

# The ODIN project: Development of food-based approaches for prevention of vitamin D deficiency throughout life

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## Abstract

Vitamin D deficiency has significant implications for human health throughout life and impacts on healthy growth and development and successful ageing. Persistent knowledge gaps are barriers to developing and implementing a safe and effective public health strategy to prevent vitamin D deficiency and maintain nutritional adequacy throughout the year. The European Commission-funded *ODIN* project (Food-based solutions for optimal vitamin D nutrition and health through the life cycle) will provide the evidence base to prevent vitamin D deficiency and improve nutrition and public health through food. *ODIN* will deliver the first internationally comparable dataset of vitamin D status and report the prevalence of vitamin D deficiency across Europe for the first time. In a series of dose-response randomised controlled trials, *ODIN* will estimate dietary requirements for vitamin D in pregnant women, children, adolescents and adults of South Asian and East African origin resident in Northern European countries. Using clinically validated, disease-specific cohorts with standardised 25(OH)D data, *ODIN* will investigate associations between vitamin D status and perinatal outcomes, atopic disease and bone growth in children, and cardiovascular and mortality risk in older adults. We will publish estimates of the distribution of vitamin D intake and serum 25(OH)D concentration resulting from changes in vitamin D in the food supply, accounting for latitude, sun exposure and diet. Utilising advanced food production systems and targeted animal and human feeding studies, *ODIN* will propose safe, novel and effective food-based strategies to eradicate vitamin D deficiency that are inclusive, sustainable and affordable.

**Keywords:** food bio-fortification, food fortification, vitamin D deficiency, vitamin D intake, vitamin D requirements, vitamin D status

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## Introduction

The European Commission funded integrated project *ODIN* (Food-based solutions for optimal vitamin D nutrition and health through the life cycle: [www.odin-vitd.eu](http://www.odin-vitd.eu)) is a multidisciplinary consortium of 31 partners from 19 countries, which commenced a 4-year programme of research in November 2013. We have

contributed this article to provide an overview of the project objectives and outline the implementation plan and roadmap of anticipated outcomes to be delivered in the first 2 years of the project in particular.

While there are many controversial issues in relation to vitamin D requirements and the impact of vitamin D intake and status on human health, there is general agreement that avoidance of vitamin D deficiency is a public health priority for prevention of nutritional rickets in infancy, to support bone growth in children and to help maintain skeletal integrity in older adults. The major source of vitamin D in humans is sunshine. Ultraviolet blue (UVB) radiation stimulates cutaneous synthesis of cholecalciferol, which is stored in adipose tissue or undergoes hydroxylation in the liver to 25-hydroxyvitamin D [25(OH)D], the biomarker of vitamin D status and further hydroxylation in the kidney to 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D], the biologically active metabolite (IOM 2011).

Several environmental factors, such as latitude and prevailing weather conditions, determine whether sunshine of sufficient strength is available to stimulate the conversion of 7-dehydrocholesterol in the skin to pre-cholecalciferol. Personal attributes, such as skin pigmentation, age, attire, sunscreen, working environment, physical activity and sun exposure behaviour can also prevent or impede vitamin D synthesis. Vitamin D occurs in the diet, both naturally and as a fortificant as cholecalciferol (D<sub>3</sub>) and ergocalciferol (D<sub>2</sub>) and in nutritional supplements. Vitamin D intakes are typically low as it occurs naturally in appreciable amounts in few foods, which are consumed sporadically, such as oil-rich fish, or in low concentrations in commonly consumed foods, such as meat and dairy products.

The well known late-winter nadir in circulating 25(OH)D concentrations means that substantial portions of the population resident at latitudes greater than around 40° rely on body stores and vitamin D in the diet to maintain healthy vitamin D status all year round. As body stores are dependent on sun exposure, the importance of the diet in maintaining vitamin D status above the level of deficiency is a corollary of sunshine deficit (Holick 2008). There is increasing evidence that dietary supply is currently unable to offset the seasonal sunshine deficit, which increases with latitude and the duration of winter (Kiely & Black 2012). While nutritional supplements contribute a high proportion to total vitamin D intake among users, supplement uptake is voluntary, and tends to be highest among infants and elderly adults and lowest among children, adolescents and young adults, who are also at risk of deficiency (Bailey *et al.* 2010). Risk is

increased in persons who have low habitual sunshine exposure, due to personal preference or custom, or diminished ability to synthesise cholecalciferol due to dark or aging skin. Risk of deficiency is further increased in persons whose food intake is low or who consume diets that are low in naturally occurring vitamin D (*e.g.* vegan or macrobiotic diets) and avoid fortified foods and supplements. Those who have poorly defined vitamin D requirements, due to insufficient data, include young children, whose dietary intake is relatively small, and pregnant and lactating women, who may have increased vitamin D requirements. In short, the groups at risk of low vitamin D status represent a sizeable proportion of the school-aged and working population, as well as the more widely acknowledged older adult demographic.

Despite the explosion in scientific research in vitamin D, there are many fundamental gaps in the field from the public health perspective (see Cashman & Kiely 2011 for a detailed overview). Briefly, these include the magnitude of the deficiency problem among European residents, based on comparable analytical methods and the effect of UVB availability across the continent on vitamin D status. Experimental data to support dietary recommendations for vitamin D during pregnancy, lactation and throughout childhood and adolescence are not known beyond infancy (IOM 2011; Gallo *et al.* 2013). Although substantial progress has been made, the ongoing question of whether associations between vitamin D status and non-skeletal health outcomes are independent of co-related factors such as pre-existing risk, obesity and compromised nutritional status, is unresolved (Newberry *et al.* 2014), as is the effect of vitamin D on perinatal outcomes (Thorne-Lyman & Fawzi 2012; Aghajafari *et al.* 2013) and early development (Christesen *et al.* 2012). There is still very little data to confirm whether long-term consumption of high dose vitamin D supplements is safe, as most studies aiming to maintain circulating 25(OH)D at high levels have been of relatively short duration (IARC 2008). While these uncertainties make it impossible at this point to achieve consensus on desirable cut-offs for circulating 25(OH)D levels that are 'optimal', there is universal agreement that the persistence of very low vitamin D status, at serum 25(OH)D below 25–30 nmol/l, is unacceptable (Cashman & Kiely 2014).

### Objectives of the ODIN project

Given the urgency and complexity of the vitamin D problem in Europe, we have adopted a triage approach

to selecting the most critical issues for attention in the *ODIN* project. The main priority at this time is to quantify the prevalence of vitamin D deficiency and to identify food-based strategies to increase vitamin D intakes across the population, in sufficient quantities to prevent deficiency without incurring risk of excessive intakes. Our perspective is that vitamin D, like all nutrients, is required in small quantities on a continuous basis. High dose, short-term pharmaceutical approaches to treating nutritional deficits have a poor record historically from a population health perspective (IARC 2008); we consider this an inappropriate strategy for vitamin D, which is a fat soluble vitamin with incompletely understood storage and mobilisation mechanisms. Implementation of strategies for deficiency prevention that are developed with the guiding principle of minimising the dual hazards of nutrient inadequacy and excess is warranted. Our overall scientific objective is to develop effective, safe and sustainable solutions to prevent vitamin D deficiency and improve vitamin D related health outcomes using a food-first approach.

## Prioritised questions in ODIN

### Exposure

- What is the measured prevalence of vitamin D deficiency in Europe and how do countries compare with each other and the rest of the world?
- What is the distribution of vitamin D intake in Europe?
- How will increasing vitamin D in the food supply affect this distribution and reduce the prevalence of inadequate intakes?
- What is the potential contribution from UVB to circulating 25(OH)D across the European latitude gradient (~35–70°N)?
- What is the dose-response of 25(OH)D to UVB at habitual or everyday skin exposure levels?

### Food-based strategies to meet dietary requirements for deficiency prevention

- What changes in the food supply will increase population intakes of vitamin D sufficiently to modify the distribution of 25(OH)D and prevent deficiency?
- How can we harness technological advances in food production and animal nutrition to increase vitamin D in the food supply with consideration for dietary diversity and local preferences?

## Nutritional requirements for vitamin D

- What are the dietary requirements during pregnancy, childhood and adolescence to prevent vitamin D deficiency?
- What is the impact of ethnicity on dietary requirements for vitamin D in adults?

### Health and safety

- Are associations between 25(OH)D and non-skeletal health in adults independent of pre-existing risk, body composition, co-morbidities and compromised nutritional status?
- Are these effects modulated by variation in the genes responsible for vitamin D metabolism or transport?
- Are associations between vitamin D and perinatal outcomes robust when examined in well powered, prospective, clinically validated, disease specific pregnancy and birth cohorts?
- Does vitamin D status modulate physical growth and development in early life?
- Are high vitamin D intakes and serum 25(OH)D concentrations safe in the long-term?

## How prevalent is vitamin D deficiency in Europe?

In *ODIN*, the prevalence of vitamin D deficiency will be reported as the percentage of the population with serum 25(OH)D <30 nmol/l and sufficiency will be represented by 25(OH)D concentrations ≥50 nmol/l. In the absence of global consensus on optimal concentrations for 25(OH)D, *ODIN* will calculate and report data across the distribution of 25(OH)D in all assessments and experiments.

Spiro and Buttriss (2014) provided an overview of the current data available and outlined the limitations of these data. For comprehensive systematic reviews of current published estimates see Hilger *et al.* (2014), who documented data from 46 countries across 200 studies of children and adults. These data are represented in the ‘Vitamin D Deficiency Map’, a joint initiative between the International Osteoporosis Foundation and DSM Nutritional Products ([www.iofbonehealth.org/facts-and-statistics/vitamin-d-studies-map](http://www.iofbonehealth.org/facts-and-statistics/vitamin-d-studies-map)). Based predominantly on convenience samples, these interactive maps highlight the lack of representative data in several European member states, not only for adults but also for other life stages, particularly pregnancy, infancy, childhood and adolescence as well as dark-skinned immigrant populations, all of whom may be at increased risk

of deficiency. While these maps represent a step in the right direction in attempting to quantify the magnitude of vitamin D deficiency in Europe, they are seriously limited by the variability in analytical measures of 25(OH)D arising from methodological differences in commercially available assays, which precludes international comparisons and makes it impossible to produce an estimate of overall and between country prevalence of vitamin D deficiency, according to life stage. International efforts to develop evidence-based guidelines for the evaluation of vitamin D status, including what constitutes 'deficiency' or 'inadequacy/insufficiency' are effectively disabled because of this knowledge deficit. For the same reason, due to modifications in assay specifications over time, it is problematic to rely on data collected on successive surveys to monitor secular trends within member states, which makes evaluation of public health policy challenging. Prevalence estimates of vitamin D deficiency in Europe using standardised serum 25(OH)D data would allow quantification of the magnitude of the public health problem and a solid platform upon which to build public health policy aimed at preventing vitamin D deficiency. This information is a key starting point towards defining food-based strategies for prevention of vitamin D deficiency and health promotion throughout the life cycle. Calls have been made to use centralised laboratories to make international comparison more reliable (van Schoor & Lips 2011) but this approach might not be feasible, given existing national structures and systems.

The Vitamin D Standardization Program (VDSP), which is a collaborative initiative led by the National Institutes of Health Office of Dietary Supplements (NIH-ODS), the Centers for Disease Control and Prevention (CDC), the National Institutes of Standards and Technology (NIST) and includes several international collaborators, including the Vitamin D Quality Assurance Scheme (DEQAS) and the Health Canada, Korean, Australian, Mexican, German, UK and Irish national nutrition and health surveys. The VDSP has developed protocols for standardising 25(OH)D data [including 25(OH)D<sub>3</sub>, 25(OH)D<sub>2</sub> and the C-3 epimer of 25(OH)D<sub>3</sub>] from current and previous nationally representative nutrition and health surveys with well curated bio-banks where 25(OH)D has been measured (Sempos *et al.* 2012). On the basis of existing 25(OH)D datasets, these protocols conduct a uniform sampling procedure to select a subset of 100–150 bio-banked serum samples for reanalysis of 25(OH)D by a standardised and certified liquid chromatography-tandem mass spectrometry (LC-tandem MS) method, which is traceable to the NIST higher order reference measurement procedure

(Tai *et al.* 2010). The results are used to develop master regression equations, which then recalibrate the existing 25(OH)D dataset for the entire survey sample (Tian *et al.* 2014). Using the *Irish National Adult Nutrition Survey (NANS)* as a case study, we tested the VDSP statistical protocols and demonstrated the potential impact of applying these protocols to existing 25(OH)D data from nationally representative European nutrition and health surveys and cohort studies (Cashman *et al.* 2013). Using an immunoassay, the prevalence of serum 25(OH)D in NANS <30 nmol/l was 6.5%. Application of the VDSP protocol projected a prevalence of 11.4%. We reanalysed all of the NANS bio-bank using our LC-tandem MS method, which is traceable to the NIST reference measurement procedure, and confirmed the true prevalence estimate as 11.2%, which was almost twice as high as the immunoassay-based estimate and almost identical to the VDSP projection.

This experiment proved that application of the VDSP protocols to existing 25(OH)D data from appropriate nationally representative surveys (and cohorts where such surveys do not exist) would enable accurate quantification of the distribution of 25(OH)D concentrations and estimates of vitamin D deficiency in adult, childhood and ethnic populations in Europe. The experiment also illustrated the potential power of the VDSP protocols to standardise prospective cohort studies for investigating vitamin D and health outcomes. With the NIH-ODS as a non-funded collaborator, ODIN will produce internationally comparable 25(OH)D data to report the prevalence of vitamin D deficiency in European adult and child populations, including ethnic subgroups, where possible. Table 1 provides a list of the studies included in ODIN to establish the prevalence of vitamin D deficiency in EU populations for the first time. This objective will be delivered and in the public domain within the first 24 months of the project.

### What is the distribution of vitamin D intake in Europe?

Regardless of whether the sun deficit is due to latitude, weather or personal behaviour, insufficient UVB for dermal vitamin D synthesis places increased importance on vitamin D in the food supply. However, foods containing naturally occurring vitamin D are limited (oil-rich fish, meat, dairy, egg yolk and mushrooms) and many are not consumed on a regular basis. Depending on legislation, some foods are fortified with vitamin D, including infant formula, milk, yogurt, spread, cheese, juice, bread and breakfast cereal. In addition, vitamin D is available as a dietary sup-

**Table 1** Population samples for inclusion in ODIN for estimation of the prevalence of vitamin D deficiency in Europe using standardised data for 25-hydroxyvitamin D

| Name (Acronym)  | Country       | Age range    | Sample size |
|---|---------------|--------------|-------------|
| <i>Infants, children and adolescents</i>  |               |              |             |
| Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland (KIGGS) [2003–6]  | Germany       | 0–17 years   | 10 000      |
| National Diet and Nutrition Survey (NDNS): Rolling Programme Year 1 to 4  | UK            | 1.5–18 years | 500         |
| The Cork Baseline Birth Cohort Study (Baseline)   | Ireland       | 2 years      | 740         |
| OPUS (Optimal Well-being, Development and Health for Danish Children Through a Healthy New Nordic Diet) School Meal Study | Denmark       | 8–11 years   | 780         |
| Infant's Nourishment and Nutritional Status (INNS)  | Greece        | 3–6 years    | 220         |
| Healthy Growth Study (HGS)  | Greece        | 9–13 years   | 800         |
| Fit futures – a part of the Tromsø Study  | Norway        | 15–18 years  | 900         |
| Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA)  | Multi centre* | 12–17 years  | 1000        |
| <i>Adults</i>   |               |              |             |
| Studie zur Gesundheit Erwachsener in Deutschland (DEGS)   | Germany       | 18–79 years  | 7000        |
| National Diet and Nutrition Survey (NDNS): Rolling Programme Year 1 to 4  | UK            | 19–90 years  | 1000        |
| National Adult Nutrition Survey (NANS)  | Ireland       | 18–90 years  | 1200        |
| The Tromsø study – 6 <sup>th</sup> Survey   | Norway        | 30–87 years  | 12 800      |
| Longitudinal Study on Ageing in Amsterdam (LASA): 3 <sup>rd</sup> Cycle.  | Netherlands   | 61–99 years  | 900         |
| Age Gene/Environment Susceptibility (AGES) Reykjavik study  | Iceland       | 66–96 years  | 5500        |
| The Ludwigshafen Risk and Cardiovascular Health study (LURIC)   | Austria       | Adults       | 3299        |
| <i>Ethnic adults</i>  |               |              |             |
| Finnish 'Maamu' (Migrant Health and Wellbeing Study)  | Finland       | 18–64 years  | 1300        |
| LASA 3 <sup>rd</sup> Cycle (Ethnic subgroup)  | Netherlands   | 55–65 years  | 800         |

\*Centres are Athens, Dortmund, Ghent, Heraklion, Lille, Pecs, Rome, Stockholm, Vienna, Zaragoza.

plement, either as vitamin D<sub>2</sub> or vitamin D<sub>3</sub>. Typical average intakes in the EU are generally around 3–7.5 µg (120–300 IU)/day, depending on the country (Vinas *et al.* 2011). There is a significant gap between typical intakes in Europe and the Estimated Average Requirement (EAR) for vitamin D of 10 µg/day (IOM 2011), which ODIN is using as its reference point for dietary adequacy. Vinas *et al.* (2011) showed that of European national nutrition surveys reporting vitamin D intake data from 2000 onwards, 77–100% and 55–100% of adults (19–64 years) and elderly (>64 years), respectively, had intakes below the EAR.

We provided a summary of vitamin D intakes and sources in adults and children, focusing on data from North America and Europe, to evaluate the evidence that intakes of vitamin D are inadequate and to explore the impact of various strategies to increase intakes (Kiely & Black 2012). Similarly, with most micronutrients, reported intakes of vitamin D in national surveys and large cohort studies vary according to country specific fortification practices, sex and age. Data from European dietary and food consumption surveys use various methods of data collection, analysis and reporting, making meaningful comparison prob-

lematic. A notable exception is the *European Prospective Investigation in Cancer (EPIC)* project, which uses a standardised dietary assessment method and food composition database. Notwithstanding the impact of methodological differences, it appears that the main source of variation in vitamin D intake estimates is the contribution from nutritional supplements. Surveys that do not include supplemental vitamin D omit the largest source of vitamin D in supplement users, which accounts for a variable proportion of the population, notably older adults and young children. This was illustrated by Whiting *et al.* (2011), who reported that supplement users aged 6–79 years, who represented 31% of the population surveyed during the 2007–2009 *Canadian Health Measures Survey-Cycle 1*, had not only higher 25(OH)D concentrations than non-users but also a much lower prevalence of serum 25(OH)D <50 nmol/l (19 vs. 37%). Intake estimates that ignore the contribution from supplements are not capable of assessing the risk to public health of low vitamin D intakes and are not fit for purpose.

Discrepancies between survey estimates of vitamin D intake are also common as reliable data on the practice and impact of discretionary fortification on the part of

**Table 2** Food consumption and nutrition surveys for estimating the distribution of vitamin D intakes and dietary modelling for food fortification in ODIN

| Name of survey (acronym)   | Country     | Age range    | Sample size |
|--|-------------|--------------|-------------|
| The Diet and Nutrition Survey of Infants and Young Children (DNSIYC)   | UK          | 4–18 months  | 600         |
| National Diet and Nutrition Survey (NDNS): Rolling Programme Years 1–4 | UK          | 1.5–18 years | 1500        |
|  | UK          | 19+ years    | 1500        |
|  | Ireland     | 1–18 years   | 1400        |
| Irish Food Consumption Surveys of Children (2004–2012)                 | Ireland     | 1–18 years   | 1400        |
| National Adult Nutrition Survey (NANS) (2010)                          | Ireland     | 18–90 years  | 1500        |
| Cork Baseline Birth Cohort Study (2012)                                | Ireland     | 2 years      | 450         |
| Dutch National Food Consumption Survey (2007–2010)                     | Netherlands | 7–69 years   | 3819        |
| Dietary Habits in Denmark (2003–2008)                                  | Denmark     | 4–18 years   | 1077        |
|  |             | 19–75 years  | 3354        |
| EFSA Comprehensive European Food Consumption Database*                 | EU          | 0–75+ years  |             |

\*ODIN will use the EFSA database for a risk analysis only.

food manufacturers is lacking. This issue is highly relevant to Europe, particularly given the varying national policies with regard to mandatory and voluntary nutrient fortification across member states. A challenge encountered with voluntary fortification is that the food composition databases are hard pressed to keep step with innovations and product reformulations. Access to current and accurate food composition data is a requirement for the estimation of vitamin D intakes. More comprehensive coverage of the vitamin D content, including D<sub>3</sub>, D<sub>2</sub> and 25(OH)D, of staple foods is needed. Investment in the provision of quality food composition data for vitamin D is necessary to support assessment of vitamin D intakes in national surveys and research in nutrition and health.

In ODIN, these and other methodological issues are being addressed in the implementation of the dietary exposure and modelling work package, which will develop a standardised approach to dietary survey analysis, from a vitamin D perspective, in methodologically comparable national survey systems (listed in Table 2). *European Food Information Resource (EuroFIR)* is constructing an ODIN food composition dataset for vitamin D using analytical data that have been quality assessed using EuroFIR standards, including fortified foods and nutritional supplements. Approaches to analysing intake data, including the contributions from recipes and composite foods, are being standardised and estimates calculated using a single data analysis platform (Crème Global) will deliver harmonised intake data from the base diet, fortified products and nutritional supplements in four countries and propose a range of approaches for dietary modelling.

### Why not use supplements to combat vitamin D deficiency?

There have been calls for use of vitamin D supplements as a means of correcting low vitamin D status in European populations. While supplementation has been shown to significantly improve vitamin D intake across a variety of age, race, ethnic and gender groups, with dose-dependent increases in serum 25(OH)D (Cashman & Kiely 2011; Cashman *et al.* 2011; Whiting *et al.* 2015), relying on supplements is not an appropriate public health strategy to increase intakes across the population distribution because supplements are effective only in those who consume them and with uptake usually lower than ~40% (Fulgoni *et al.* 2011; Whiting *et al.* 2011; Black *et al.* 2015). It is important to remember that vitamin D is a nutrient, and many authors now acknowledge that it is best taken in moderate amounts on a regular basis. Intermittent, high dose regimens correct deficiency only in the short term and may have unintended adverse effects (Sanders *et al.* 2010). While we acknowledge the usefulness of supplements under medical supervision for immediate correction of clinical deficiency [(25(OH)D < 30 nmol/l)], public health strategy must be designed to meet the needs of the unsupervised majority, on an on-going basis.

### Evidence for food fortification

Many countries including the US, Canada, Australia, the UK, Finland, Denmark and Ireland have opted for mandatory or voluntary food fortification with vitamin D. Indeed, fortified foods, including milk, yogurt, butter, margarine, cheese, orange juice, bread and breakfast cereal, constitute the major dietary sources of vitamin D

in the US (Bailey *et al.* 2010; Fulgoni *et al.* 2011). The problem of fortifying a single staple, for example milk, or focusing on a commodity sector such as dairy, is that it does not increase the vitamin D supply in non-consumers. For example, Babu and Calvo (2010) suggested that fortification of wheat flour may have potential to alleviate vitamin D deficiency in countries such as India and Jordan, where pasteurised milk is not widely consumed. Van Horn *et al.* (2011) showed that African-American girls relied more heavily on meat and beans as a source of vitamin D than White girls, emphasising the need to account for diversity in food consumption patterns when developing fortification strategies.

Our systematic review of the efficacy of vitamin D food fortification (Black *et al.* 2012), which updated that of O'Donnell *et al.* (2008), showed that of sixteen separate randomised controlled trials (RCTs) from around the world, all but two showed a significant effect of supplementation on circulating 25(OH)D. Both reviews identified the over-reliance on milk as a drawback and emphasised that consideration must be given to the range of products used for fortification and the amount of vitamin D used in each, to optimise effectiveness and minimise risk of excessive intakes. Thus, there is a need for well-designed, sustainable natural enhancement, fortification, and bio-fortification strategies, which use a range of foods to accommodate diversity. This can be achieved only by modelling usual food consumption intakes in representative populations, evaluating potential fortification initiatives by carrying out high quality food-based randomised controlled studies in the community, such as that recently reported by Madsen *et al.* (2013) in Denmark, and combining data from these sources to determine the impact of fortification with vitamin D on serum 25(OH)D in the population to achieve efficacy in terms of deficiency prevention, without compromising safety.

### The ODIN approach to food fortification

Following the establishment of (1) standardised datasets for vitamin D status in EU populations, which will define the size of the deficiency problem and the magnitude of the changes required in population distributions of 25(OH)D, as well as (2) standardised approaches to vitamin D intake assessment and dietary modelling, ODIN will conduct an integrated analysis of food fortification for application in Europe and will establish a framework to extend this approach in other settings. The range of food products in which the vitamin D content should be enhanced is the initial consideration, as well as the pattern of consumption.

One of the challenges is that vitamin D in the typical western diet does not follow a typical consumption pattern, due to its occurrence in high concentrations in foods that are taken episodically and in low concentrations in commodities used on a daily basis. In countries that practice voluntary or mandatory fortification, it can be more widespread in the diet, depending on prevailing dietary patterns. The variable rate of supplement consumption and wide dose range adds further complication, given the high rate of non-consumers. These variables present significant analytical challenges in describing and modelling the intake distribution for vitamin D.

There are further complexities, in terms of the 'unknown' components and the 'hidden' additional contribution of meat and eggs has been discussed recently (Heaney *et al.* 2013; Taylor *et al.* 2014). As there are currently no standard reference materials for measuring 25(OH)D in food matrices, data for 25(OH)D, available in some food composition databases, including the UK, are not considered to be completely reliable. For example, the U.S. Department of Agriculture (USDA) food composition database does not include the quantity of 25(OH)D in muscle foods, such as fish and meat, or eggs, therefore *National Health and Nutrition Examination Survey (NHANES)* estimates of vitamin D intake, although considerably higher than UK and Irish estimates largely based on the UK composition data, do not include the contribution from 25(OH)D. Interrogation of this contribution to vitamin D nutrition is an intriguing aspect of the ODIN project. We recently showed that each microgram of orally consumed synthetic 25(OH)D<sub>3</sub> is five times more effective in raising serum 25(OH)D in winter than an equivalent amount of vitamin D<sub>3</sub> (Cashman *et al.* 2012). The implications of these data are that the total vitamin D activity [vitamin D<sub>3</sub> plus 5\*25(OH)D<sub>3</sub>] of meat and eggs is potentially much more important than is currently acknowledged and that there is considerable scope to exploit these foods as bio-fortified sources of vitamin D, as they are commonly consumed, and by individuals who avoid usual fortification vehicles, such as dairy. Some animal feeding studies, including Jakobsen *et al.* (2007), have shown that increases in vitamin D<sub>3</sub> and 25-hydroxyvitamin D in animal feed can increase the vitamin D and 25-hydroxyvitamin D content of meat and eggs.

Briefly, ODIN will build on previous studies that have interrogated the potential of bio-fortification and will conduct novel investigations using both UVB and animal feed as a source of vitamin D in animals, fish and fowl, as well as UVB irradiation of mushrooms and

baker's yeast, for which evidence of efficacy and safety are required for regulatory approval in the European Union. We are extending these food production experiments into humans by testing the efficacy of the bio-fortified foods in increasing serum 25(OH)D [and distinguishing effects on 25(OH)D<sub>3</sub> and 25(OH)D<sub>2</sub>] in a number of human intervention studies. By using a single analytical platform for serum 25(OH)D, at University College Cork, and for vitamin D analysis in food, at the Danish Technological University, ODIN will produce uniquely comparable data and a firm basis on which to evaluate the potential benefits and risks of bio-fortification. All of these data will be included in the dietary modelling experiments, alongside more usual methods of fortification, including addition to dairy foods, cereals and other common vehicles.

### What is the availability of UVB in Europe and is there a safe exposure level?

During wintertime in latitudes greater than ~38°, the angle of the sun is too oblique for UVB rays to pass through ozone, so little or no vitamin D is dermally synthesised. This vitamin D winter increases with latitude; it lasts about 3 months in Athens, Greece (37°N), ~6 months in Cork, Ireland or London, UK (both at 51°N) and 7–8 months in Helsinki, Finland (at 60°N) and Tromsø, Norway (at 70°N). Personal behaviour also limits UVB exposure, even in sunny countries. As excessive sun exposure is the principal risk factor for most skin cancers, public education campaigns recommend limiting exposure to sunlight. Improved adherence to sun safety recommendations and awareness of the links between excessive sun exposure and skin cancer, as well as premature wrinkles, has led to the widespread use of sunscreen and inclusion of sun protection factor (SPF) ingredients in cosmetic products. Correct application of a product containing an SPF of 15 almost completely prevents cutaneous skin production of pre-vitamin D<sub>3</sub> (Matsuoka *et al.* 1988). Dermal synthesis of vitamin D is less efficient in older than in younger adults (Holick 2008). Discreet clothing habits limit sun exposure particularly in veiled women and long working hours spent indoors mean that most adults rely on weekends and vacation to spend time outdoors during the day. Furthermore, melanin in skin reduces the penetration of UVB and thus contributes to lower vitamin D status in dark-skinned individuals. These factors reemphasise the need for public health strategies to exploit food-based solutions for prevention of vitamin D deficiency. However, the question of whether a minimal risk approach to UVB exposure

would enable vitamin D production without increasing the risk of skin cancer is outstanding. While such information would not offset the dietary requirement for deficiency prevention during winter, it could have a massive impact on the dietary requirements for vitamin D for health given the more powerful ability of skin synthesis to increase serum 25(OH)D concentrations relative to dietary intake.

ODIN will provide new data to test whether there is a minimal or threshold UVB exposure level that enables subcutaneous vitamin D synthesis and avoids risk of skin cancer. In particular, it will test the traditionally held notion that 6–8% and 15% of body surface exposure (*i.e.* face and hands, and face, hands and arms), to obtain one minimal erythemal dose (MED: the minimum amount of time to cause slight reddening of the skin without burning after which vitamin D production ceases; typically ~15 minutes for White Europeans) of summer sunlight is enough to increase serum 25(OH)D above 30 nmol/l and importantly, whether such exposure induces significant DNA damage in the skin. These data will be of huge value in informing vitamin D public health policy in the future.

In addition, meteorological data will be used in ODIN to develop models to predict serum 25(OH)D concentrations across populations in different geographical locations. These models will be tested using the standardised status data obtained in the population studies listed in Table 1 to predict the response of different populations to changes in the dietary supply of vitamin D. This combination of approaches will provide much needed data on the current and potential role of sunshine in helping to meet vitamin D requirements without increasing risk of skin damage. The modelling data will also be used in ODIN to project the impact of such dietary changes on serum 25(OH)D distributions in European populations, while accounting for vitamin D arising from exposure to summer UVB sunlight.

### Experimental dose-response data in under researched population groups

It is important to acknowledge that setting Dietary Reference Intervals (DRIs) is an iterative process, and decisions often have to be made in the absence of empirical evidence. One of the issues highlighted by the IOM (2011) and other regulatory authorities recently charged with making recommendations for vitamin D intakes, including Health Council of The Netherlands (2012) and the Nordic countries (NNR 2014), is the relative lack of experimental data from studies designed to esti-



mate the dietary intakes of vitamin D required to maintain serum 25(OH)D above specified thresholds during wintertime in pregnancy, childhood and adolescence [see Cashman & Kiely (2014) for a detailed overview]. The IOM's recommendations for pregnant and lactating women are the same for non-pregnant women, on the basis that there were no data to indicate otherwise. Similarly, data were few on which to base dose-response models in children; of the three RCTs in children and teenagers used in the IOM dose-response model, one was conducted in a small group of 20 participants (Schou *et al.* 2003) and one was conducted in 1988 (Ala-Houhala *et al.* 1988). Specifically designed studies in these under researched groups are required to develop DRIs that are evidence-based. ODIN is implementing three dose-response RCTs in pregnant women (Cork, Ireland), children (Copenhagen, Denmark) and teenagers (Surrey, UK), powered specifically to define the vitamin D intake requirement to meet the 25(OH)D thresholds of 30 and 50 nmol/l.

While the DRIs for vitamin D are also intended to meet the requirements of dark-skinned populations, this is based on an assumption, in the absence of data, that ethnicity does not have a major influence on requirements. However, Aloia *et al.* (2008) showed in a 6 month, prospective, randomised, double-blinded, placebo-controlled study of vitamin D<sub>3</sub> supplementation and serum 25(OH)D, that although both Black and White adult Americans achieved the experimental target of 75 nmol/l by week 18, Black participants required a 50% higher dose than Whites. Therefore, specific studies are required in individual ethnic groups, resident at northern latitudes, who we know are at increased risk of vitamin D deficiency, but who may also have a higher dietary requirement for vitamin D. ODIN will conduct a fourth RCT to provide experimental data to specify these intake requirements among East African immigrants resident in Helsinki, Finland and an additional food-based study in South Asian women in Copenhagen, Denmark.

### Vitamin D and health throughout life

While a large body of observational data indicate that vitamin D deficiency is associated with various adverse aging-related health outcomes, including mortality, cardiovascular disease (CVD) and cognitive decline, as well as perinatal outcomes and growth and development in early life, the current consensus is that there is insufficient evidence that vitamin D has an independent role in disease prevention (Newberry *et al.* 2014). Currently, 370 RCTs are registered on ClinicalTrials.gov under the

topic of 'vitamin D and cardiovascular disease', including a number of large studies in the US and Europe, such as the VITAL, DoHealth and FIND trials, which will report in the coming years. Effect modifiers, such as the dose-response of specific population groups, the influence of circulating 25(OH)D at the baseline of a vitamin D supplementation study, genetic variability in the response to vitamin D supplementation, plus data showing reverse J-shaped distributions with increasing risk of adverse effects at relatively high, albeit easily achievable, concentrations of 25(OH)D, convinced the ODIN consortium not to implement RCTs to examine vitamin D and health effects in ODIN, but to take an alternative approach, maximising existing resources, to inform future studies, if warranted. Data from existing cohort meta-analyses of vitamin D are based on 25(OH)D data analysed using variable analytical methods, which impacts on the prevalence of deficiency and study power.

To address these data requirements, ODIN is conducting patient level meta-analyses from prospective cohort studies in older adults, provided by ODIN participants (total *n* of ~46 000 subjects), with standardised 25(OH)D data, according to the VDSP protocols described above and harmonised phenotypes, including validated clinical endpoints and subject characteristics. Mendelian randomisation experiments will elucidate the role of genetic variation in vitamin D synthesis, transport and metabolism. Similarly, 25(OH)D will be reanalysed in existing RCTs with stated *a priori* objectives to investigate the effect of vitamin D on these clinical endpoints (total *n* of 2200 subjects). Individual patient data meta-analysis on the relationship between 25(OH)D and cardiovascular events and CVD risk factors will significantly add to the existing literature that is currently mainly based on unstandardised 25(OH)D levels. Individual patient data meta-analysis of vitamin D RCTs will also provide novel data on whether there are effects of vitamin D supplementation on cardiovascular risk factors in individuals with vitamin D deficiency, classified according to baseline 25(OH)D levels. These data will be crucial for the optimal design of future RCTs.

Similarly, associations between low 25(OH)D during pregnancy and increased risk of adverse perinatal outcomes including pre-eclampsia, gestational diabetes, spontaneous preterm birth and obstructed labour are inconsistent. Problems include reliance on retrospective analysis of data, sometimes with inadequate and inconsistent clinical phenotyping, and variability in measurement of 25(OH)D, which has led to a lack of clarity, conflicting messages and potentially spurious results.

ODIN will standardise or analyse *de novo* 25(OH)D data in four large pregnancy cohorts, contributed by partners (total *n* of ~10 000 subjects), with prospectively collected validated clinical endpoints, quality bio-banks and meta-data. We will also use this approach in four disease-specific maternal-infant birth cohorts to examine associations between 25(OH)D in pregnancy and infancy and normal growth and development.

### The ODIN approach to safety

Nutrient intake, unlike substances such as drugs or chemical toxicants where there is zero to minimal background exposure, can pose a dual risk, due either to inadequate or excessive consumption. To minimise the risk of excess micronutrient intakes, safe upper intake levels (ULs) for micronutrients are established by authoritative agencies. The UL for vitamin D for adults is 100 µg/day (IOM 2011; EFSA 2012). While higher doses are not associated with short-term adverse effects, analysis of data to assess adverse effects of long-term exposure to high doses of vitamin D and chronic maintenance of high circulating 25(OH)D is warranted (IARC 2008), especially since past experiences with other compounds (*e.g.* some antioxidants and hormone replacement therapies) have showed serious adverse effects. U- and reverse J-shaped distributions have been described for serum 25(OH)D and all-cause mortality, CVD risk, parathyroid hormone (PTH) suppression and intrauterine growth restriction, which deserve serious consideration by researchers investigating health effects of vitamin D. ODIN will document safety across the project, including dietary intakes of vitamin D, prevalence of high serum 25(OH)D concentrations in national nutrition surveys and cohort studies, as well as modelled predictions at a population level. We are also evaluating potential adverse effects of sustained high concentrations of serum 25(OH)D in prospective cohort studies as well as from high-dose vitamin D RCTs. The project will also consider the impact of a 'do nothing' option from the risk/safety perspective for Europe in terms of addressing vitamin D deficiency through food.

### Conclusions

In conclusion, the ODIN project will measure the distribution of circulating 25(OH)D vitamin D intake and potential sunshine exposure levels across representative samples of the European population. The research effort will concentrate on currently available bio-banks and databases from national nutrition and health surveys

within the framework of an internationally standardised laboratory analytical platform for 25(OH)D, which is traceable to a higher order reference measurement procedure, and a harmonised approach to estimating potential exposure to vitamin D, both from sunshine and the food supply. This research strategy, which uses existing infrastructure to maximise European Commission and member state investment, will describe the prevalence of vitamin D deficiency in European populations and the relative contributions of sun and dietary sources of vitamin D to circulating 25(OH)D across the geographical area from the Mediterranean to the Arctic Circle and the Atlantic to the Black Sea.

The ODIN consortium includes experts in diverse fields including human and animal nutrition, food science, epidemiology, analytical chemistry, biostatistics, applied mathematics, genetics, various clinical specialties, physics, bioinformatics and information technology and will apply these specialisms to integrate data from ODIN research with knowledge from previous and ongoing experiments to provide original solutions to persistent problems in the vitamin D field. Dose-response data from the four RCTs to define vitamin D requirements in neglected population groups will be combined with data from previous RCTs carried out by consortium members to define dietary requirements for vitamin D across the life course. These, plus data from mathematical modelling of nationally representative dietary surveys and sun exposure data will inform food technologists, animal nutritionists and food ingredient producers in the development of innovative food-based solutions to increase vitamin D in the European food supply. A combination of bio-fortification of meats, fish, eggs, mushrooms and yeast and nutrient addition will test the efficacy and safety of these products in food-based RCTs varying in scale from small product-specific trials to a large total diet study in vulnerable indigenous and immigrant population groups. This multidisciplinary research strategy will provide definitive answers to key technological challenges, deliver quality data on the efficacy and safety of adding vitamin D to food in a dose-dependent manner and reflect the diversity of the European food supply and eating habits. ODIN has assembled the largest critical mass of prospective adult, pregnancy and birth cohort studies to date and will conduct a series of meta-analyses and individual subject-level meta-regression analyses to integrate standardised data on vitamin D status. Clinical and genotype endpoints defined *a priori* to examine relationships between vitamin D and human health, including beneficial and adverse effects on perinatal outcomes, growth and atopic disease in children and CVD and mortality in

adults. On the basis of these analyses, alongside life stage-specific data on dose-responses and the relative effects of sun exposure and diet on vitamin D status across the European population, it will become possible to implement long-term vitamin D RCTs across the life cycle with predictable safety outcomes.

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## Conflict of interest

The authors have no conflict of interest to disclose.

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