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## *Horizons in Nutritional Science*

# Towards prevention of vitamin D deficiency and beyond: knowledge gaps and research needs in vitamin D nutrition and public health

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## Abstract

The North American Institute of Medicine (IOM) recently published their report on dietary reference intakes (DRI) for Ca and vitamin D. The DRI committee's deliberations underpinning this most comprehensive report on vitamin D nutrition to date benefited hugely from a much expanded knowledge base in vitamin D over the last decade or more. However, since their release, the vitamin D DRI have been the subject of intense controversy, which is largely due to the persistence of fundamental knowledge gaps in vitamin D. These can be identified at the levels of exposure, metabolism, storage, status, dose–response, function and beneficial or adverse health effects, as well as safe and effective application of intake recommendations at the population level through sustainable food-based approaches. The present review provides a brief overview of the approach used by the IOM committee to revise the DRI for vitamin D and to collate from a number of authoritative sources key knowledge gaps in vitamin D nutrition from the public health perspective. A number of research topics are outlined and data requirements within these are identified and mapped to the risk assessment framework used by the DRI committee. While not intended as an exhaustive list, it provides a basis for organising and prioritising research efforts in the area of vitamin D, which may offer a perspective on the major areas in need of attention. It is intended to be of use to researchers, national policy makers, the public health community, industry groups and other relevant stakeholders including funding institutions.

**Key words: Vitamin D deficiency: Vitamin D and health: Knowledge gaps: Research needs: European Micronutrient Recommendations Aligned (EURRECA)**

## Background and objective

During the period between 1997, when the North American Institute of Medicine (IOM) published dietary reference intakes (DRI) for Ca and related nutrients, and 2010, when it revised the DRI for Ca and vitamin D[(1)], the research output in the field of vitamin D increased exponentially, yielding a considerable body of data to inform the IOM DRI consensus committee in its deliberations. The DRI report[(1)] is the most comprehensive document on vitamin D nutrition to date. Devising nutrient recommendations for population intakes relies on scientific analysis and judgement of data that exist within a specified time frame and is an iterative process. The amount of research data generated since 1997 advanced the knowledge base in vitamin D to the extent that for the first time, the DRI committee had sufficient evidence on which to base estimated average requirements (EAR). Taking indicators of bone health, including rickets and osteomalacia, bone mineral density and Ca absorption, for which there was sufficient evidence to provide a 'reasonable and supportable basis' for DRI development, the committee proposed a serum 25-hydroxyvitamin D (25(OH)D) level of 40 nmol/l as the median value above which approximately half the population might meet its vitamin D requirement (and below which half might not) and 50 nmol/l as its estimate of the serum 25(OH)D level that would meet the requirement of nearly all (i.e. 97·5 %) 'normal healthy persons'[(1)]. These serum 25(OH)D concentrations, which reflect exposure to

**Abbreviations:** 25(OH)D, 25-hydroxyvitamin D; DRI, dietary reference intakes; EAR, estimated average requirements; EC, European Commission; EFCOVAL, European Food COnsumption and VALidation; EUROFIR, EUROpean Food Information Resource; IOM, Institute of Medicine; RCT, randomised controlled trial; SEBR, systematic evidence-based reviews; UVB, UV blue.

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vitamin D from a combination of sun-derived endogenous synthesis and diet, were used to specify EAR values for vitamin D intakes of 400 IU (10 μg)/d in all age and sex subgroups in the population above 1 year, assuming minimal UV blue (UVB) sunlight exposure. RDA values were derived for application to individuals (600 and 800 IU (15 and 20 μg)/d of vitamin D for those aged 1–70 and 70 + years, respectively). Insufficient data in infants permitted the committee to set an adequate intake value only, of 400 IU/d of vitamin D for < 1-year-olds.

The extensive data evaluation and analysis undertaken by the DRI committee, facilitated largely by the outcomes of two Agency for Healthcare Research and Quality systematic evidence-based reviews (SEBR) from the Ottawa[2] and Tufts[3] evidence-based practice centres, placed a focus upon the vitamin D research conducted to date and has provided a valuable opportunity to reflect and identify data requirements to meet the needs of planned and on-going revisions of recommended nutrient intakes by several authoritative agencies, including the European Food Safety Authority, the UK Scientific Advisory Committee for Nutrition and the Nordic Council of Ministers, among others, as well as future revisions of the IOM DRI. The DRI for vitamin D have been the subject of intense controversy since the IOM report was launched in November 2010, which is largely due to the persistence of fundamental knowledge gaps in vitamin D. These can be identified at the levels of exposure, metabolism, storage, status, dose–response, function and beneficial or adverse health effects in healthy individuals and in patient groups, as well as safe and effective application of intake recommendations at the population level through sustainable food-based approaches. The scarcity of information in some life stages, particularly pregnancy, infancy and adolescence, as well as insufficient experimental data in human volunteers for non-skeletal health indicators, were all identified by the DRI committee as obstacles to defining vitamin D requirements using any but the indices of bone health listed above[1]. Experimental data in appropriately designed studies are required to progress the debate and enable consideration of data appropriate to potentially vulnerable life stages as well as clarify the putative role for vitamin D in non-skeletal health outcomes.

The purpose of the present review is to provide a brief overview of the approach used by the IOM committee to revise the DRI for vitamin D and to collate from a number of authoritative sources[1–13], as well as those identified by us on behalf of the European Commission (EC)-funded 'European Micronutrient Recommendations Aligned' (EURRECA) Network of Excellence, key knowledge gaps in vitamin D nutrition from the public health perspective. A number of research topics are outlined and data requirements within these are identified and mapped to the risk assessment framework. While this is not meant to be an exhaustive list, it provides a basis for organising and prioritising research efforts in the area of vitamin D, which may offer a perspective on the major areas in need of attention. It is intended to be of use to academic and medical researchers, national policy makers, the public health community, industry groups and other relevant stakeholders including funding institutions.

## Risk assessment framework used to establish dietary reference intakes for vitamin D

Following a 10-year period of review of the process of DRI development, documented across several reports[14–16], the IOM committee approached the task of revising DRI for Ca and vitamin D using the risk assessment framework commonly applied to setting tolerable upper intake levels[16], which has also largely been adopted by the European Food Safety Authority for deriving and applying dietary reference values for Europe[17]. Application of the framework to establishing the EAR for vitamin D and Ca ensured independence and transparency in decision-making, facilitated objectivity throughout the process and offered flexibility to allow the committee to make scientific judgements when decisions had to be taken on the basis of limited or incomplete data, because 'no decision is not an option'[16]. By ensuring accountability, these advantages of the framework benefited the process and the report as well as on-going debates.

Risk analysis is a process for managing situations where public health monitoring and interventions are expected or needed by analysing and controlling the risks that may be experienced by a population. The terminology used in risk assessment, such as hazard identification and hazard characterisation and even the concept of 'risk' in association with nutrient intakes, is unfamiliar to nutrition scientists and practitioners[16]. However, nutritionists are mindful that nutrient intakes, unlike substances such as drugs or chemical toxicants where there is zero to minimal background exposure, can pose a dual risk, due either to consumption at a level too low to deliver benefit (deficient), or sufficiently high to pose the threat of an adverse effect (toxic). Widespread adoption of the risk assessment framework would encourage international collaboration and potentially harmonisation of recommended dietary intakes and could potentially include the major authorities as well as expertise from smaller or less developed countries that would not be able to undertake the process independently[16].

The risk assessment framework used by the DRI committee on vitamin D and Ca[1] is organised across four steps, summarised here and in Fig. 1.

### *Step 1. Hazard identification*

The committee used SEBR[2,3] to identify, describe and rate potential indicators (including clinical outcomes, biomarkers of effect, functional outcomes and biomarkers of exposure) to be used in developing the DRI for vitamin D and Ca and to select the critical indicators. The committee found an overall lack of causal evidence from intervention studies for the task of identifying health outcome indicators. This was especially true for non-skeletal outcomes for vitamin D, but also true for skeletal outcomes, particularly in certain life-stage groups[1]. The SEBR found that (1) most vitamin D studies were conducted using older persons or postmenopausal women (a fact

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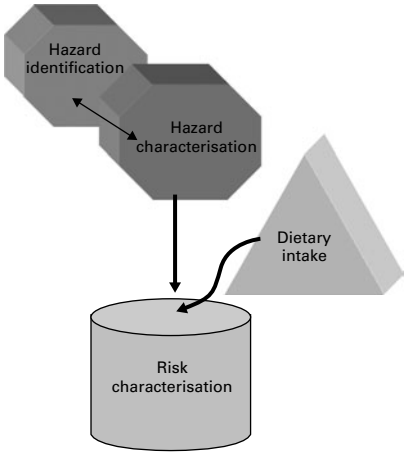


Step 1.
*Identification and review of potential health status indicators to be used in developing the DRIs – based on systematic evidence-based reviews*

Step 2.
*Selection of critical health effect with consideration of life stage and sex;*
*Definition of relationship between intake and health effect;*
*Development of EARs and ULs*

Step 3.
*Assessment of usual population intakes and comparison with proposed EARs/ULs*

Step 4.
*Communication from the risk assessors to the risk managers – description of the assessment process including uncertainties therein and implications for public health policy and scientific research*

**Fig. 1.** Summary of the four steps that constitute the dietary reference intake (DRI) Risk Assessment Framework following problem formulation (adapted from Taylor[16]). EAR, estimated average requirement; UL, upper intake level.

highlighted for Europe also in the 'Vitamin D Deficiency Map' (see later) in relation to available data on status), (2) some available data suggested the possibility of ethnic differences in relation to bone health and nutrient interactions, but this suggestion could not be further clarified, (3) very few studies were designed to explore the effects of Ca and vitamin D independently and (4) very limited data were available on adverse health effects[1]. These information gaps presented challenges in synthesising evidence for Ca and vitamin D separately and in combination. Further, lack of clarity concerning the physiology and metabolism of vitamin D was problematic as was the ability to judge the effects of vitamin D as a nutrient given its role as a prohormone[1].

### *Step 2. Hazard characterisation*

This step of the framework is concerned with specification of the DRI on the basis of clarifying the relationship of the nutrient exposure and the reference level of the critical indicator(s), taking into consideration sex, life-stage and vulnerable groups. The DRI committee indicated that they encountered major challenges in determining the dose–response relationships for Ca and vitamin D, particularly given the extreme variability and lack of data about UVB sunlight exposure and vitamin D status[1].

### *Step 3. Intake assessment*

This step of the framework compares the EAR and upper intake levels values specified in step 2 to habitual population intake data. While great strides have been made in providing intake data on Ca and notably on vitamin D, more data as well as a consistent approach to data reporting would be helpful[1]. The DRI committee encountered challenges in identifying standardised and consistent data on vitamin D intakes across general populations in the USA and Canada, particularly for population subgroups who may be at risk for inadequate or excessive intake. In addition, reliable data on the practice and impact of discretionary fortification on the part of food manufacturers are lacking. These issues are also highly relevant to Europe, particularly given the varying national policies with regard to mandatory and voluntary nutrient fortification across member states.

### *Step 4. Risk characterisation*

This is essentially the reporting step of the framework where the committee details each aspect of the approach used, outcomes, decisions, special concerns and uncertainties relevant to risk managers and regulatory bodies charged with public health policy and scientists. Once reporting is completed, the committee rests and risk management agencies implement the DRI by reforming public health policy and implementing education programmes as well as addressing research recommendations based on the knowledge gaps and data requirements identified in the report.

## Research needs in vitamin D nutrition and public health

The risk assessment framework is bracketed by the linked tasks of problem identification and formulation and implementation of corrective/preventive public policy, which are within the remit of the authoritative agencies charged with public health protection and promotion. Notwithstanding the importance of on-going discussions with respect to thresholds for serum 25(OH)D that represent insufficiency/adequacy, there is widespread acknowledgement of the presence of vitamin D deficiency in the community and the pressing need to address this deficiency.

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Taking serum 25(OH)D concentrations of 30 nmol/l as the cut-off point below which the risk of vitamin D deficiency increases, the first priority from a public health perspective is to ensure that this risk is minimised. The following three critical research requirements, which require significant infrastructural resources, national investment and international collaboration, are:

Distribution of (1) serum 25(OH)D concentrations and (2) vitamin D intakes and food sources in nationally representative populations with appropriate consideration of sex, life stage and ethnicity. (3) Sustainable food-based strategies to bridge the gap between current and recommended intakes of vitamin D to minimise the prevalence of serum 25(OH)D concentrations $<30$ nmol/l.

Prioritising these research requirements would enable quantification of vitamin D deficiency in the EU population and would prevent that deficiency, and, by increasing vitamin D status across the distribution of vitamin D requirements, potentially prevent disease. The infrastructure necessary to meet these critical requirements would also make an immense contribution to the research needs described below in relation to vitamin D metabolism, tissue-specific requirements and relationships with health outcomes throughout the life cycle.

## Distribution of serum 25-hydroxyvitamin D concentrations in nationally representative populations with appropriate consideration of sex, life stage and ethnicity

While the National Health and Nutritional Examination Survey in the USA[18,19] and the Canadian Health Measures Survey[20] have provided useful descriptions of vitamin D status in North America, equivalent data for Europe are of variable quality, making it difficult to estimate the prevalence of vitamin D deficiency across member states. The 'Vitamin D Deficiency Map', a joint initiative between the International Osteoporosis Foundation and DSM Nutrition Products (Basel, Switzerland)[21], aims to provide an overview of vitamin D status in Europe; raise awareness of differences in vitamin D status across Europe; pinpoint the missing data in each region for specific population groups; educate health care professionals and provide guidance to ultimately improve inadequate vitamin D levels in various regions of Europe and beyond. A prototype was launched in spring 2011 and the final online version will go live at the end of this year.

The prototype map clearly showed that nationally representative serum 25(OH)D data are lacking for several European member states[21]. This was highlighted as an information gap well over a decade ago by the EC in its 'Report on Osteoporosis in the European Community: Action for Prevention'[22], and despite progress in this recommendation by individual countries, 'there is an on-going need to assess vitamin D status in representative populations within Europe'. The prototype vitamin D deficiency map also highlighted the lack of representative data at key life stages, particularly pregnancy, infancy, childhood and adolescence and data in representative samples of dark-skinned immigrant populations who may be at additional risk of deficiency[1,3,6,11]. In particular, there is a need for seasonally adjusted reference ranges for serum 25(OH)D throughout gestation in women at different latitudes with appropriate consideration of occupational status, ethnic background and dietary and sun exposure practices and in infants during the first 6–12 months on different feeding regimens.

### *Underpinning infrastructure*

*Standardisation of the measurement of serum 25-hydroxyvitamin D.* Currently[1,3,6,8,9,23], different assays for the determination of serum 25(OH)D levels are in use and they provide disparate results[1,9]. In turn, reported measures are confounded by the need to understand the assay used and research reports contain results that are not readily compared[1]. The role of standard reference materials and interlaboratory collaboration is an important aspect of overcoming the challenges that the assay methodologies present[1,3,23]. In addition, utilisation of methodology that is able to discriminate $25(OH)D_2$ and $25(OH)D_3$ as well as the C-3 epimer of 25(OH)D would be important in population studies, particularly National Nutrition and Health Surveys. Should evidence emerge that the C-3 epimer has biological activity (a research need in its own right), it will need to be quantified[9]. The issue of international standardisation of serum 25(OH)D measurement is being progressed by the Vitamin D Standardization Program – a collaborative initiative between the Office of Dietary Supplements of the National Institutes of Health, and the Centers for Disease Control and Prevention, the National Institutes of Standards and Technology and a number of national health surveys around the world[24]. The Program may in time be applicable also to health surveys, cohort studies and clinical trials.

## Distribution of vitamin D intakes and food sources in nationally representative populations with appropriate consideration of sex, life stage and ethnicity

Nationally representative data on habitual vitamin D intakes and food sources, including the contributions from fortified foods and nutritional supplements, are required for Europe. Bailey *et al.*[25] presented a useful summary of vitamin D intakes and contributors in the US population using data from National Health and Nutritional Examination Survey 2005–6. While representative data on vitamin D intakes in several EU countries exist, for example in the UK from the National Diet and Nutrition Surveys, summarised recently[26], Ireland[27], Finland[28], Germany[29] and others, as well as *trans*-European data in European Prospective Investigation into Cancer and Nutrition (EPIC) study participants[30], in general, data from European national nutrition and food consumption surveys are fragmented and use various methods of food consumption data collection, analysis and reporting, making meaningful comparison problematic.

It is important to note that while we have identified nationally representative intake data as a critical requirement for immediate action to prevent vitamin D deficiency, these data also comprise the evidence basis for step 3 of the risk assessment framework, enabling assessors to compare specified DRI with habitual population intakes.

*Underpinning infrastructure*

*Standardisation of the assessment of habitual vitamin D intakes*. Major advances in dietary assessment methodology and particularly the statistical treatment of dietary intake data, which has been the focus of the EC-funded European Food COnsumption and VALidation (EFCOVAL) project, will hopefully facilitate the development of a validated system for pan-EU food consumption data monitoring and harmonised estimates of vitamin D intake. The EFCOVAL project in its current form concluded in 2010, with the main recommendation that the repeated 24 h dietary recall method using EPIC-Software for standardisation in combination with a food propensity questionnaire and modelling of usual intake is a suitable method for pan-European surveillance of nutritional adequacy and food safety among healthy adults and maybe in children aged 7 years and older[31]. Provision and standardisation of an implementation plan that accounts for maintenance and updates, sampling designs, national surveillance programmes, tailored capacity building and training, and linkage to food composition and occurrence databases in countries outside the EFCOVAL project is the next step in the process to realise this vision.

*Standardisation of food composition data*. More comprehensive coverage of the vitamin D content, including 25(OH)D, of staple foods is required within food composition databases[1,3,13]. Currently, the most comprehensive and widely used food composition databases are probably the UK McCance & Widdowson's Composition of Foods[32] and the US Department of Agriculture National Nutrient Database[33], and with a few exceptions, such as Denmark and Finland, most other countries borrow a large proportion of their vitamin D composition data values from these sources. In addition to optimising the analysis of raw foods or commodities, consistent monitoring of the levels of addition of vitamin D (and correct identification of the isomer) to manufactured foods including supplements is also required to maintain currency of the databases. The most significant advance in the standardisation and harmonisation of food composition data to date has been the EC-funded EUROpean Food Information Resource (EUROFIR) Network of Excellence, which included forty-nine partners from twenty-seven countries, most of them national food composition database compilers, including the US Department of Agriculture. Through the EUROFIR eSearch Prototype, the project succeeded in linking twenty-five European food composition databases compiled using the standardised EUROFIR approach for food description, using LanguaL, and component and value description, using standard vocabularies, thus ensuring harmonised data description and associated nutrient value information[34]. While some additional funding has been made available by the EC through Framework 7 to help sustain the effort through to 2013, the task of maintaining currency of food composition data, both from the analytical and compilation perspectives, and ensuring knowledge transfer through training is resource-intensive and requires ongoing commitment from national and international agencies. Investment in the provision of quality food composition data for vitamin $D_3$, $D_2$ and 25(OH)D is necessary to support assessment of vitamin D intakes in national surveys and research in nutrition and health.

## *Sustainable food-based strategies to bridge the gap between current and recommended intakes of vitamin D to minimise the prevalence of serum 25-hydroxyvitamin D < 30 nmol/l*

Given the gap between typical intakes of vitamin D (approximately 160–300 IU (4–7·5 μg)/d on average, depending on the country) and the recently established North American EAR of 400 IU (10 μg)/d[1], strategies to increase the distribution of intakes in the population are urgently required. Dietary advice and supplementation are unlikely to increase intakes 'across' the distribution as rich food sources of vitamin D are few and infrequently consumed and the proportion of supplement users is relatively low; at about a quarter to a third of the US and a third of the Canadian adult populations[19,20,25]. Many countries including the USA, Canada, the UK, Finland, Denmark, Ireland and Australia have opted for mandatory or voluntary food fortification with vitamin D[35]. Indeed, fortified foods, including milk, yogurt, butter, margarine, cheeses, orange juice, bread and breakfast cereals, constitute the major dietary source of vitamin D in the USA[35]. However, mandatory fortification of a single staple, for example milk, does not increase the vitamin D supply in non-consumers or those who consume low amounts. For example, according to Bailey *et al.*[25], less than 7 % of the US population over the age of 51 years met the previous adequate intake of 200 IU (5 μg)/d for vitamin D through diet alone[25]. Careful consideration must be given to the range of products used for both mandatory and voluntary fortification and level of vitamin D used in each, to optimise the effectiveness of fortification. This can only be achieved by modelling usual food consumption intakes in representative populations, detailed above, and evaluating potential fortification initiatives by carrying out food-based randomised controlled trials (RCT) in the community that measure the impact on circulating concentrations of 25(OH)D in the population to achieve efficacy without compromising safety.

Related to this research need, there is a requirement for further studies on the differences between vitamin $D_2$ and $D_3$. While vitamin $D_3$ is the dominant food-derived source of the vitamin, $D_2$ has been the main isoform added to many manufactured foods and supplements and thus can be present in the food chain of some populations. Physiological responses as well as potential for differences in safety risks for the two forms of the nutrient should be further explored[1,10]. This is particularly relevant to ethnic groups, given the unacceptability of vitamin $D_3$ supplements, or its use in food fortification, to some vegetarians[8]. An associated area is that of vehicle suitability, as a recent meta-analysis showed that oil vehicles produce greater increases in serum 25(OH)D than powder or ethanol-based ones, although studies have been limited[36].

With considerable cooperation and organisation and some resources, trans-European, nationally representative data in life stage, sex and ethnic populations on the distribution of vitamin D status and intakes, supported by standardised analytical methods for serum 25(OH)D, appropriate harmonised sampling and survey methodology and up-to-date quality

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food composition data, could be achievable by pooling existing resources within the EC and nationally funded survey and cohort bio-banks, databases and expertise, and could be progressed within a reasonable time frame. The data would provide an invaluable foundation for addressing the core issue of clarifying relationships between vitamin D and skeletal and non-skeletal health status indicators and, crucially, specifying the levels of circulating 25(OH)D that are desirable to prevent disease and promote health throughout the life cycle. However, there are numerous areas where little or no data exist or where confounding issues and biological variability obscure the answer. In terms of the Risk Assessment Framework, these are the core data that comprise the knowledge infrastructure evaluated in step 1 in order to progress the DRI specifications in step 2[16], and can be summarised as follows.

## *Relationship between vitamin D and health throughout the life cycle*

As mentioned already, while there has been considerable progress in understanding the relationship of serum 25(OH)D to bone health outcomes in the elderly and in postmenopausal women, less is known about its impact on other stages of the life cycle and in racial and ethnic groups[5]. Furthermore, while investigations of the relationship of serum 25(OH)D to non-skeletal health outcomes are expanding, some key knowledge gaps persist. The following is a brief synopsis of the research needs in this important area, many of which were highlighted by the recent DRI committee.

*Clarify threshold effects of calcium and vitamin D on skeletal health outcomes by life-stage and for different racial/ethnic groups*. While there is a solid body of evidence related to bone health and the role of Ca and vitamin D, many data gaps remain for younger age groups and for the effect under menopausal conditions[1]. The issue of 'calcium economy' (i.e. mechanisms to maintain Ca homeostasis) among certain groups and ethnic differences in vitamin D utilisation require attention[1]. Future RCT with vitamin D and bone outcomes need to adequately consider key confounders such as baseline vitamin D status, interactions with Ca, muscle quality, physical activity among other issues of trial conduct and compliance in key targeted populations to determine the efficacy of vitamin D supplementation in reducing falls and fractures[5]. Research protocols that examine the effects of vitamin D and Ca separately rather than as a combined administration, and which better clarify the nature of the inter-relationship, are clearly required. Studies that do not incorporate this requirement into the design are not fit for purpose.

*Explore causal role for vitamin D in non-skeletal health outcomes*. Investigation[1,6–8,10–13] of causal relationships between vitamin D nutrition and potential non-skeletal health outcomes throughout the life cycle for which cross-sectional or cohort data already exist should undergo further research. These may include but are not limited to innate and adaptive immune function, inflammation (especially related to obesity), total and site-specific cancers, glucose metabolism and metabolic risk, hypertension, diabetes, CVD[1], as well as infectious disease outcomes, including respiratory infections[7] and cognitive decline. There is a need for long-term human studies in well-characterised 'at-risk' populations to investigate the effects on these non-skeletal health outcomes of maintaining 25(OH)D levels above chosen cut-offs. The International Agency for Research on Cancer working group on vitamin D and cancer recently concluded that while new cohort studies on serum 25(OH)D levels and breast cancer are warranted and a need for more research to establish what specific health conditions contribute to the reduction in all-cause mortality with vitamin D supplementation, hypothesis on vitamin D status and colorectal cancer, CVD and all-cause mortality should be tested in appropriately designed RCT[12].

Special attention needs to be paid to the measurement and statistical analysis of confounding in these studies, both in the design and analytical phases of experiments, as certain risk factors for ageing-related chronic diseases, such as metabolic syndrome-related adverse health outcomes, cognitive impairment and cancer, are all hugely affected by lifestyle factors such as physical activity and individual variability, for example in the degree of adiposity, which itself interacts with vitamin D metabolism, summarised below. Additional complication arises from the interactions between vitamin D and Ca/phosphate metabolism, outlined under the section 'Clarify threshold effects of calcium and vitamin D on skeletal health outcomes by life-stage and for different racial/ethnic groups'. This is such a key and major research requirement that several RCT will be required as opposed to one large trial, because each of these outcomes has its own potential confounders and possibly a serum 25(OH)D concentration that minimises its risk.

*Specific attention is required for pregnancy, lactation and infancy*. In addition[1,3,11,37–39] to the urgent need for nationally representative data on serum 25(OH)D levels during pregnancy, lactation and infancy (and its determinants) as already mentioned, there are several key knowledge gaps and research needs that require attention for these potentially vulnerable life-cycle groups. These range from fundamental knowledge gaps such as the role that vitamin D plays in successful pregnancy, lactation and fetal or early infant development[1] to clarification of the mechanisms by which physiological changes occur in maternal vitamin D metabolism during pregnancy and lactation[37]. The contradictory evidence on the relationship between maternal vitamin D status and both fetal skeletal development and mineralisation, as well as with adverse non-skeletal health outcomes for the fetus (such as lower birth weight, small-for-gestational age, length of gestation and developmental programming) and mother (such as pre-eclampsia, difficulties at labour and delivery, gestational diabetes and infectious disease) that currently exist[1,3], emphasises the need for well-designed RCT with vitamin D to establish proof of causality[37] as well as to inform maternal dietary vitamin D requirements. Such RCT may help provide the evidence base upon which to base a clear public health strategy and guidance on vitamin D supplementation during pregnancy. Such information and data are necessary to overcome poor understanding and advice

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among health professionals and at-risk groups of the population[7,38,39] and for a better understanding of the common dietary and supplementation practices during pregnancy that have an impact on vitamin D status[38]. There is also a need to understand the impact of vitamin D status at birth and during the first year of life on healthy growth and development, including bone growth, muscle strength, resistance to infection, and psychomotor development. Linked to this research need is an enhanced understanding of the determinants of serum 25(OH)D during the first 3, 6 and 12 months of life. Furthermore, the impact of maternal vitamin D intake/status, including supplementation, on breast milk concentration of vitamin D and 25(OH)D warrants further investigation. Deficits in the standardisation of breast milk sampling methods have created uncertainty in the interpretation of research on this area in the past. In relation to high maternal serum 25(OH)D levels, there is an ongoing need to better understand the relevance of emerging evidence of increased risk (from U-shaped relationships at both low and high serum 25(OH)D levels) at higher levels of serum 25(OH)D (125–150 nmol/l) and adverse consequences in adults (outlined under the section 'Elucidate adverse effects of long-term, high-dose calcium and vitamin D') as well as with intra-uterine growth restriction and childhood eczema (at maternal serum 25(OH)D levels > 70/75 nmol/l), summarised recently[37].

*Underpinning infrastructure*

*Vitamin D physiology, biology and molecular pathways*. Understanding more clearly several aspects of the physiology and biology of vitamin D and its metabolites, as outlined in brief below, would undoubtedly greatly enhance our understanding of the role of vitamin D in health and disease and the dietary requirement for vitamin D in different life stages.

*Gain a better understanding of the limitations in using serum/plasma 25-hydroxyvitamin D to define vitamin D status*. While the responsiveness[5] of serum/plasma 25(OH)D to increased vitamin D intake has been illustrated in a recent systematic review of RCT of vitamin D supplementation[40], it has been suggested that the ability to use the relatively accessible measure of serum 25(OH)D as an indicator of vitamin D exposure and status is limited by a number of factors including not only its role as a prohormone, rather than as a nutrient *per se*, but also its variability which is due to a number of non-nutritional factors[1,5]. These include season, geographic latitude, clothing, institutionalisation, use of sunscreen as well as physiological state of the individual such as BMI, extracellular volume, and vitamin D-binding protein concentration and affinity[5], among others.

*Determine appropriateness of serum 25-hydroxyvitamin D as a biomarker of effect*. A clearer understanding of the limitations of serum 25(OH)D as a marker of exposure and status will provide for a better understanding of its relationship to specific health outcome, enhancing both the quality and quantity of research available[1]. The strength of the relationship of 25(OH)D to functional outcomes varies according to outcome and life or reproductive stage[5]. More research is needed to clarify its usefulness as an indicator of functional outcome at all life stages. It has also been suggested that there is an ongoing need for identification of novel functional markers beyond serum 25(OH)D[5,7,13].

*Clarify 25-hydroxyvitamin D distribution in body pools including storage and mobilisation from adipose tissue*. We know that 99 % of 25(OH)D circulates bound to the D-binding protein[1], but it is unclear how and to what extent 25(OH)D (or other metabolites) are mobilised from lipid and other body pools to enter the circulation[5]. Understanding the distribution, storage and mobilisation of 25(OH)D in body pools would enhance the understanding regarding relationships among exposure to vitamin D from intake or endogenous synthesis, circulating levels of 25(OH)D, and health outcomes[1,11]. The role of storage compartments and factors important to the mobilisation of vitamin D is noticeably lacking[1] and yet may have an important impact on vitamin D dietary requirements. In addition to addressing the question of what is the biological effect of fat/muscle mass storage on 25(OH)D status, it would be important to examine what differences are due to age and ethnicity[8]. On a related but separate point, the potential dangers of accumulating vitamin D in adipose tissue, regulation of its mobilisation from these stores, and the consequences for the saturation of storage compartments are also unclear[5].

*Clarify the variation between individuals in the half-life of 25-hydroxyvitamin D*. Such variation could be attributable to specific individual variation in the rates of utilisation and breakdown of vitamin D or 25(OH)D. It may be possible to calculate from the rate of decline in vitamin D status what the specific dietary requirements for vitamin D might be for individuals[8].

*Elucidate the effect of genetic variation on serum 25-hydroxyvitamin D*. Recent genome-wide analysis studies have identified SNP in key enzymes and transport proteins within the vitamin D metabolic pathway(s) which explain some of the inter-individual variability in serum/plasma 25(OH)D concentrations[41,42]. Further such genetic research is warranted in studies that account for other determinants of vitamin D status so as to understand the magnitude of the variability in serum/plasma 25(OH)D concentration explained by SNP. This is related to emerging research on the effect of genetic variation, including that among racial/ethnic groups on developmental outcomes, which will probably prove relevant to DRI development[1], as well as epigenetic regulation of vitamin D on developmental outcomes and interactions with other nutrients such as folate, another emerging field of study. Studies in this area may contribute notably to an understanding of population differences related to chronic disease risk[1,7].

*Evaluate the nature and significance of extra-renal production of calcitriol for health outcomes*. While 25(OH)D[1] is the storage form of the vitamin, calcitriol ($1,25(OH)_2D$) is the biologically active form and drives the biological processes. Once thought to synthesised by the kidney, it is now known that there is non-renal synthesis. There is a need to examine the influence of Ca and phosphate on the regulation of vitamin D activation and catabolism through parathyroid hormone and fibroblast-like growth factor 23[1]. Determining

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the significance of extra-renal production of $1,25(OH)_2D$ for health outcomes is essential to understand whether local production of $1,25(OH)_2D$ has an impact on health outcomes, and, in turn, the relevance of vitamin D nutriture and serum 25(OH)D for such an effect should be established[1,5].

## Dose–response relationships, impact of sun exposure, and adverse effects, toxicity, and safety

As more research, such as that outlined above, will clarify which health outcomes are influenced by vitamin D status (arising from vitamin D intake and that synthesised by UVB exposure), the question of how much vitamin D intake (accounting for UVB sun exposure) is needed to achieve desirable health outcomes, and how much is too much becomes key considerations. These were the three central questions addressed by the DRI report[43], and will remain at the core of any planned or on-going re-evaluation of dietary vitamin D requirements. The following are some of the key knowledge gaps/research needs that need to be addressed in this area.

*Conduct studies to identify specific health outcomes in relation to graded and fully measured intakes of vitamin D or where a defined serum 25-hydroxyvitamin D has been shown to optimise a health outcome, conduct studies to estimate the dietary requirement for vitamin D which maintains nearly all (97–98 %) of the population subgroup above that serum threshold (during winter)*. Too few studies[1] are specifically designed to study the effects of graded doses of vitamin D (and/or Ca) on health outcomes, both overall and as part of the same study using the same subjects and outcome measures[1]. Further, many studies in the vitamin D (and Ca) area are confounded by the failure to specify or measure and thereby take into account 'background' intakes of the nutrient being studied when dose–response is being explored[1]. While some recent RCT studies have estimated the dietary requirement for vitamin D which maintains 97·5 % of the population subgroup above that serum threshold during winter[44–46], these have largely been limited to adolescents, young adults and the elderly, and such studies have not been performed for 'at-risk' groups such as non-Caucasian, children, pregnant and lactating women, and the obese. Furthermore, the meta-regression model used by the DRI committee to establish the RDA for vitamin D, which used intake and status data from relevant vitamin D RCT, was very focused on a serum 25(OH)D target of 50 nmol/l[1]. This would need to be assessed from a European perspective, especially if a European or member-state agency decides to use a serum 25(OH)D target other than 50 nmol/l which has implications for which vitamin D intake-status model is most appropriate for estimation of DRI values[47].

*Clarify the influence of age, body weight and body composition on serum 25-hydroxyvitamin D levels in response to intake/exposure*. Information about how factors such as age, body weight and body composition affect the variability in serum 25(OH)D response to intake or exposure would assist in the process of establishing requirements for vitamin D[1]. Such information is also important to ascertaining the measure's utility as a biomarker of effect and in making judgements about excess intake of the vitamin.

*Investigate whether a minimal-risk UV blue sunlight exposure relative to skin cancer exists that also enables vitamin D production*. Whether a minimal or threshold[1,5,11] UVB exposure level is possible to both enable subcutaneous vitamin D synthesis and avoid risk of skin cancer needs to be examined urgently. Research should include assessment of the risk for skin cancer compared with the benefit of endogenous synthesis of vitamin D[1,5], particularly for at-risk populations[8].

*Clarify how physiological factors (such as skin pigmentation, genetics, age, body weight and body composition) and environmental factors (such as sunscreen use) influence vitamin D synthesis*. Understanding how subcutaneous synthesis of vitamin D is affected by physiological and environmental factors and the impact of these factors on maintenance of serum 25(OH)D levels within normal physiological ranges is important to integrating information about dietary intake and interpretation of serum 25(OH)D levels[1].

*Clarify whether the initial metabolic partitioning of endogenously produced and dietary supplied vitamin D influences vitamin D economy*. Endogenously produced vitamin D enters the peripheral circulation and then binds to D-binding protein, which transports it to the liver for further metabolism. In contrast, dietary vitamin D enters the peripheral circulation through the lymph bound to chylomicrons and is transported to the liver in remnant particles after peripheral metabolism[5].

*Elucidate adverse effects of long-term, high-dose calcium and vitamin D*. The DRI committee importantly suggested[1] that the question of nutrient safety should not be a secondary aspect of study design nor can the failure to detect adverse effects as part of a study not designed for that purpose be considered an adequate assessment of safety. Dedicated studies are needed to assess adverse health effects related to long-term, high-dose (although not necessarily 'toxic') levels of Ca and vitamin D[1]. The International Agency for Research on Cancer pointed to the fact that there are no data available on the health hazards of maintenance of high serum 25(OH)D levels in healthy subjects over long periods, and caution to be mindful of past experiences with other compounds (e.g. several antioxidants and hormone replacement therapies) that have shown serious adverse effects of the chronic use of supplements or long-term maintenance of higher serum levels[12]. U- and reverse J-shaped distributions have been described for serum 25(OH)D and adverse consequences, including all-cause mortality[48,49], parathyroid hormone suppression[50] and intra-uterine growth restriction, summarised recently[37].

The DRI committee also suggested the need to develop innovative methodologies (possibly *in vitro* and *in vivo* using relevant animal models) to provide for identification and assessment of adverse effects of excess Ca and vitamin D, which might be implemented to further explore the nature of vitamin D toxicity, particular issues such as timing, doses and mechanisms of action[1].

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### *Synthesising evidence and research methodology*

As mentioned already, devising nutrient recommendations for population intakes relies on scientific analysis and judgement of data that exist within a specified time frame and is an iterative process. The following two research areas have been identified as important to this activity.

*Explore enhanced methodologies for data synthesis*. Alternative methods[1] for synthesising evidence from different study types and multiple parameters that consider uncertainties (including measurement error) include teleoanalysis, confidence profile predictive meta-analysis and generalised multi-parameter evidence synthesis[1]. In the case of Ca and vitamin D, such approaches should facilitate quantitative estimates of effect size and dose–response relationships to inform DRI development[1]. In relation to the use of systematic reviews in the DRI process, the suggestion by Chung *et al.* [4,51] that a repository of data extracted from primary studies might be considered as a joint effort of both the USA and EU considering both regions are engaged in this activity.

*Identify approaches to weight better potential health outcomes*. In order to ensure the most objective and comprehensive systematic evidence reviews in future, approaches to better weight potential health outcomes are needed[1].

## Conclusions

Vitamin D deficiency is a public health issue which affects all age, sex, economic, educational and ethnic groups, with huge potential human and economic cost implications for many societies within Europe and elsewhere. Thus, there is a pressing need to address this deficiency. While there are important ongoing discussions with respect to thresholds of serum 25(OH)D that represent vitamin D insufficiency/adequacy, taking a serum 25(OH)D concentration of $<30$ nmol/l as the cut-off below which the risk of clinical vitamin D deficiency (manifesting as vitamin D-dependent rickets in children and osteomalacia in adults) increases, the first priority from a public health perspective in Europe must be to ensure that this risk is minimised. We highlight three critical and prioritised research requirements (data on the distribution of serum 25(OH)D and vitamin D intakes (and their sources) in nationally representative populations with appropriate consideration of sex, life stage and ethnicity, and sustainable food-based strategies to bridge the gap between current and newly recommended intakes of vitamin D to minimise the prevalence of serum 25(OH)D concentrations of $<30$ nmol/l), which would enable the quantification of vitamin D deficiency in the EU population and would prevent that deficiency, and, by increasing vitamin D status across the distribution of vitamin D requirements, potentially prevent disease. These will require infrastructural resources, national investment and international collaboration so as to be realised.

In addition to these priority research requirements, we highlight many other areas of vitamin D research which need to be addressed so as to provide the vitamin D knowledge infrastructure used in the Risk Assessment Framework in order to specify DRI. These include an urgent need for well-designed RCT to test the effects of vitamin D on skeletal and non-skeletal health outcomes in different stages of the life cycle, as well as to identify threshold effects and possible adverse effects where present, all underpinned by a better understanding of the biology and physiology of vitamin D.

Finally, the serum 25(OH)D concentrations that will prevent adverse effects of both excessively low or high levels and will promote health 'throughout the life cycle' are likely to reside within a distribution between 30 and 80 nmol/l. In our opinion, one of the greatest immediate needs that remain is for an accountable, transparent and systematic evidence-based consensus development process, engaging all the relevant stakeholders, and culminating in the specification of threshold values for serum 25(OH)D levels that define vitamin D sufficiency. There is an opportunity, now at the outset of the next phase of evidence building, for authoritative agencies and funding bodies to work strategically and co-operatively towards implementing current guidelines effectively and safely and ensuring that persistent gaps and uncertainties are resolved. From the clinical perspective, practitioners require clear consensus-based guidance to evaluate, treat and prevent vitamin D deficiency in patients. Such clinical guidelines should ideally be informed by the population DRI, but have a separate function and ought to be developed from additional synthesis of research data in specific patient groups.

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