, constipation, polyuria and polydipsia,
decreased heart rate and arrhythmias [143]. The long-term consequences include soft tissue calcification of the blood vessels, nephrocalcinosis and kidney stones. Generally, hypercalcemia does not occur for vitamin D supplementation less than 40,000 IU/day [144]. However, sometimes high 25(OH)D concentrations are reached by accident, such as a manufacturing and labeling errors [118,143,145]. “Hydration, diuretics and prednisone induced a progressive reduction of calcium levels” [143]. It can take several months to a year for 25(OH)D concentrations to return to normal, although hypercalcemia disappeared below 25(OH)D concentrations of 1000 nmol/L in one study [118].

3.2.4. Reverse Causality

Concern has been raised that 25(OH)D concentration–health outcome relations found in observational studies could be due to reverse causation, that is, that having disease affects 25(OH)D concentrations. This concern has been raised in large part since vitamin D RCTs generally have not confirmed the findings of observational studies [146]. This effect is most likely to be found in cross-sectional studies of disease prevalence, and most authors are careful to acknowledge this possibility. However, reverse causation is not thought to affect prospective studies with long follow-up times, especially if health outcomes occurring in the first year or two are omitted. Those outcomes might be due to undiagnosed disease, since it is assumed that the health outcome developed after measurement of 25(OH)D concentration. However, reverse causation might affect case–control studies in which 25(OH)D concentrations are measured near time of diagnosis.

Breast cancer is one health outcome for which reverse causality is often claimed for case-control studies since nested case-control studies do not find significant inverse correlations with 25(OH)D concentrations for follow-up times longer than 3 years [86]. A recent paper argues that case-control studies do not show evidence of reverse causality for breast cancer since the 25(OH)D concentration-incidence relations for 10 studies overlay each other very well [107]. One of the 10 studies included in the meta-analysis used 25(OH)D concentrations measured about 1 year before diagnosis and had similar findings to the other studies, which measured 25(OH)D concentrations shortly after diagnosis. The reason for the disparity between case-control studies and nested case-control studies is attributed to the rapid development of breast cancer tumors. Breast cancer screening is recommended annually, whereas colorectal cancer screening is recommended every 10 years.

3.2.5. Randomized Controlled Trials

Several recent papers have pointed out that vitamin D RCTs do not support the findings of observational studies [67,146,147]. In response to the paper by Autier [146], three of us analyzed all the RCTs examining the effect of vitamin D on biomarkers of inflammation. Half of the trials with baseline 25(OH)D concentration <48 nmol/L resulted in significant inverse correlations between vitamin D supplementation and inflammation, whereas only 25% of those with higher baseline 25(OH)D concentrations did [148]. One problem with most vitamin D RCTs conducted to date is that they have largely been based on guidelines for pharmaceutical drugs, which assume that the trial is the only source of the agent and that a linear dose–response relation is in effect. Vitamin D satisfies neither assumption since UVB exposure, diet, and supplements are common sources of vitamin D. Another problem is that
those conducting the trials generally did not design the trials to evaluate the 25(OH)D concentration-health outcome relation. In a recent paper, Heaney outlined guidelines for trials of nutrients such as vitamin D.

The important steps include starting with an understanding of the 25(OH)D concentration-health outcome relation, measuring 25(OH)D concentrations of potential participants, enrolling only those with 25(OH)D concentrations near the low end of the relation, supplementing them with enough vitamin D to raise 25(OH)D concentrations to near the upper end of quasi-linear region of the relation, remeasuring 25(OH)D concentrations, and ensuring that important cofactors have been optimized [13]. Very few vitamin D RCTs conducted to date satisfy these guidelines; thus, few found significant effects. Also, some question exists of whether the trials were conducted at the right age and for a long enough period.

3.2.6. Vitamin D3 (Cholecalciferol) vs. Vitamin D2 (Ergocalciferol)

Vitamin D3 (cholecalciferol) is synthesized in human skin, whereas vitamin D2 (ergocalciferol) comes from yeast and fungi. Most vitamin D supplements are vitamin D3. Reports of the effectiveness of the two types conflict. In a study supplementing healthy adults with 50,000 IU of vitamin D2 or D3, vitamin D3 was 87% more potent in raising and maintaining 25(OH)D concentrations [149].

A 2012 study with 50,000 IU of vitamin D2 supplementation every other week increased total serum 25(OH)D concentration from 78 to 120 nmol/L but lowered 25(OH)D concentration from 68 to 35 nmol/L [150]. The most recent study found that treating those with T2DM with 50,000 IU of vitamin D2 per day for 10 days yielded increases comparable to those taking 40,000 IU of vitamin D3 daily for 10 days [151]. Heavier people require larger vitamin D doses [152]. A meta-analysis of all-cause mortality rate from vitamin D supplementation trials found a RR of 0.89 (95% CI, 0.80, 0.99) for trials using vitamin D3 and 1.04 (95% CI, 0.97, 1.11) for trials using vitamin D2 [104]. In other words, vitamin D3 significantly reduced risk of death, whereas vitamin D2 did not.

Another consideration is that 50,000-IU vitamin D2 capsules can be prescribed, but 50,000-IU vitamin D3 capsules cannot. However, prescription-grade vitamin D3 is available at lower cost than vitamin D2 (Bio-Tech Pharmacal, Fayetteville, AR, USA). Vitamin D capsules of 50,000 IU can be given once per month, a daily average of 1640 IU. Alternatively, for example, 20,000 IU per week could be given, a daily average of 2860 IU. Since 25(OH)D has a half-life in the blood of 4–6 weeks, such dosing is acceptable.

3.2.7. Diet and 25(OH)D Concentrations

Few foods contain vitamin D. The primary food sources of vitamin D in the United States are fatty fish and vitamin D-fortified milk or other foods; however, many other countries do not fortify any food with vitamin D. In the United States, the mean daily vitamin D intake from food for adults is about 250 IU [153]. However, some diets provide more vitamin D than others. A UK study found that meat eaters had 25(OH)D concentrations 20 nmol/L higher than those of vegans [154]. Fish eaters had slightly lower concentrations than those of meat eaters, whereas vegetarians, who may eat milk and eggs, had concentrations about halfway between those of meat eaters and vegans. Meat evidently has vitamin D as 25(OH)D, which tests generally do not measure. Diet has important effects on health, but the amount of vitamin D derived from food is not enough to raise 25(OH)D concentrations to recommended values.
3.2.8. Testing Serum 25(OH)D Concentrations

Since the recommendations are primarily for serum 25(OH)D concentrations, those with MCDD should have their serum 25(OH)D concentrations tested before beginning supplementation as well as after 6 months to see whether the dose is correct, then annually thereafter. Achieved 25(OH)D concentrations vary considerably with respect to oral vitamin D intake [155]. Taking vitamin D2 and vitamin D3 also yields different 25(OH)D concentrations. Apparently, some individuals can take up to 1 year to obtain a steady-state serum level of 25(OH)D, so a 3- or 6-month level is not necessarily the maximum obtainable.

However, 25(OH)D assays still have some problems. Several approaches for measuring 25(OH)D concentrations exist, including immunoassays, high-performance liquid chromatography, and liquid chromatography–tandem mass spectrometry. Liquid blood or dried blood spots can also be used. Recent reports compared automated immunoassays with liquid chromatography-tandem mass spectrometry methods [156,157]. Both methods have generally good reproducibility and low bias. Other assays did not compare well. Thus, investigating the assay used to measure 25(OH)D concentration is important.

The international Vitamin D External Quality Assessment Scheme sends blood samples to laboratories throughout the world to check measurement accuracies. By 2011, intra-laboratory imprecision was down to 15% [158]. From a clinical point of view, a good policy would probably be to ask the assay company for accuracy and repeatability values of 25(OH)D measurements and whether vitamin D2 and vitamin D3 are measured separately or together.

4. Conclusions

This review summarizes evidence that vitamin D has important health benefits for those with MCDD as well as others. The vitamin D recommendations by health organizations and vitamin D researchers are that 25(OH)D concentrations for optimal health are in the range of 75 to 100 or 125 nmol/L (30 to 50 ng/mL) and that to reach these concentrations takes 800 to 4000 IU/day vitamin D3. However, since solar UVB exposure is the natural way to obtain vitamin D3, and since there appear to be additional health benefits associated with solar UV exposure, sensible solar UVB exposure should also be considered when the sun is high enough that one's shadow is shorter than one’s height. We hope that physicians who treat those with MCDD will incorporate vitamin D supplementation in their practice. Tracking results of vitamin D supplementation, either formally or informally, would also be advisable.

Author Contributions

PM conceived the idea for the review. WBG led the preparation of the paper. JJC, WBG, MFH, JML, PM, MP, PP, and SJW contributed ideas and/or papers for consideration. WBG and SJW wrote the paper.

Conflicts of Interest

WBG receives funding from Bio-Tech Pharmacal (Fayetteville, AR, USA) and MediSun Technology (Highland Park, IL, USA). JJC is director of the Vitamin D Council, earns royalties from Purity Products Inc., and is on the Scientific Advisory Board for OPKO Health Inc. The other authors declare no conflict of interest.
References

1. PEDD Webinar Series: The Common Characteristics of Neurodevelopmental Disorders. Available online: http://aadmd.org/articles/pedd-webinar-series-common-characteristics-neurodevelopmental-disorders (accessed on 1 March 2014).

2. Sullivan, W.F.; Berg, J.M.; Bradley, E.; Cheetham, T.; Denton, R.; Heng, J.; Hennen, B.; Joyce, D.; Kelly, M.; Korossy, M.; et al. Primary care of adults with developmental disabilities: Canadian consensus guidelines. *Can. Fam. Physician* 2011, 57, 541–553, e154–e168.

3. Kilpinen-Loisa, P.; Arvio, M.; Ilvesmaki, V.; Makitie, O. Vitamin D status and optimal supplementation in institutionalized adults with intellectual disability. *J. Intellect. Disabil. Res.* 2009, 53, 1014–1023.

4. Srikanth, R.; Cassidy, G.; Joiner, C.; Teeluckdharry, S. Osteoporosis in people with intellectual disabilities: A review and a brief study of risk factors for osteoporosis in a community sample of people with intellectual disabilities. *J. Intellect. Disabil. Res.* 2011, 55, 53–62.

5. Martinez-Leal, R.; Salvador-Carulla, L.; Gutierrez-Colosia, M.R.; Nadal, M.; Novell-Alsina, R.; Martorell, A.; Gonzalez-Gordon, R.G.; Merida-Gutierrez, M.R.; Angel, S.; Milagrosa-Tejonero, L.; et al. Health among persons with intellectual disability in Spain: The European POMONA-II study. *Rev. Neurol.* 2011, 53, 406–414.

6. Jasien, J.; Daimon, C.M.; Maudsley, S.; Shapiro, B.K.; Martin, B. Aging and bone health in individuals with developmental disabilities. *Int. J. Endocrinol.* 2012, 2012, 469235.

7. McCarron, M.; Swinburne, J.; Burke, E.; McGlinchey, E.; Carroll, R.; McCallion, P. Patterns of multimorbidity in an older population of persons with an intellectual disability: Results from the intellectual disability supplement to the irish longitudinal study on aging (IDS-TILDA). *Res. Dev. Disabil.* 2013, 34, 521–527.

8. Dixon-Ibarra, A.; Horner-Johnson, W. Disability status as an antecedent to chronic conditions: National health interview survey, 2006–2012. *Prev. Chronic Dis.* 2014, 11, 130251.

9. Bloemers, B.L.; Broers, C.J.; Bont, L.; Weijerman, M.E.; Gemke, R.J.; van Furth, A.M. Increased risk of respiratory tract infections in children with down syndrome: The consequence of an altered immune system. *Microbes Infect.* 2010, 12, 799–808.

10. Oliveira, J.S.; Prado Junior, R.R.; de Sousa Lima, K.R.; de Oliveira Amaral, H.; Moita Neto, J.M.; Mendes, R.F. Intellectual disability and impact on oral health: A paired study. *Spec. Care Dentistry* 2013, 33, 262–268.

11. Hossein-nezhad, A.; Holick, M.F. Vitamin D for health: A global perspective. *Mayo Clin. Proc.* 2013, 88, 720–755.

12. Coppus, A.M. People with intellectual disability: What do we know about adulthood and life expectancy? *Dev. Disabil. Res. Rev.* 2013, 18, 6–16.

13. Heaney, R.P. Guidelines for optimizing design and analysis of clinical studies of nutrient effects. *Nutrit. Rev.* 2014, 72, 48–54.

14. Pludowski, P.; Karczmarewicz, E.; Bayer, M.; Carter, G.; Chlebna-Sokol, D.; Czech-Kowalska, J.; Debski, R.; Decsi, T.; Dobrzanska, A.; Franek, E.; et al. Practical guidelines for the supplementation of vitamin D and the treatment of deficits in central europe-recommended vitamin D intakes in the general population and groups at risk of vitamin D deficiency. *Endokrynol. Pol.* 2013, 64, 319–327.
15. De Winter, C.F.; Echteld, M.A.; Evenhuis, H.M. Chronic kidney disease in older people with intellectual disability: Results of the HA-ID study. *Res. Dev. Disabil.* **2014**, *35*, 726–732.

16. Schrager, S.; Kloss, C.; Ju, A.W. Prevalence of fractures in women with intellectual disabilities: A chart review. *J. Intellect. Disabil. Res.* **2007**, *51*, 253–259.

17. Morgan, J.P.; Minihan, P.M.; Stark, P.C.; Finkelman, M.D.; Yantsides, K.E.; Park, A.; Nobles, C.J.; Tao, W.; Must, A. The oral health status of 4732 adults with intellectual and developmental disabilities. *J. Am. Dent. Assoc.* **2012**, *143*, 838–846.

18. Zylstra, R.G.; Porter, L.L.; Shapiro, J.L.; Prater, C.D. Prevalence of osteoporosis in community-dwelling individuals with intellectual and/or developmental disabilities. *J. Am. Med. Dir. Assoc.* **2008**, *9*, 109–113.

19. Binkley, C.J.; Haugh, G.S.; Kitchens, D.H.; Wallace, D.L.; Sessler, D.I. Oral microbial and respiratory status of persons with mental retardation/intellectual and developmental disability: An observational cohort study. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* **2009**, *108*, 722–731.

20. Ram, G.; Chinen, J. Infections and immunodeficiency in down syndrome. *Clin. Exp. Immunol.* **2011**, *164*, 9–16.

21. Bastiaanse, L.P.; Hilgenkamp, T.I.; Echteld, M.A.; Evenhuis, H.M. Prevalence and associated factors of sarcopenia in older adults with intellectual disabilities. *Res. Dev. Disabil.* **2012**, *33*, 2004–2012.

22. Center for Disease Control and Prevention. 2013. Developmental Disabilities. Available online: http://www.cdc.gov/ncbddd/dd (accessed on 18 December 2014).

23. American Association on Intellectual and Developmental Disability. Definition of intellectual Disabilities. Available online:http://aaidd.org/intellectual-disability/definition#.VJLnTYrF9EI (accessed on 18 December 2014).

24. Dworkin, M.S.; Park, L.; Barringer, J.; Curtis, R. An outbreak of noninvasive group a streptococcal disease in a facility for the developmentally disabled. *Am. J. Infect. Control* **2006**, *34*, 296–300.

25. Perez-Lopez, F.R.; Brincat, M.; Erel, C.T.; Tremollieres, F.; Gambacciani, M.; Lambrinoudaki, I.; Moen, M.H.; Schenck-Gustafsson, K.; Vujovic, S.; Rozenberg, S.; et al. Emas position statement: Vitamin D and postmenopausal health. *Maturitas* **2012**, *71*, 83–88.

26. Vanlint, S.; Nugent, M.; Durvasula, S. Vitamin D and people with intellectual disability. *Aust. Fam. Phys.* **2008**, *37*, 348–351.

27. Vanlint, S.; Nugent, M.; Durvasula, S.; Downs, J.; Leonard, H. A guide for the assessment and management of vitamin D status in people with intellectual disability (developed as an AADDM working party initiative). *J. Intellect. Dev. Disabil.* **2008**, *33*, 184–188.

28. Vanlint, S.; Nugent, M. Vitamin D and fractures in people with intellectual disability. *J. Intellect. Disabil. Res.* **2006**, *50*, 761–767.

29. Frighi, V.; Morovat, A.; Stephenson, M.T.; White, S.J.; Hammond, C.V.; Goodwin, G.M. Vitamin D deficiency in patients with intellectual disabilities: Prevalence, risk factors and management strategies. *Br. J. Psychiatry J. Ment. Sci.* **2014**, *205*, 458–464.

30. Rajakumar, K.; Greenspan, S.L.; Thomas, S.B.; Holick, M.F. Solar ultraviolet radiation and vitamin D: A historical perspective. *Am. J. Public Health* **2007**, *97*, 1746–1754.
31. Priemel, M.; von Domarus, C.; Klatte, T.O.; Kessler, S.; Schlie, J.; Meier, S.; Proksch, N.; Pastor, F.; Netter, C.; Streichert, T.; et al. Bone mineralization defects and vitamin D deficiency: Histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. J. Bone Miner. Res. 2010, 25, 305–312.

32. Dhesi, J.K.; Bearne, L.M.; Moniz, C.; Hurley, M.V.; Jackson, S.H.; Swift, C.G.; Allain, T.J. Neuromuscular and psychomotor function in elderly subjects who fall and the relationship with vitamin D status. J. Bone Miner. Res. 2010, 25, 305–312.

33. Lips, P.; Binkley, N.; Pfeifer, M.; Recker, R.; Samanta, S.; Cohn, D.A.; Chandler, J.; Rosenberg, E.; Papanicolaou, D.A. Once-weekly dose of 8400 IU vitamin D(3) compared with placebo: Effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency. Am. J. Clin. Nutr. 2010, 91, 985–991.

34. Rejnmark, L. Effects of vitamin D on muscle function and performance: A review of evidence from randomized controlled trials. Ther. Adv. Chronic Dis. 2011, 2, 25–37.

35. Bischoff-Ferrari, H.A.; Willett, W.C.; Orav, E.J.; Lips, P.; Meunier, P.J.; Lyons, R.A.; Flicker, L.; Wark, J.; Jackson, R.D.; Cauley, J.A.; et al. A pooled analysis of vitamin D dose requirements for fracture prevention. N. Engl. J. Med. 2012, 367, 40–49.

36. Holick, M.F.; Binkley, N.C.; Bischoff-Ferrari, H.A.; Gordon, C.M.; Hanley, D.A.; Heaney, R.P.; Murad, M.H.; Weaver, C.M. Evaluation, treatment, and prevention of vitamin D deficiency: An endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. 2011, 96, 1911–1930.

37. Wong, T.S.; Lau, V.M.; Lim, W.; Fung, G. A survey of vitamin D level in people with learning disability in long-stay hospital wards in hong kong. J. Intellect. Disabil. JID 2006, 10, 47–59.

38. Sholas, M.G.; Tann, B.; Gaebler-Spira, D. Oral bisphosphonates to treat disuse osteopenia in children with disabilities: A case series. J. Pediatr. Orthop. 2005, 25, 326–331.

39. Carmel, A.S.; Shieh, A.; Bang, H.; Bockman, R.S. The 25(OH)D level needed to maintain a favorable bisphosphonate response is ≥33 ng/mL. Osteoporos. Int. 2012, 23, 2479–2487.

40. Peiris, A.N.; Youssef, D.; Grant, W.B. Secondary hyperparathyroidism: Benign bystander or culpable contributor to adverse health outcomes? South. Med. J. 2012, 105, 36–42.

41. Valcour, A.; Blocki, F.; Hawkins, D.M.; Rao, S.D. Effects of age and serum 25-OH-vitamin D on serum parathyroid hormone levels. J. Clin. Endocrinol. Metab. 2012, 97, 3989–3995.

42. Ahmadieh, H.; Arabi, A. Vitamins and bone health: Beyond calcium and vitamin D. Nutrit. Rev. 2011, 69, 584–598.

43. Bonjour, J.P. Protein intake and bone health. Int. J. Vitamin Nutr. Res. 2011, 81, 134–142.

44. Michaelsson, K.; Olofsson, H.; Jensevik, K.; Larsson, S.; Mallmin, H.; Berglund, L.; Vessby, B.; Melhus, H. Leisure physical activity and the risk of fracture in men. PLoS Med. 2007, 4, e199.

45. Korpelainen, R.; Keinanen-Kiukaanniemi, S.; Nieminen, P.; Heikkinen, J.; Vaananen, K.; Korpelainen, J. Long-term outcomes of exercise: Follow-up of a randomized trial in older women with osteopenia. Arch. Intern. Med. 2010, 170, 1548–1556.

46. Sohl, E.; van Schoor, N.M.; de Jongh, R.T.; Visser, M.; Deeg, D.J.; Lips, P. Vitamin D status is associated with functional limitations and functional decline in older individuals. J. Clin. Endocrinol. Metab. 2013, 98, E1483–E1490.

47. Gombart, A.F. The vitamin D-antimicrobial peptide pathway and its role in protection against infection. Future Microbiol. 2009, 4, 1151–1165.
48. Conesa-Botella, A.; Meintjes, G.; Coussens, A.K.; van der Plas, H.; Goliath, R.; Schutz, C.; Moreno-Reyes, R.; Mehta, M.; Martineau, A.R.; Wilkinson, R.J.; et al. Corticosteroid therapy, vitamin D status, and inflammatory cytokine profile in the HIV-tuberculosis immune reconstitution inflammatory syndrome. *Clini. Infect. Dis.* **2012**, *55*, 1004–1011.

49. Jeffery, L.E.; Wood, A.M.; Qureshi, O.S.; Hou, T.Z.; Gardner, D.; Briggs, Z.; Kaur, S.; Raza, K.; Sansom, D.M. Availability of 25-hydroxyvitamin D(3) to APCs controls the balance between regulatory and inflammatory T cell responses. *J. Immunol.* **2012**, *189*, 5155–5164.

50. Cannell, J.J.; Vieth, R.; Umhau, J.C.; Holick, M.F.; Grant, W.B.; Madronich, S.; Garland, C.F.; Giovannucci, E. Epidemic influenza and vitamin D. *Epidemiol. Infect.* **2006**, *134*, 1129–1140.

51. Aloia, J.F.; Li-Ng, M. Re: Epidemic influenza and vitamin D. *Epidemiol. Infect.* **2007**, *135*, 1095–1096.

52. Urashima, M.; Segawa, T.; Okazaki, M.; Kurihara, M.; Wada, Y.; Ida, H. Randomized trial of vitamin D supplementation to prevent seasonal influenza a in schoolchildren. *Am. J. Clin. Nutr.* **2010**, *91*, 1255–1260.

53. Bergman, P.; Lindh, A.U.; Bjorkhem-Bergman, L.; Lindh, J.D. Vitamin D and respiratory tract infections: A systematic review and meta-analysis of randomized controlled trials. *PLoS One* **2013**, *8*, e65835.

54. Bener, A.; Kamal, M. Predict attention deficit hyperactivity disorder? Evidence-based medicine. *Glob. J. Health Sci.* **2014**, *6*, 47–57.

55. Brehm, J.M. Vitamin D and asthma-life after VIDA? *Curr. Allergy Asthma Rep.* **2014**, *14*, 461.

56. Castro, M.; King, T.S.; Kunselman, S.J.; Cabana, M.D.; Denlinger, L.; Holguin, F.; Kazani, S.D.; Moore, W.C.; Moy, J.; Sorkness, C.A.; *et al.* Effect of vitamin D3 on asthma treatment failures in adults with symptomatic asthma and lower vitamin D levels: The vida randomized clinical trial. *J. Am. Med. Assoc.* **2014**, *311*, 2083–2091.

57. Puhan, M.A.; Siebeling, L.; Frei, A.; Zoller, M.; Bischoff-Ferrari, H.; Ter Riet, G. No association of 25-hydroxyvitamin D with exacerbations in primary care patients with copd. *Chest* **2014**, *145*, 37–43.

58. Martineau, A.R.; James, W.Y.; Hooper, R.L.; Barnes, N.C.; Jolliffe, D.A.; Greiller, C.L.; Islam, K.; McLaughlin, D.; Bhowmik, A.; Timms, P.M.; *et al.* Vitamin D supplementation in patients with chronic obstructive pulmonary disease (ViDiCO): A multicentre, double-blind, randomised controlled trial. *Lancet Respir. Med.* **2015**, *3*, 120–130.

59. Pojsupap, S.; Iliriani, K.; Sampaio, T.Z.; O’Hearn, K.; Kovesi, T.; Menon, K.; McNally, J.D. Efficacy of high-dose vitamin D in pediatric asthma: A systematic review and meta-analysis. *J. Asthma* **2014**, *21*, 1–9.

60. Von Hurst, P.R.; Stonehouse, W.; Coad, J. Vitamin D supplementation reduces insulin resistance in south asian women living in new zealand who are insulin resistant and vitamin D deficient—A randomised, placebo-controlled trial. *Br. J. Nutr.* **2010**, *103*, 549–555.

61. Song, Y.; Wang, L.; Pittas, A.G.; Del Gobbo, L.C.; Zhang, C.; Manson, J.E.; Hu, F.B. Blood 25-hydroxy vitamin D levels and incident type 2 diabetes: A meta-analysis of prospective studies. *Diabetes Care* **2013**, *36*, 1422–1428.
62. Schafer, A.L.; Napoli, N.; Lui, L.; Schwartz, A.V.; Black, D.M. Serum 25-hydroxyvitamin D concentration does not independently predict incident diabetes in older women. *Diabet. Med. J. Br. Diabet. Assoc.* 2014, 31, 564–569.

63. Dutta, D.; Mondal, S.A.; Choudhuri, S.; Maisnam, I.; Hasanoor Reza, A.H.; Bhattacharya, B.; Chowdhury, S.; Mukhopadhyay, S. Vitamin-D supplementation in prediabetes reduced progression to type 2 diabetes and was associated with decreased insulin resistance and systemic inflammation: An open label randomized prospective study from eastern india. *Diabetes Res. Clin. Pract.* 2014, 103, e18–e23.

64. Breslavsky, A.; Frand, J.; Matas, Z.; Boaz, M.; Barnea, Z.; Shargorodsky, M. Effect of high doses of vitamin D on arterial properties, adiponectin, leptin and glucose homeostasis in type 2 diabetic patients. *Clin. Nutr.* 2013, 32, 970–975.

65. Wang, L.; Song, Y.; Mansoon, J.E.; Pilz, S.; Marz, W.; Michaelsson, K.; Lundqvist, A.; Jassal, S.K.; Barrett-Conner, E.; Zhang, C.; *et al.* Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: A meta-analysis of prospective studies. *Circ. Cardiovasc. Qual. Outcomes* 2012, 5, 819–829.

66. Schnatz, P.F.; Jiang, X.; Vila-Wright, S.; Aragaki, A.K.; Nudy, M.; O’Sullivan, D.M.; Jackson, R.; LeBlanc, E.; Robinson, J.G.; Shikany, J.M.; *et al.* Calcium/vitamin D supplementation, serum 25-hydroxyvitamin D concentrations, and cholesterol profiles in the women’s health initiative calcium/vitamin D randomized trial. *Menopause* 2014, 21, 823–833.

67. Bolland, M.J.; Grey, A.; Gamble, G.D.; Reid, I.R. The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: A trial sequential meta-analysis. *Lancet Diabetes Endocrinol.* 2014, 2, 307–320.

68. Warren-Gash, C.; Hayward, A.C.; Hemingway, H.; Denaxas, S.; Thomas, S.L.; Timmis, A.D.; Whittaker, H.; Smeeth, L. Influenza infection and risk of acute myocardial infarction in england and wales: A caliber self-controlled case series study. *J. Infect. Dis.* 2012, 206, 1652–1659.

69. Afzal, S.; Bojesen, S.E.; Nordestgaard, B.G. Reduced 25-hydroxyvitamin D and risk of alzheimer’s disease and vascular dementia. *Alzheimers Dement. J. Alzheimers Assoc.* 2014, 10, 296–302.

70. De la Torre, J.C. Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. *Cardiovasc. Psychiatry Neurol.* 2012, 2012, 367516.

71. Gezen-Ak, D.; Yilmazer, S.; Dursun, E. Why vitamin D in Alzheimer’s disease? The hypothesis. *J. Alzheimers Dis.* 2014, 40, 257–269.

72. Annweiler, C.; Karras, S.N.; Anagnostis, P.; Beauchet, O. Vitamin D supplements: A novel therapeutic approach for alzheimer patients. *Front. Pharmacol.* 2014, 5, 6.

73. Littlejohns, T.J.; Henley, W.E.; Lang, I.A.; Annweiler, C.; Beauchet, O.; Chaves, P.H.; Fried, L.; Kestenbaum, B.R.; Kuller, L.H.; Langa, K.M.; *et al.* Vitamin D and the risk of dementia and Alzheimer disease. *Neurology* 2014, 83, 920–928.

74. Cannell, J.J. Autism and vitamin D. *Med. Hypotheses* 2008, 70, 750–759.

75. Grant, W.B.; Cannell, J.J. Autism prevalence in the united states with respect to solar UV-B doses: An ecological study. *Dermato-endocrinology* 2013, 5, 159–164.

76. Patrick, R.P.; Ames, B.N. Vitamin D hormone regulates serotonin synthesis. Part 1: Relevance for autism. *FASEB J.* 2014, 28, 2398–2413.
77. Cannell, J.J.; Grant, W.B. What is the role of vitamin D in autism? *Dermato-endocrinology* 2013, 5, 199–204.
78. Cannell, J.J. Autism, will vitamin D treat core symptoms? *Med. Hypotheses* 2013, 81, 195–198.
79. Jia, F.; Wang, B.; Shan, L.; Xu, Z.; Staal, W.G.; Du, L. Core symptoms of autism improved after vitamin D supplementation. *Pediatrics* 2015, 135, e196–e198.
80. Neece, C.L.; Baker, B.L.; Blacher, J.; Crnic, K.A. Attention-deficit/hyperactivity disorder among children with and without intellectual disability: An examination across time. *J. Intellect. Disabil. Res.* 2011, 55, 623–635.
81. Goksugur, S.B.; Tufan, A.E.; Semiz, M.; Gunes, C.; Bekdas, M.; Tosun, M.; Demircioglu, F. Vitamin D status in children with attention-deficit-hyperactivity disorder. *Pediatr. Intern.* 2014, 56, 515–519.
82. Rucklidge, J.J.; Johnstone, J.; Gorman, B.; Boggis, A.; Frampton, C.M. Moderators of treatment response in adults with ADHD treated with a vitamin-mineral supplement. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 2014, 50, 163–171.
83. Grant, W.B. Ecological studies of the UVB-vitamin D-cancer hypothesis. *Anticancer Res.* 2012, 32, 223–236.
84. Moukayed, M.; Grant, W.B. Molecular link between vitamin D and cancer prevention. *Nutrients* 2013, 5, 3993–4021.
85. Grant, W.B. Relation between prediagnostic serum 25-hydroxyvitamin D level and incidence of breast, colorectal, and other cancers. *J. Photochem. Photobiol. B.* 2010, 101, 130–136.
86. Grant, W.B. Effect of interval between serum draw and follow-up period on relative risk of cancer incidence with respect to 25-hydroxyvitamin D level: Implications for meta-analyses and setting vitamin D guidelines. *Dermato-endocrinology* 2011, 3, 199–204.
87. Gilbert, R.; Metcalfe, C.; Fraser, W.D.; Donovan, J.; Hamdy, F.; Neal, D.E.; Lane, J.A.; Martin, R.M. Associations of circulating 25-hydroxyvitamin D with prostate cancer diagnosis, stage and grade. *Int. J. Cancer* 2012, 131, 1187–1196.
88. Lappe, J.M.; Travers-Gustafson, D.; Davies, K.M.; Recker, R.R.; Heaney, R.P. Vitamin D and calcium supplementation reduces cancer risk: Results of a randomized trial. *Am. J. Clin. Nutr.* 2007, 85, 1586–1591.
89. Bolland, M.J.; Grey, A.; Gamble, G.D.; Reid, I.R. Calcium and vitamin D supplements and health outcomes: A reanalysis of the women’s health initiative (WHI) limited-access data set. *Am. J. Clin. Nutr.* 2011, 94, 1144–1149.
90. Bjelakovic, G.; Gluud, L.L.; Nikolova, D.; Whitfield, K.; Wetterslev, J.; Simonetti, R.G.; Bjelakovic, M.; Gluud, C. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database Syst. Rev.* 2014, 1, CD007470.
91. Tretli, S.; Schwartz, G.G.; Torjesen, P.A.; Robsahm, T.E. Serum levels of 25-hydroxyvitamin D and survival in Norwegian patients with cancer of breast, colon, lung, and lymphoma: A population-based study. *Cancer Causes Control* 2012, 23, 363–370.
92. Mellanby, M.; Pattison, C.L. The action of vitamin D in preventing the spread and promoting the arrest of caries in children. *Br. Med. J.* 1928, 2, 1079–1082.
93. Grant, W.B. A review of the role of solar ultraviolet-B irradiance and vitamin D in reducing risk of dental caries. *Dermato-endocrinology* 2011, 3, 193–198.
94. Hujoel, P.P. Vitamin D and dental caries in controlled clinical trials: Systematic review and meta-analysis. *Nutr. Rev.* 2013, 71, 88–97.
95. Grant, W.B.; Boucher, B.J. Are hill’s criteria for causality satisfied for vitamin D and periodontal disease? *Dermato-endocrinology* 2010, 2, 30–36.
96. Jimenez, M.; Giovannucci, E.; Krall Kaye, E.; Joshipura, K.J.; Dietrich, T. Predicted vitamin D status and incidence of tooth loss and periodontitis. *Pub. Health Nutr.* 2014, 17, 844–852.
97. Villasenor, A.; Ballard-Barbash, R.; Ambs, A.; Bernstein, L.; Baumgartner, K.; Baumgartner, R.; Ulrich, C.M.; Hollis, B.W.; McTierman, A.; Neuhausser, M.L. Associations of serum 25-hydroxyvitamin D with overall and breast cancer-specific mortality in a multiethnic cohort of breast cancer survivors. *Cancer Causes Control* 2013, 24, 759–767.
98. Alshouibi, E.N.; Kaye, E.K.; Cabral, H.J.; Leone, C.W.; Garcia, R.I. Vitamin D and periodontal health in older men. *J. Dent. Res.* 2013, 92, 689–693.
99. Slinin, Y.; Paudel, M.; Taylor, B.C.; Ishani, A.; Rossom, R.; Yaffe, K.; Blackwell, T.; Lui, L.Y.; Hochberg, M.; Ensrud, K.E. Association between serum 25(OH) vitamin D and the risk of cognitive decline in older women. *J. Gerontol. A Biol. Sci. Med. Sci.* 2012, 67, 1092–1098.
100. Kunutsor, S.K.; Apekey, T.A.; Steur, M. Vitamin D and risk of future hypertension: Meta-analysis of 283,537 participants. *Eur. J. Epidemiol.* 2013, 28, 205–221.
101. Plotnikoff, G.A.; Quigley, J.M. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin. Proc.* 2003, 78, 1463–1470.
102. Le Goaziou, M.F.; Kellou, N.; Flori, M.; Perdrix, C.; Dupraz, C.; Bodier, E.; Souweine, G. Vitamin D supplementation for diffuse musculoskeletal pain: Results of a before-and-after study. *Eur. J. Gen. Pract.* 2014, 20, 3–9.
103. Garland, C.F.; Kim, J.J.; Mohr, S.B.; Gorham, E.D.; Grant, W.B.; Giovannucci, E.L.; Baggerly, L.; Hofflich, H.; Ransdell, J.W.; Zeng, K.; et al. Meta-analysis of all-cause mortality according to serum 25-hydroxyvitamin D. *Am. J. Public Health* 2014, 104, e43–e50.
104. Chowdhury, R.; Kunutsor, S.; Vitezova, A.; Oliver-Williams, C.; Chowdhury, S.; Kieffe-de-Jong, J.C.; Khan, H.; Baena, C.P.; Prabhakaran, D.; Hoshen, M.B.; et al. Vitamin D and risk of cause specific death: Systematic review and meta-analysis of observational cohort and randomised intervention studies. *BMJ* 2014, 348, g1903.
105. Spedding, S.; Vanlint, S.; Morris, H.; Scragg, R. Does vitamin D sufficiency equate to a single serum 25-hydroxyvitamin D level or are different levels required for non-skeletal diseases? *Nutrients* 2013, 5, 5127–5139.
106. Ogan, D.; Pritchett, K. Vitamin D and the athlete: Risks, recommendations, and benefits. *Nutrients* 2013, 5, 1856–1868.
107. Grant, W.B. 25-hydroxyvitamin D and breast cancer, colorectal cancer, and colorectal adenomas: Case-control vs. nested case-control studies. *Anticancer Res.* 2015, 35, 1153–1160.
108. Looker, A.C.; Mussolino, M.E. Serum 25-hydroxyvitamin D and hip fracture risk in older U.S. White adults. *J. Bone Miner. Res.* 2008, 23, 143–150.
109. Rothenbacher, D.; Klenk, J.; Denkinger, M.D.; Herbsheimer, F.; Nikolaus, T.; Peter, R.; Boehm, B.O.; Rapp, K.; Dallmeier, D.; Koenig, W. Prospective evaluation of renal function, serum vitamin D level, and risk of fall and fracture in community-dwelling elderly subjects. *Osteoporos. Int.* 2014, 25, 923–932.
110. Burgi, A.A.; Gorham, E.D.; Garland, C.F.; Mohr, S.B.; Garland, F.C.; Zeng, K.; Thompson, K.; Lappe, J.M. High serum 25-hydroxyvitamin D is associated with a low incidence of stress fractures. *J. Bone Miner. Res.* **2011**, *26*, 2371–2377.

111. Costan, A.R.; Vulpoi, C.; Mocanu, V. Vitamin D fortified bread improves pain and physical function domains of quality of life in nursing home residents. *J. Med. Food* **2014**, *17*, 625–631.

112. Sabetta, J.R.; DePetriillo, P.; Cipriani, R.J.; Smardin, J.; Burns, L.A.; Landry, M.L. Serum 25-hydroxyvitamin D and the incidence of acute viral respiratory tract infections in healthy adults. *PLoS One* **2010**, *5*, e11088.

113. Parekh, A.K.; Kronick, R.; Tavenner, M. Optimizing health for persons with multiple chronic conditions. *J. Am. Med. Assoc.* **2014**, *312*, 1199–1200.

114. Holick, M.F.; Binkley, N.C.; Bischoff-Ferrari, H.A.; Gordon, C.M.; Hanley, D.A.; Heaney, R.P.; Murad, M.H.; Weaver, C.M. Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. *J. Clin. Endocrinol. Metab.* **2012**, *97*, 1153–1158.

115. Millen, A.E.; Hovey, K.M.; LaMonte, M.J.; Swanson, M.; Andrews, C.A.; Kluczynski, M.A.; Genco, R.J.; Wactawski-Wende, J. Plasma 25-hydroxyvitamin D concentrations and periodontal disease in postmenopausal women. *J. Periodontol.* **2013**, *84*, 1243–1256.

116. Ginde, A.A.; Liu, M.C.; Camargo, C.A., Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988–2004. *Arch. Intern. Med.* **2009**, *169*, 626–632.

117. Vieth, R. Critique of the considerations for establishing the tolerable upper intake level for vitamin D: Critical need for revision upwards. *J. Nutr.* **2006**, *136*, 1117–1122.

118. Araki, T.; Holick, M.F.; Alfonso, B.D.; Charlap, E.; Romero, C.M.; Rizk, D.; Newman, L.G. Vitamin D intoxication with severe hypercalcemia due to manufacturing and labeling errors of two dietary supplements made in the united states. *J. Clin. Endocrinol. Metab.* **2011**, *96*, 3603–3608.

119. Haussler, M.R.; Whitfield, G.K.; Kaneko, I.; Haussler, C.A.; Hsieh, D.; Hsieh, J.C.; Jurutka, P.W. Molecular mechanisms of vitamin D action. *Calcif. Tissue Int.* **2013**, *92*, 77–98.

120. Souberbielle, J.C.; Body, J.J.; Lappe, J.M.; Plebani, M.; Shoenfeld, Y.; Wang, T.J.; Bischoff-Ferrari, H.A.; Cavalier, E.; Ebeling, P.R.; Fardellone, P.; et al. Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: Recommendations for clinical practice. *Autoimmun. Rev.* **2010**, *9*, 709–715.

121. Godar, D.E.; Pope, S.J.; Grant, W.B.; Holick, M.F. Solar UV doses of adult americans and vitamin D(3) production. *Dermato-endocrinology* **2011**, *3*, 243–250.

122. Rolland, Y.; de Souto Barreto, P.; Abellan Van Kan, G.; Annweiler, C.; Beauchet, O.; Bischoff-Ferrari, H.; Berrut, G.; Blain, H.; Bonnefoy, M.; Cesari, M.; et al. Vitamin D supplementation in older adults: Searching for specific guidelines in nursing homes. *J. Nutr. Health Aging* **2013**, *17*, 402–412.

123. Pludowski, P.; Holick, M.F.; Pilz, S.; Wagner, C.L.; Hollis, B.W.; Grant, W.B.; Shoenfeld, Y.; Lerchbaum, E.; Llewellyn, D.J.; Kienreich, K.; et al. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality—a review of recent evidence. *Autoimmun. Rev.* **2013**, *12*, 976–989.
124. Rizzoli, R.; Boonen, S.; Brandi, M.L.; Bruyere, O.; Cooper, C.; Kanis, J.A.; Kaufman, J.M.; Ringe, J.D.; Weryha, G.; Reginster, J.Y. Vitamin D supplementation in elderly or postmenopausal women: A 2013 update of the 2008 recommendations from the European society for clinical and economic aspects of osteoporosis and osteoarthritis (ESCEO). *Curr. Med. Res. Opin.* **2013**, *29*, 305–313.

125. Parks, S.M.; Harper, G.M.; Fernandez, H.; Sauvigne, K.; Leipzig, R.M. American geriatrics society/association of directors of geriatric academic programs curricular milestones for graduating geriatric fellows. *J. Am. Geriatr. Soc.* **2014**, *62*, 930–935.

126. Ross, A.C. The 2011 report on dietary reference intakes for calcium and vitamin D. *Public Health Nutr.* **2011**, *14*, 938–939.

127. Heaney, R.P.; Holick, M.F. Why the IOM recommendations for vitamin D are deficient. *J. Bone Miner. Res.* **2011**, *26*, 455–457.

128. Hart, J.T. Cochrane lecture 1997. What evidence do we need for evidence based medicine? *J. Epidemiol. Commun. Health* **1997**, *51*, 623–629.

129. Gillie, O. Controlled trials of vitamin D, causality and type 2 statistical error. *Public Health Nutr.* **2014**, *5*, 1–6.

130. Hathcock, J.N.; Shao, A.; Vieth, R.; Heaney, R. Risk assessment for vitamin D. *Am. J. Clin. Nutr.* **2007**, *85*, 6–18.

131. Ekwaru, J.P.; Zwicker, J.D.; Holick, M.F.; Giovannucci, E.; Veugelers, P.J. The importance of body weight for the dose response relationship of oral vitamin D supplementation and serum 25-hydroxyvitamin D in healthy volunteers. *PLoS One* **2014**, *9*, e111265.

132. Michaelsson, K.; Baron, J.A.; Snellman, G.; Gedeborg, R.; Byberg, L.; Sundstrom, J.; Berglund, L.; Arnlov, J.; Hellman, P.; Blomhoff, R.; *et al.* Plasma vitamin D and mortality in older men: A community-based prospective cohort study. *Am. J. Clin. Nutr.* **2010**, *92*, 841–848.

133. Durup, D.; Jorgensen, H.L.; Christensen, J.; Schwarz, P.; Heegaard, A.M.; Lind, B. A reverse J-shaped association of all-cause mortality with serum 25-hydroxyvitamin D in general practice: The copd study. *J. Clin. Endocrinol. Metab.* **2012**, *97*, 2644–2652.

134. Brouwer-Brolsma, E.M.; Bischoff-Ferrari, H.A.; Bouillon, R.; Feskens, E.J.; Gallagher, C.J.; Hypponen, E.; Llewellyn, D.J.; Stoecklin, E.; Dierkes, J.; Kies, A.K.; *et al.* Vitamin D: Do we get enough? A discussion between vitamin D experts in order to make a step towards the harmonisation of dietary reference intakes for vitamin D across Europe. *Osteoporos. Int.* **2013**, *24*, 1567–1577.

135. Ensrud, K.E.; Ewing, S.K.; Fredman, L.; Hochberg, M.C.; Cauley, J.A.; Hillier, T.A.; Cummings, S.R.; Yaffe, K.; Caawthon, P.M. Circulating 25-hydroxyvitamin D levels and frailty status in older women. *J. Clin. Endocrinol. Metab.* **2010**, *95*, 5266–5273.

136. Amrein, K.; Quraishi, S.A.; Litonjua, A.A.; Gibbons, F.K.; Pieber, T.R.; Camargo, C.A., Jr.; Giovannucci, E.; Christopher, K.B. Evidence for a U-shaped relationship between prehospital vitamin D status and mortality: A cohort study. *J. Clin. Endocrinol. Metab.* **2014**, *99*, 1461–1469.

137. Hypponen, E.; Berry, D.J.; Wjst, M.; Power, C. Serum 25-hydroxyvitamin D and IgE—A significant but nonlinear relationship. *Allergy* **2009**, *64*, 613–620.
138. Ensrud, K.E.; Blackwell, T.L.; Cauley, J.A.; Cummings, S.R.; Barrett-Connor, E.; Dam, T.T.; Hoffman, A.R.; Shikany, J.M.; Lane, N.E.; Stefanick, M.L.; et al. Circulating 25-hydroxyvitamin D levels and frailty in older men: The osteoporotic fractures in men study. *J. Am. Geriatr. Soc.* 2011, 59, 101–106.

139. Mellenthin, L.; Wallaschofski, H.; Grotevendt, A.; Volzke, H.; Nauck, M.; Hannemann, A. Association between serum vitamin D concentrations and inflammatory markers in the general adult population. *Metab. Clin. Exp.* 2014, 63, 1056–1062.

140. Zittermann, A.; Prokop, S. The role of vitamin D for cardiovascular disease and overall mortality. *Adv. Exp. Med. Biol.* 2014, 810, 763–767.

141. Maddock, J.; Geoffroy, M.C.; Power, C.; Hypponen, E. 25-hydroxyvitamin D and cognitive performance in mid-life. *Br. J. Nutr.* 2014, 111, 904–914.

142. Lerchbaum, E.; Pilz, S.; Trummer, C.; Rabe, T.; Schenk, M.; Heijboer, A.C.; Obermayer-Pietsch, B. Serum vitamin D levels and hypogonadism in men. *Andrology* 2014, 2, 748–754.

143. Conti, G.; Chirico, V.; Lacquaniti, A.; Silipigni, L.; Fede, C.; Vitale, A. Vitamin D intoxication in two brothers: Be careful with dietary supplements. *J. Pediatri. Endocrinol. Metab.* 2014, 27, 763–767.

144. Vieth, R. Vitamin D and cancer mini-symposium: The risk of additional vitamin D. *Ann. Epidemiol.* 2009, 19, 441–445.

145. Kara, C.; Gunindi, F.; Ustyol, A.; Aydin, M. Vitamin D intoxication due to an erroneously manufactured dietary supplement in seven children. *Pediatrics* 2014, 133, 240–244.

146. Autier, P.; Boniol, M.; Pizot, C.; Mullie, P. Vitamin D status and ill health: A systematic review. *Lancet Diabetes Endocrinol.* 2014, 2, 76–89.

147. Theodoratou, E.; Tzoulaki, I.; Zgaga, L.; Ioannidis, J.P. Vitamin D and multiple health outcomes: Umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. *BMJ* 2014, 348, g2035.

148. Cannell, J.J. Paracetamol, oxidative stress, vitamin D and autism spectrum disorders. *Int. J. Epidemiol.* 2014, 43, 974–975.

149. Heaney, R.P.; Recker, R.R.; Grote, J.; Horst, R.L.; Armas, L.A. Vitamin D(3) is more potent than vitamin D(2) in humans. *J. Clin. Endocrinol. Metab.* 2011, 96, 447–452.

150. Demetriou, E.T.; Travison, T.G.; Holick, M.F. Treatment with 50,000 IU vitamin D(2) every other week and effect on serum 25-hydroxyvitamin D(2), 25-hydroxyvitamin D(3), and total 25-hydroxyvitamin D in a clinical setting. *Endocr. Pract.* 2012, 18, 399–402.

151. Alam, U.; Chan, A.W.; Buazon, A.; Van Zeller, C.; Berry, J.L.; Jugdey, R.S.; Asghar, O.; Cruickshank, J.K.; Petropoulos, I.N.; Malik, R.A. Differential effects of different vitamin D replacement strategies in patients with diabetes. *J. Diabetes Complications* 2014, 28, 66–70.

152. Rouillon, V.; Dubourg, G.; Gauvain, J.B.; Baron, D.; Glemarec, J.; Cormier, G.; Guillot, P. Vitamin D insufficiency: Evaluation of an oral standardized supplementation using 100,000 IU vials of cholecalciferol, depending on initial serum level of 25OH vitamin D. *Joint Bone Spine* 2012, 79, 399–402.
153. Wallace, T.C.; Reider, C.; Fulgoni, V.L., 3rd. Calcium and vitamin D disparities are related to gender, age, race, household income level, and weight classification but not vegetarian status in the United States: Analysis of the NHANES 2001–2008 data set. *J. Am. Coll. Nutr.* **2013**, *32*, 321–330.

154. Crowe, F.L.; Steur, M.; Allen, N.E.; Appleby, P.N.; Travis, R.C.; Key, T.J. Plasma concentrations of 25-hydroxyvitamin D in meat eaters, fish eaters, vegetarians and vegans: Results from the EPIC-Oxford study. *Public Health Nutr.* **2011**, *14*, 340–346.

155. Garland, C.F.; French, C.B.; Baggerly, L.L.; Heaney, R.P. Vitamin D supplement doses and serum 25-hydroxyvitamin D in the range associated with cancer prevention. *Anticancer Res.* **2011**, *31*, 607–611.

156. Denimal, D.; Ducros, V.; Dupre, T.; Dousset, B.; Meunier, C.; Aho, S.; Guillard, J.C.; Lemaire-Ewing, S. Agreement of seven 25-hydroxy vitamin D(3) immunoassays and three high performance liquid chromatography methods with liquid chromatography tandem mass spectrometry. *Clin. Chem. Lab. Med.* **2014**, *52*, 511–520.

157. Enko, D.; Fridrich, L.; Rezanka, E.; Stolba, R.; Ernst, J.; Wendler, I.; Daniel, F.; Hauptlorenz, S.; Halwachs-Baumann, G. 25-hydroxy-vitamin D status: Limitations in comparison and clinical interpretation of serum-levels across different assay methods. *Clin. Lab.* **2014**, *60*, 1541–1550.

158. Carter, G.D. 25-hydroxyvitamin D: A difficult analyte. *Clin.Chem.* **2012**, *58*, 486–488.

© 2015 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/4.0/).