



PUBLISHABLE SUMMARY REPORT – Section 4.1

Grant Agreement number: 613977

Project acronym: ODIN

Project title: Food-based solutions for Optimal vitamin D Nutrition and health through the life cycle

A. Executive summary

Prevention of vitamin D deficiency is a public health priority, as nutritional rickets and osteomalacia have severe and lasting consequences for bone growth and skeletal integrity throughout life. Non-skeletal effects of low vitamin D status, including respiratory infection, perinatal health outcomes and cardiovascular disease, for example, are the subject of a global research effort.

The European Commission funded **ODIN project (Food-based solutions for optimal vitamin D nutrition and health throughout life: www.odin-vitd.eu)** is a multidisciplinary consortium of 30 partners from 18 countries. ODIN completed a 4-year programme of research in December 2017. Led by Prof Mairead Kiely and Prof Kevin Cashman, at University College Cork, the ODIN project was built around a prioritised agenda, outlining current knowledge gaps in vitamin D nutrition.

As much of Europe experiences 4-6 winter months during which UVB availability is too low to permit skin synthesis of vitamin D, the diet is critical to meeting population requirements. Vitamin D is present in the food supply, in few foods and in low concentrations and intakes are typically <5 µg (<200 IU)/day, which is insufficient to offset the seasonal sunshine UVB deficit. Nutritional supplements contribute a high proportion of vitamin D intake among users, but supplement uptake is not universal and generally low among adolescents and young adults, who are at risk of vitamin D deficiency. **The ODIN mission 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.** With a budget of €6M, ODIN adopted a triage approach to prioritise its objectives, which were delivered by the consortium across an ambitious programme encompassing both dose-response and food-based randomised controlled trials, research in primary food production and food technology, data mining of epidemiological cohort studies and dietary and UVB modelling experiments.

To date, ODIN has published 75 peer-reviewed scientific articles in quality journals, many of which are the first in their field, with more under review/in preparation for publication in 2018.

Significant achievements:

ODIN generated reliable prevalence data for vitamin D deficiency across Europe for the first time. Among 55,844 individuals in 18 representative studies of children, teens, adults and elderly persons across a latitude gradient of 35°N to 69°N, 13% (or 1 in 8) had vitamin D deficiency, on the basis of a serum 25-hydroxyvitamin D (25(OH)D) concentration <30 nmol/L and 40% had low vitamin D status, with 25(OH)D <50 nmol/L. Persons of ethnic minority were at much higher risk than their white counterparts, <http://www.odin-vitd.eu/public/7-european-vitamin-d-deficiency-map/>.

Among 6000 women in early pregnancy in the UK, Sweden and Ireland, there was a slightly higher prevalence of vitamin D deficiency and low vitamin D status. In this largest study of vitamin D in pregnancy to date, 15% (or 1 in 7) had 25(OH)D <30 nmol/L and 44% were <50 nmol/L. Almost half of infants had vitamin D deficiency at delivery, particularly if their mothers had low vitamin D status.

ODIN conducted an individual participant data analysis among 26,916 older adults of mortality in studies with mortality and cardiovascular outcomes. The lowest risk was at a 25(OH)D concentration of 78 nmol/L and the risk of mortality increased as 25(OH)D decreased from <50 to <30 nmol/L.

In dose-response vitamin D intervention studies, ODIN researchers provided vitamin D intake requirement estimates in young children, teens, pregnant women and individuals of ethnic minority.

Using a farm to fork approach, ODIN demonstrated that natural enhancement of animal feed could deliver measurable increases in vitamin D in meats and hens eggs, which increased vitamin D status in human volunteers. Similarly, ODIN successfully increased the vitamin D content of low-fat cheese and demonstrated benefits for deficiency prevention in older women.

Over-reliance on a single food source (e.g. dairy) will not ensure population coverage and we need to accommodate dietary diversity for effective delivery of additional vitamin D to the population. ODIN developed a specialized food composition dataset for vitamin D and conducted dietary modelling experiments in 10 dietary surveys from 4 countries to demonstrate the feasibility of achieving dietary recommendations for vitamin D, without increasing the risk of excessive intakes.

The ODIN hypothesis, that careful application of fortification and bio-fortification strategies could safely increase intakes of vitamin D across the distribution and prevent deficiency, is technically feasible. Societal and economic benefits require further investigation.

B. Summary description of the ODIN project context and objectives

ODIN (Food-based solutions for optimal vitamin D nutrition and health through the life cycle www.odin-vitd.eu) was a 4-year integrated project, which commenced in November 2013 and finished in October 2017. The *Cork Centre for Vitamin D and Nutrition Research* at University College Cork, Ireland led the ODIN consortium of 30 partners from 19 countries.

Project context and motivation

Vitamin D is a nutrient that has captured the attention of the public, the scientific and medical communities, regulatory agencies and the food industry. While there are many controversies in relation to vitamin D requirements and its impact on human health, it is generally agreed that prevention of vitamin D deficiency, for prevention of nutritional rickets and osteomalacia, is a public health priority, as these disorders have severe and lasting consequences for bone growth and skeletal integrity throughout life. While data showing associations between vitamin D and non-skeletal disorders are abundant, the evidence base to support a role for vitamin D in prevention of non-bone related disorders is currently less robust. Nonetheless, public health authorities are now aware of the importance of preventing vitamin D deficiency, which was until recently an unacknowledged health problem.

The major source of vitamin D in humans is sunshine; ultraviolet B (UVB) radiation stimulates skin synthesis of cholecalciferol (vitamin D₃), which is stored in adipose tissue or metabolised in the liver to 25-hydroxyvitamin D [25(OH)D], the biomarker of vitamin D status, and further metabolised in the kidney to calcitriol, the biologically active metabolite. The most extensively documented function of vitamin D is regulation of serum calcium and phosphate homeostasis, a critical component of normal skeletal mineralisation throughout the growing years and during the ageing process.

Several environmental factors, such as latitude and prevailing weather conditions, determine the availability of sunshine of sufficient strength to stimulate skin synthesis of vitamin D. 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. Substantial portions of the European population, including all who reside at latitudes greater than around 40°N rely on body stores and vitamin D in the diet to maintain healthy vitamin D status all year round. As much of Europe experiences 4-6 winter months during which UVB availability is too low to permit cutaneous synthesis of vitamin D₃, dietary supply is critical to meeting population requirements. Thus, a sizeable proportion of the school-aged and working population, as well as the more widely acknowledged older adult demographic is at risk of low vitamin D status.

Vitamin D does occur in the diet, both naturally and as an added nutrient for fortification, and in nutritional supplements. However, vitamin D intakes are typically low, as it occurs naturally in few foods and in low concentrations, and the dietary supply is currently unable to offset the seasonal sunshine deficit. Nutritional supplements contribute a high proportion of vitamin D intake among users, however supplement uptake is too low to make it viable for deficiency prevention across the population. Despite much scientific research in vitamin D,

there are still many fundamental gaps in the field from the public health perspective and these impede the development of strategies for prevention of vitamin D deficiency. ODIN aimed to address some of these gaps and in so doing facilitate a food-first approach to tackling vitamin D deficiency in Europe.

Overall objective of ODIN

To develop effective, safe and sustainable solutions to prevent vitamin D deficiency and improve vitamin D related health outcomes using a food-first approach. We adopted a triage approach to selecting the most critical issues for attention:

Prioritised Questions

Vitamin D status and exposure

- What is the actual 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 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 and possible modulation by genetic variation?
- Are associations between vitamin D and perinatal outcomes robust 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?

Project organisation and architecture to address these prioritized questions

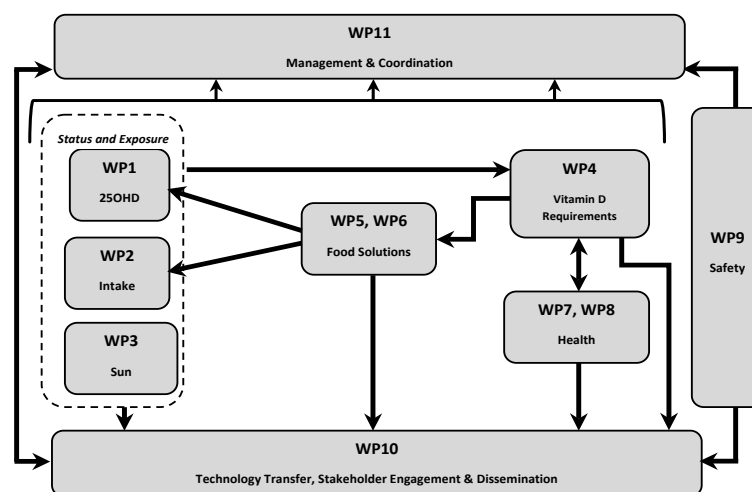
ODIN assembled a world-leading, multidisciplinary partnership of scientific and medical researchers from academia and research organizations with complementary expertise in the area of vitamin D nutrition and health to work closely with significant food and nutrition

industries and SMEs active in food and ingredient development. The ODIN consortium of 20 European academic and research institutional partners, 10 industry and SME partners across 19 countries, as well as the Office of Dietary Supplements of the National Institutes of Health (NIH) in the US as a non-funded collaborator (see Part 2 of the report for partner list), was configured to have the expertise and excellence, necessary ethos of cooperation and collaboration as well as overall skill sets required to address the prioritised research questions and to define food-based strategies and solutions which would be feasible, safe and effective for prevention of vitamin D deficiency in Europe.

ODIN implemented an integrated program of research across nine RTD work-packages (WPs) dealing with vitamin D status and exposure (diet and sun), dietary requirements, food-based solutions, human health and safety, as per the priority questions posed, as well as a dedicated WP for project coordination and a WP providing an innovative technology transfer and stakeholder engagement strategy to generate and translate the knowledge required to prevent vitamin D deficiency through food and confirm European leadership of vitamin D public health nutrition globally. These WPs were:

- WP1: Vitamin D status: distribution of standardized serum 25-hydroxyvitamin D concentrations in European populations [VDSP Europe]
- WP2: Dietary exposure to vitamin D in European populations
- WP3: Sunlight exposure: risk-benefit analysis, implications for vitamin D requirements and status
- WP4: Dietary requirements for vitamin D during pregnancy, childhood and adolescence using dose-response RCTs
- WP5: Food- and food-technology-based solutions for prevention of vitamin D deficiency: Natural sources, fortification and biofortification with vitamin D₂/D₃ and 25-hydroxyvitamin D
- WP6: Proof of effectiveness of food-based solutions to prevent vitamin D deficiency using food-based RCT
- WP7: Vitamin D and health outcomes in pregnancy and early-life
- WP8: Vitamin D and health outcomes in adults: mortality and CVD
- WP9: Safety considerations in relation to increasing vitamin D intake and serum 25OHD levels
- WP10: Technology transfer, stakeholder engagement & dissemination
- WP11: Management and coordination

The work-flow and interdependencies of ODIN's 11 WPs are shown in the Figure below.



C. Description of the main S&T results/foregrounds

The ODIN project was built around the research recommendations from a comprehensive review of persistent knowledge gaps in vitamin D nutrition and public health, provided by the project coordinators (Cashman & Kiely; <https://www.ncbi.nlm.nih.gov/pubmed/22017772>) in 2011. ODIN adopted a pragmatic approach to addressing its priorities within this wider suite of knowledge gaps, as mentioned in Section B above and more comprehensively detailed by Kiely & Cashman (<http://onlinelibrary.wiley.com/doi/10.1111/nbu.12159/epdf>) on behalf of the project consortium. The ODIN mission 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. Underpinning data to achieve these outcomes were delivered by the consortium across its ambitious programme encompassing both dose-response and food-based randomised controlled trials (RCTs) with vitamin D, research in primary food production and food technology, data mining of epidemiological cohort studies and dietary modelling experiments. The quality and reliability of ODIN analytical data, both serum 25(OH)D and related metabolites, as well as food composition data, was a cornerstone of excellence in the project and its findings, assuring validity of experimental outcomes and providing reference data for previously under-researched population groups.

Many of the key S&T results and foreground information gathered within ODIN have been presented in the 75 papers arising from the project (see Section 4.2A below). A more detailed overview of the work undertaken in each of ODIN's 9 RTD work packages (WP), including their key achievements, is provided below.

Work package 1: *Vitamin D status: distribution of standardized serum 25(OH)D concentrations in European populations*

The main objective of WP1 was to estimate the prevalence of vitamin D deficiency in European populations and quantify the magnitude of the public health problem as well as highlight at-risk population subgroups. The distributions of standardized serum 25(OH)D concentrations in national surveys and epidemiological cohorts/samples of European children, adolescents, adults and elderly (including ethnic subgroups) were to be established via a major underpinning infrastructural development in the form of the international, NIH-led *Vitamin D Standardization Program* (VDSP) and its protocols.

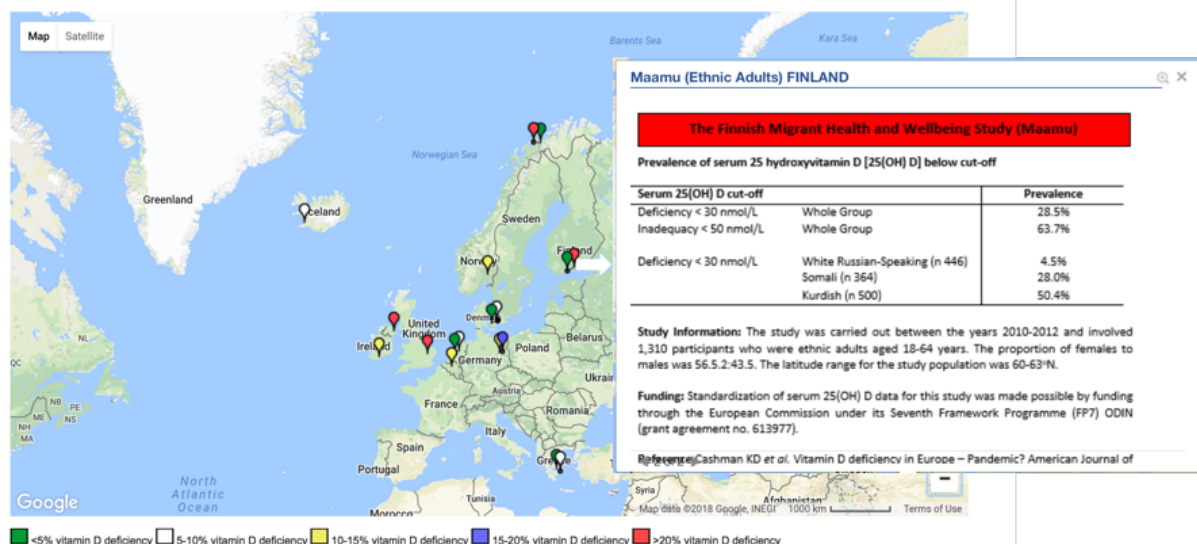
WP1 was completed on schedule (month 18) and successfully applied the VDSP protocols to existing serum 25(OH)D data from 14 representative childhood/teenage (eight) and adult/older adult (six) European populations, representing a sizeable geographical footprint and a total sample size of 55,844, to quantify the prevalence of vitamin D deficiency in Europe. This first internationally comparable dataset of vitamin D status was published in the *American Journal of Clinical Nutrition* in 2016 (under open access at <http://www.ncbi.nlm.nih.gov/pubmed/26864360>) and described "*An overall pooled estimate, irrespective of age group, ethnic mix, and latitude of study populations, of 13.0% of the 55,844 European individuals had serum 25(OH)D concentrations <30 nmol/L on average in the year, with 17.7% and 8.3% in those sampled during the extended winter (October-March) and summer (April-November) periods, respectively. According to an alternate suggested definition of vitamin D deficiency (<50 nmol/L), the prevalence was 40.4%. Dark-skinned ethnic subgroups had much higher (3- to 71-fold) prevalence of serum 25(OH)D <30 nmol/L*

than did white populations". The concerning magnitude of the deficiency estimates, from a public health perspective, attracted an accompanying editorial in the *American Journal of Clinical Nutrition* (open access at <https://www.ncbi.nlm.nih.gov/pubmed/26984486>) which highlighted the importance of the data. In addition, and of key relevance to ODIN, the authors of the editorial suggested that 'because food fortification is deeply lacking within the EU, we suggest that future work, which may lead to realistic and actionable public health policies, should focus on determining the most effective fortification strategies to meet requirements for vitamin D among community-dwelling Europeans'. This is the overall objective of the ODIN project, namely to develop effective, safe and sustainable solutions to prevent vitamin D deficiency and improve vitamin D related health outcomes using a food-first approach.

Of note, the paper has been cited >190 times already since its publication in March 2016 and was included in the 'The Top 18 Vitamin D Papers in 2015-2016' (source: Orthomolecular Medicine News Service, February 13, 2017). To enhance translation and accessibility of the data, as well as engagement with ODIN, we developed an online *European Vitamin D Deficiency Map*. This map, generated by the Cork Centre for Vitamin D and Nutrition Research presents data on standardized serum 25(OH)D from ODIN as well as a number of associated projects, where the ODIN leaders at University College Cork, together with the NIH Office of Dietary Supplements and collaborating European partners have standardized 25(OH)D data in a number of important European population studies. These data are presented in summary and user-friendly format in this new interactive map (see below) available at: <http://www.odin-vitd.eu/public/7-european-vitamin-d-deficiency-map/>, which has been disseminated widely through the ODIN newsletter, conferences, VDSP webinars.

Prevalence of vitamin D deficiency in Europe using standardised 25-hydroxyvitamin D (25(OH)D) data.

The Cork Centre for Vitamin D and Nutrition Research together with the Office of Dietary Supplements at NIH who lead the Vitamin D Standardization Program (VDSP) and several collaborating European partners have applied protocols for standardizing 25(OH)D data in a number of important European population studies. Standardized 25(OH)D data allow for more meaningful comparisons within and across European countries and also for a better estimate of true prevalence estimates of vitamin D deficiency to be generated. These new important data are presented in summary in this new interactive map. Select the population/country you are interested in by pressing on the flag symbol. The flags representing different populations are colour coded based on prevalence of vitamin D deficiency (see key below). Copyright Cashman & Higgins 2016



Some of the prevalence data in this map has also been cross-connected to UVB availability data in an ODIN online 'Vitamin D winter' map (see under WP3).

Other WP1 S&T results were:

Findings in relation to vitamin D status in Central and Eastern European Countries (CEEC)

- Based on a systematic literature review of vitamin D status in the CEEC, no nationally representative datasets were identified that could be used to conduct analysis of appropriately phenotyped and curated biobanks using the ODIN analytical platform as used in the above mentioned representative populations from elsewhere in Europe.
- From the literature, it could be concluded that 25(OH)D levels are, on average, below 75 nmol/L in most studies in CEEC.
- In winter season, 25(OH)D levels in adults are, on average, below 50 nmol/L in most studies included in this review (based on Bulgaria, Estonia, Hungary, Lithuania, Poland, Serbia, Ukraine).
- No studies on vitamin D status were found for Albania, Bosnia and Herzegovina, and Macedonia.
- National studies are limited for children, adolescents, pregnant women and the elderly in CEEC. This work is currently in preparation for peer review and the full data and findings will be made publically available after publication.

Findings in relation to vitamin D status in Southern European countries

- The results from a systematic literature review of studies from Southern European countries, published in the *European Journal of Nutrition* in 2017 (open access at <https://www.ncbi.nlm.nih.gov/pubmed/29090332>), were indicative of a relatively high heterogeneity of published evidence regarding serum 25(OH)D concentrations and vitamin D status among Southern European countries.
- Data were extracted from 107 studies, stratified by sex and age group, representing 630,093 individuals. More than one-third of the studies reported mean serum 25(OH)D concentrations below 50 nmol/L and ~10% reported mean serum 25(OH)D concentrations below 25 nmol/L. Overall, females, neonates/ infants and adolescents had the higher prevalence of poor vitamin D status. As expected, there was considerable variability between studies. Specifically, mean serum 25(OH)D ranged from 6.0 (in Italian centenarians) to 158 nmol/L (in elderly Turkish men); the prevalence of serum 25(OH)D<50 nmol/L ranged from 6.8 to 97.9% (in Italian neonates).
- An audit of available quality bio-banks in southern European countries identified that serum and/or plasma samples existed for a total number of 22,346 subjects aged 10 years and older from four countries in southern Europe (France, Greece, Italy and Spain) as well as from Israel and Turkey. The quality of bio-banks identified could represent candidate bio-banks, the serum or plasma samples of which could be used for conducting future biochemical analyses (i.e. with LC-MS/MS) to measure 25(OH)D levels as per the VDSP protocols, in the respective populations.

Work package 2: *Dietary exposure and modelling for food fortification*

The main objectives of WP2 were to describe vitamin D intakes from food and supplement sources, using standardized food composition data and a consistent approach to food indexing and grouping, in nationally representative food consumption and nutrition European surveys. Data on ethnic and traditional foods to inform food-based strategies to ensure adequate vitamin D in the food supply of all European citizens were to be compiled. An integrated approach to data compilation in the nutrition surveys in Central and Eastern European Countries (CEEC) was to be used for vitamin D intake assessment. Dietary modeling in case datasets would be used to predict the impact on the vitamin D supply in foods and the distribution of intakes using fortification and bio-fortification strategies in ODIN. This would ensure appropriate levels of addition to ensure efficacy in terms of inadequate intakes and minimize the risk of exceeding tolerable upper intake levels (ULs).

WP2 was successfully completed during the 2nd reporting period (month 30). The ODIN-EUROFIR vitamin D food composition database was constructed in the first reporting period and has since been published in Food Chemistry (open access) at <https://www.sciencedirect.com/science/article/pii/S030881461731289X?via%3Dihub> and widely disseminated. In the 1st period we also described the first harmonised, validated vitamin D intake data in 10 nationally representative surveys from 4 EU countries and reported intakes of 3-5 µg/d in the UK, Denmark, the Netherlands and Ireland with 77-100% of people at risk of inadequate vitamin D intakes. Some traditional sources of vitamin D, such as eggs, were still important, while others such as oily fish, made a limited contribution due to low consumption levels in most countries, particularly among children. These data are under review in an extended joint publication with the intake modelling experiments.

In WP2, we developed and validated a novel system for ODIN to progress step-wise dietary modelling of incremental food fortification scenarios, based on data from WP5, and completed these analyses in the 2nd period (month 19-30). Data from incremental and combined dietary modelling experiments in 10 nationally representative surveys in 4 EU countries showed that proposed combined ODIN fortification and enhancement strategies, including milk, eggs, cheese and meat achieve desired population intakes and distributions of vitamin D, relative to the EAR of 10 µg/day/d, without increasing the risk of excessive intakes. Supplemental doses exceeding 25 µg/day in children and 50 µg/day in adults were associated with risk of exceeding the age-specific ULs.

In general, we confirmed that current levels of vitamin D fortification are low and to date, no EU country other than Finland has taken a strategic approach to fortification, which limits its benefit, discussed in our open access *Journal of Nutrition* article <https://academic.oup.com/jn/article-lookup/doi/10.3945/jn.114.209106>. There is currently no evidence of excessive intakes of vitamin D across the 10 surveys in the four countries we studied.

Variable estimates of vitamin D intakes from a systematic review of CEEC showed very low intakes of vitamin D, which is probably a function of the dietary assessment method and food composition data available, but no survey was identified to contribute to the ODIN databank. There is an urgent need for quality dietary survey data in CEEC countries. These data are being prepared for peer-review, in conjunction with the data from WP1.

The analysis of ethnic and traditional foods in ODIN confirmed that targeted approaches to designing food fortification strategies were required for ethnic subgroups. Potentially useful foods are baked goods and vegetable oils. However, contemporary intake data are urgently required among ethnic subgroups to perform dietary modelling experiments as these are currently not available or insufficiently small datasets.

Work package 3: *Sunlight exposure: risk-benefit analysis*

The main objectives of WP3 were to model solar-derived, vitamin D-effective UVB availability across several European member states, based on local climatology, to corroborate the prevalence of vitamin D deficiency/inadequacy, defined in WP1. Estimates of potential UVB exposure as well as nationally representative vitamin D intake estimates were also to be used in the development of mathematical models for predicting population serum 25(OH)D distributions arising from changes in vitamin D intake while accounting for solar UVB-derived sources. WP3 also aimed to provide new UV risk-benefit data in terms of the response of serum 25(OH)D to UVB exposure in a controlled human study with artificial UV light. The study aimed at testing whether simulated summer UVB exposure level of public health relevance (~12% body surface to 15-25 min of summer noon equivalent sun) enables adequate subcutaneous vitamin D synthesis while avoiding risk of DNA damage in skin.

WP3 was completed on schedule (month 36) and using a validated UV irradiance model successfully modelled vitamin D-effective UVB availability across the European member states (nine) for which vitamin D status data was generated in WP1. The results, published in *Nutrients* in 2016 (open access at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5037520/>), showed that UVB availability decreased with increasing latitude (from 35°N to 69°N), while all locations exhibited significant seasonal variation in UVB (see Figure below).

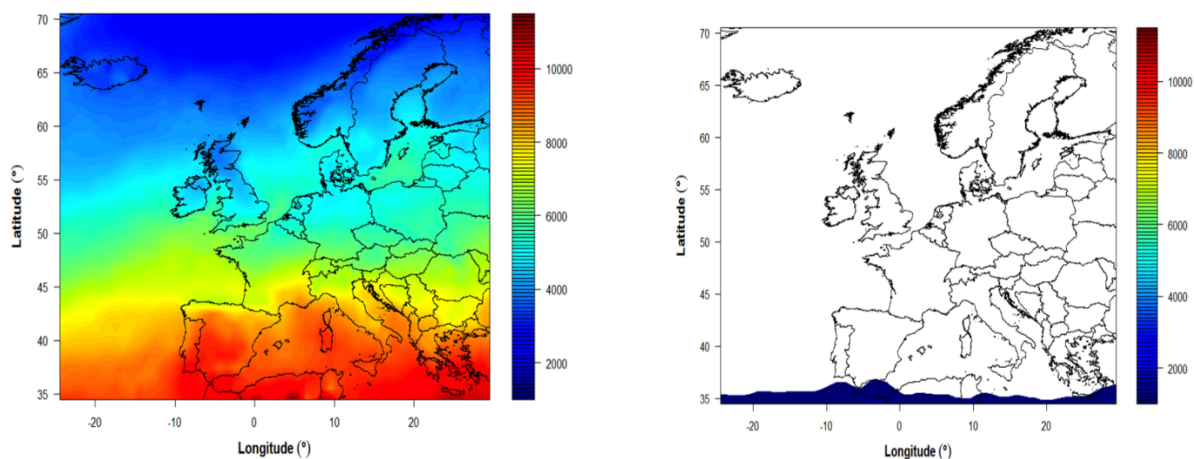
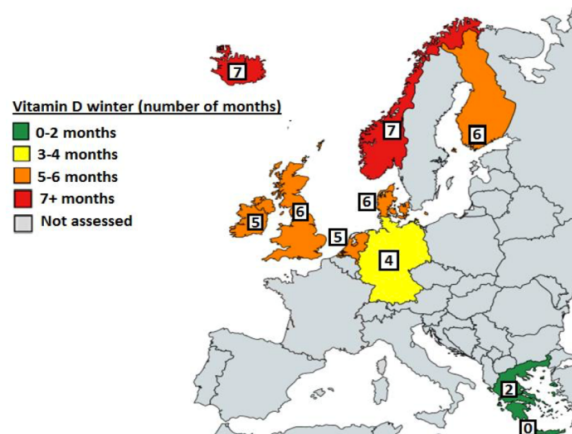


Figure. Mean monthly modeled UVB doses effective for pre-vitamin D₃ synthesis (Jm^{-2}) across Europe for June (*left hand panel*) and December (*right hand panel*), based on average of data from years 2003–2012.

The UVB data suggested that the duration of vitamin D winters ranged from none (at 35°N) to eight months (at 69°N). This data was also translated into an online *Vitamin D Winter Map* (see below; and available at: <http://www.odin-vitd.eu/files/vit%20D%20winter%20map%20landscape%20new.pdf>).

Vitamin D winter map

The Cork Centre for Vitamin D and Nutrition Research together with several collaborating European partners have assessed UVB availability across several European locations ranging from 35°N to 69°N. The UVB data suggested that the duration of vitamin D winters ranged from zero (at 35° N) to eight months (at 69° N) as shown in the map below. The countries are colour coded based on the duration of the vitamin D winter (as per legend). Copyright Cashman & O'Neill 2016.



Reference

O'Neill CM, Kazantzidis A, Ryan MJ, Barber N, Sempos CT, Durazo-Arvizu RA, Jorde R, Grimnes G, Eiriksdottir G, Gudnason V, Cotch MF, Kiely M, Webb AR, Cashman KD (2016). Seasonal changes in vitamin D-effective UVB availability in Europe and associations with population serum 25-hydroxyvitamin D. *Nutrients*; 8(9):533. Click [here](#) to read the publication.

WP3 has successfully developed and validated the two planned European case-study integrated models of sun-diet-25(OH)D, and has demonstrated their utility in predicting population serum 25(OH)D distributions arising from changes in vitamin D intake, accounting for solar UVB-derived sources. These models enable food-based strategies for the prevention of vitamin D deficiency to be evidence-based. In the first model, which was developed for Ireland and published in the *Journal of Nutrition* (open access at <https://www.ncbi.nlm.nih.gov/pubmed/26290010>), the UVB- and vitamin D intake-serum 25(OH)D components of the integrated model were both validated with the use of independent data, including standardized serum 25(OH)D data from the nationally representative *National Adult Nutrition Survey* in Ireland (generated in WP1). The model predicted that the percentage of vitamin D deficiency [serum 25(OH)D <30 nmol/L] in the adult population during an extended winter period was 18.1% (vs. 18.6% measured). The performance of the integrated model was tested with the use of 3 hypothetical fortification scenarios as exemplars. This showed that the prevalence of vitamin D deficiency in the adult Irish population could be reduced in a stepwise manner with the incorporation of an increased number of vitamin D-fortified foods, down to 6.6% with the inclusion of enhanced fortified dairy-related products, fat spreads, fruit juice and drinks, and cereal products.

The second model, which was for the UK and published in the *Journal of Steroid Biochemistry and Molecular Biology* (open access at <https://www.ncbi.nlm.nih.gov/pubmed/27637325>), was a more complex model as it had to take account of the fact that unlike the Irish population, the UK population is an ethnically mixed one (consisting of ~90% white and ~10% black and Asian minority ethnic individuals, based on recent census data). This UK model used key data from UVB observational and interventional studies in Manchester, UK to inform the design of the dark-skinned model component, which was then successfully integrated with that for the white population to generate an overall model. This was validated against standardized serum 25(OH)D in the nationally representative *National Diet and Nutrition Survey* – 4 year rolling programme in the UK (generated in WP1). The integrated UK model successfully predicted measured average wintertime 25(OH)D concentrations in addition to the prevalence of serum 25(OH)D <30 nmol/L in adult white and black and Asian ethnic minority groups [BAME] (18-70 y) in the UK-based *National Diet*

and Nutrition Survey both separately (21.7% and 49.3% predicted versus 20.2% and 50.5% measured, for white and BAME, respectively) and when combined at UK population-relevant proportions of 97% white and 7% BAME (23.2% predicted versus 23.1% measured).

Thus, the Irish and UK integrated models, as case-studies, highlight how mathematical models present a viable approach to estimating changes in the population concentrations of 25(OH)D and prevalence of vitamin D deficiency that may arise from various dietary fortification approaches. Data from WP2 (above) which showed that a combined food fortification approach, which included milk and cheese as well as biofortified eggs, beef and pork, was most effective at increasing the population intakes, were used in the two models in terms of predicting population serum 25(OH)D distributions arising from changes in vitamin D intake arising from food-based solutions for prevention of vitamin D deficiency, while accounting for solar UVB-derived sources. The combined food fortification approach brought about 39-46% modelled reductions on the prevalence of vitamin D deficiency in these two populations. Such models can be of great utility to public health bodies in devising food-based strategies and policies. Equivalent models could be considered for other age-groups, once the underpinning data are available. This work is currently in preparation for peer review and the full data and findings will be made publically available after publication.

The sun exposure trial (at 12-14% skin area exposure) within WP3, which explored the response of serum 25(OH)D to UVB exposure in a controlled human study with artificial UV light to provide data to test whether simulated summer UVB exposure level of public health relevance, was also successfully completed in 55 volunteers. The results show that exposure of hands, forearms and face only to simulated Manchester summer sunlight in white Caucasian adults produces a small but significant increase in circulating serum 25(OH)D. This resulted in over three-quarters with serum 25(OH)D concentrations above a deficiency cut-off (30 nmol/L) but only about one quarter of the volunteers achieving circulating 25(OH)D \geq 50 nmol/L, reflective of vitamin D adequacy. These findings are important in terms of informing the impact of summer sunlight exposure on vitamin D status. The urinary-based biomarker of DNA damage in skin was not found to be sensitive enough to explore whether such beneficial exposures from a vitamin D perspective, had any adverse consequences in terms of DNA damage in skin. This work is currently in preparation for peer review and the full data and findings will be made publically available after publication.

Work package 4 (and part of WP6): Dietary requirements for vitamin D in under-researched population subgroups using dose-response RCTs

Pregnancy and infancy are life-stages for which evidence of low vitamin D status is widespread but the evidence basis for setting dietary requirements for vitamin D is weakest. Currently, dietary recommendations for pregnant and lactating women are the same as for non-pregnant individuals, due to the absence of dose-response trial data on which to base pregnancy-specific recommendations. At a minimum, maternal vitamin D deficiency should be prevented to safeguard fetal skeletal development. However, due to the gap between maternal and fetal circulating 25-hydroxyvitamin D, maternal deficiency prevention will not ensure fetal protection. We proposed that maternal vitamin D recommendations must be established from the perspective of the fetal requirement, which is unknown. This signifies a paradigm shift in determining nutritional requirements during pregnancy. Dietary requirements for vitamin D during both childhood and adolescence have been predominantly based on two studies in 8 and 11 y olds, leaving under-8's and over-12's unanswered. Finally,

it is not known whether ethnic differences in the response to vitamin D supplementation affects dietary requirements for vitamin D, which has implications for policy makers, consumers, the medical profession and the food industry. Accordingly, the main objectives of WP4 were to conduct 3 dose-response RCTs in Northern European countries (UK, Denmark and Ireland) to establish the distribution of vitamin D dietary requirements for the maintenance of winter serum 25(OH)D concentrations at threshold levels ranging from 30 to 50 nmol/L in children and adolescents and to estimate the dietary intake of vitamin D required to maintain maternal 25(OH)D in late gestation at concentrations sufficient to prevent neonatal deficiency at the 25-30 nmol/L threshold. Likewise, one of the key objectives in WP6 was to conduct a dose-response RCT to establish vitamin D requirements of adults of non-European race/ethnicity resident in Helsinki, Finland during wintertime.

All four of these vitamin D requirement RCTs were successfully completed safely and to a high standard. The two WP4 dose-response RCTs to establish the dietary requirement for vitamin D in children and adolescents were both published in the same issue of the *American Journal of Clinical Nutrition* in 2017 (available under open access at: <https://www.ncbi.nlm.nih.gov/pubmed/27733403> and <https://www.ncbi.nlm.nih.gov/pubmed/27655438>, respectively). The new vitamin D requirement estimates from these two papers attracted an accompanying editorial in the *American Journal of Clinical Nutrition* (open access at <https://www.ncbi.nlm.nih.gov/pubmed/27733393>), which highlighted the importance of the data. The data from these two RCTs have also been combined with data from 5 other vitamin D RCTs and used in the ODIN-based individual participant data (IPD)-level meta-regression analyses of vitamin D requirements, the first of its kind and published in 2017 in *Nutrients* (open access at <https://www.ncbi.nlm.nih.gov/pubmed/28481259>). This important IPD analyses of vitamin D dietary requirements within ODIN clearly showed the benefit of using pooled data from individual participants in vitamin D RCTs compared to the aggregate-based approach used by several of the authoritative agencies in their re-evaluation of vitamin D requirements. The former captures the between-individual variability, where the latter does not (see below), and such variability is of intrinsic importance to establishing RDA estimates.

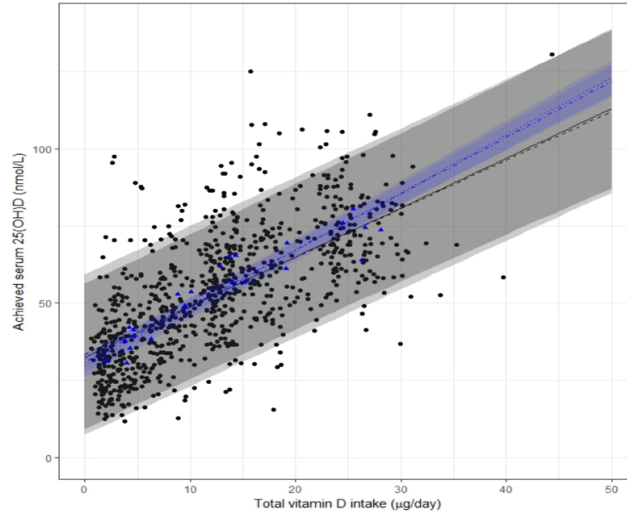


FIGURE 1. The relation between serum 25-hydroxyvitamin D [25(OH)D] concentrations (in late winter) and total vitamin D intake (diet and supplemental) in healthy persons aged 4-86 years ($n=882$) living at northerly latitudes (between 51 and 60°N): The solid and dashed lines through the black circle data points correspond to the fitted regression lines based on the (age and baseline 25(OH)D adjusted) 2-step and 1-step IPD analyses; respectively, and their corresponding 95% prediction bands are shown in light shades of grey, the lightest being the band for the 1-step IPD analysis. The fitted regression lines for the unadjusted and age and baseline 25(OH)D adjusted standard meta-regression based on aggregate data from same RCTs (blue triangles) are shown as dotted and dotdashed lines with corresponding 95% confidence bands shown in light shades of blue.

The 3rd WP4 vitamin D RCT in pregnant women is in press at the *American Journal of Clinical Nutrition* (DOI: *nqy064*). Briefly, the study showed that 30 µg/d vitamin D safely maintained serum 25(OH)D concentrations ≥ 50 nmol/L in almost all white-skinned women during pregnancy at northern latitude, which kept 25(OH)D >25 nmol/L in 99% and ≥ 30 nmol/L in 95% of umbilical cord sera.

The main group findings of the WP6 Vitamin D RCT in Finnish Caucasian women and women of East African descent resident in Helsinki will soon be published in the *British Journal of Nutrition* (in press), and the associated vitamin D requirement data from this trial will be submitted for publication during Q1 2018.

The major vitamin D dietary requirement outcomes of these WP4 and WP6 RCTs in children, adolescents, and the IPD analyses as well as that in pregnancy and in women of East African descent versus those of white descent are shown in summary form in the Table below:

Table. ODIN-derived dietary requirements for vitamin D for under-researched population subgroups as well as its IPD-derived estimates

Serum 25(OH)D cut-off ¹	≥ 30 nmol/L		≥ 50 nmol/L
	RDA (µg/d) ²	EAR (µg/d) ³	RDA(µg/d) ²
Children (4-8 y)	8.3 (6.9, 10.2)	8.0 (6.8, 9.2)	19.5 (17.2, 23.0)
Teenagers (14-18 y)	13.1 (10.5, 16.6)	11.6 (9.2, 13.9)	>30
IPD estimate (4-90 y)	12.7 (10.0, 15.5)	10.4 (8.6, 12.3)	25.7 (21.2, 30.2)
Pregnancy ⁴	13.8 (8.8, 18.1)	-	28.9 (20.6, 41.1)

¹25(OH)D, 25-hydroxyvitamin D; IPD, individual participant-level data.

²The vitamin D intake that will maintain serum 25(OH)D concentrations in 97.5% of individuals above the indicated cut-off concentration during winter, representing a Recommended Dietary Allowance (RDA).

³The vitamin D intake that will maintain serum 25(OH)D concentrations in 50% of individuals above the indicated cut-off concentration during winter, representing an Estimated Average Requirement (EAR).

⁴Based on year-round estimates.

- The individual RCTs show that intakes in the range of 8 to 13 µg/day are needed to ensure that nearly all (i.e., 97.5%) white children and teenagers avoid vitamin D deficiency (serum 25(OH)D <30 nmol/L) during winter at Northern latitudes. This agrees well with the estimate from the IPD analysis based on 7 RCT ($n=882$), namely 12.7 µg/day.
- The two individual RCTs also show that in relation to adequacy (serum 25(OH)D ≥50 nmol/L) during winter at Northern latitudes, intakes in the range of 8 to 12 µg/day are needed to ensure that half, and 20 to ~30 µg/day are needed to ensure nearly all (i.e., 97.5%), reach this cut-off.
- The RCT in pregnancy shows that intakes of 14 and 30 µg/day are needed to ensure that 25(OH)D concentrations in pregnant women are > 30 nmol/L and >50 nmol/L, respectively. Maintenance of maternal 25(OH)D > 50 nmol/L prevents umbilical cord concentrations < 30 nmol/L in 95% of infants, on a year-round basis.
- Dietary requirements for vitamin D are significantly higher in women of East African descent than in women of Finnish descent. This work is currently in preparation for peer review and the full data and findings will be made publically available after publication.

Work package 5: Food- and food-technology-based solutions for prevention of vitamin D deficiency: Natural sources, fortification and biofortification with vitamin D₂/D₃ and 25-hydroxyvitamin D.




The main objectives of WP5 were to explore technological solutions in the food sector which may underpin sustainable food-based strategies, beyond fluid milk and fat spreads, to bridge the gap between current intakes of vitamin D in European populations and dietary targets and in so doing help prevent vitamin D deficiency. The advantages and limitations of such technological solutions were evaluated using a combination of animal and human studies.




Much of the new data from these WP5 studies on UVB-exposed mushrooms and bakers' yeast, vitamin D-biofortified eggs, beef, pork and cultured fish, as well as vitamin D-fortified, low-fat, cheese have been, or are in preparation, for publication (see Table below). The investigation of the potential advantages and limitations of use of UVB-exposed mushrooms and bakers' yeast food-based solutions for prevention of vitamin D deficiency has clearly shown that from a technological perspective dramatic increases in the content of vitamin D₂ in the food produce is feasible, but evidence of their efficacy in terms of raising serum 25(OH)D in RCTs is more mixed. The vitamin D₂ in the UVB-exposed yeast survived baking and was confirmed analytically in the resulting bread, but it did not induce an increase in serum total 25(OH)D (i.e., 25(OH)D₂ plus 25(OH)D₃) in subjects who consumed the bread over 8 weeks of winter in Finland as part of one of our ODIN WP5 RCTs (paper published in *British Journal of Nutrition*; <https://www.ncbi.nlm.nih.gov/pubmed/26864127>). The paper suggested that these findings are likely stemming from the fact that the vitamin D₂ was not bioavailable to transit the intestine into the circulation, which interestingly has since being shown in an *in vitro* digestion model also. Likewise, despite dramatic increases in vitamin D₂ content of UV exposed mushrooms, their effect on serum total 25(OH)D in available RCTs is very variable. The meta-analysis performed in WP5 suggested that individuals with lower vitamin D status may get the benefit, but potentially not those with higher vitamin D status (paper published in *Journal of Nutrition*; <https://www.ncbi.nlm.nih.gov/pubmed/26865648>), although this should be confirmed experimentally.

The feeding studies in pigs, cattle, and farmed fish within WP5 exploring the potential of biofortification (enhancement via inclusion of additional vitamin D and/or 25-hydroxyvitamin D [in the case of fish and pigs] in feedstuffs) demonstrated that small to moderate increases in the total vitamin D activity of the resulting meats/fish flesh are achievable. In contrast the hen feeding study showed that eggs containing about 5 µg total vitamin D activity/egg could be generated by this biofortification means, and this had a measurable impact on winter-time prevalence of vitamin D deficiency in a RCT of older adults (published in the *American Journal of Clinical Nutrition*; <https://www.ncbi.nlm.nih.gov/pubmed/27488236>). A dedicated food-based RCT in WP5, which aimed to provide proof of effectiveness of a novel, vitamin D-fortified food, showed that consumption of 60 g of vitamin D₃ enriched, reduced-fat Gouda type cheese (providing a daily dose of 5.7 µg of additional vitamin D₃) was effective in increasing mean serum 25(OH)D concentration and in counteracting of vitamin D deficiency during winter months in postmenopausal women in Greece. This work was published in the *European Journal of Nutrition* (open access at: <https://www.ncbi.nlm.nih.gov/pubmed/27449925>).

Overall, these WP5 data informed the modelling experiments in WP2 and 3. WP5 also tested the possibility of novel treatment of hens and pigs with UV light to mimic summer sunshine, on vitamin D activity of eggs and pork. For hens, the UV dose/treatment which did not lead to erythema was not sufficient to increase the vitamin D content of eggs, while for pigs it could increase the total vitamin D activity of pork. Further research on the potential of use of artificial UV light as a means of increasing vitamin D in animal foods is necessary.

Table. Technological advances for improving the vitamin D content in selected priority food groups/products, their associated knowledge gaps, and how ODIN research tackled.

Food grouping	Pre-ODIN vit D nutritional value	Technological advances for improving the vitamin D content	Associated knowledge gaps related to these advances	What has ODIN added to our knowledge in this area?
Mushrooms 	~0.1µg/100 g cultivated mushrooms	<ul style="list-style-type: none"> • Irradiation of mushrooms with UVB light can dramatically increase the content of vitamin D₂ • These vitamin D₂-enriched mushrooms can be consumer as is or can be powdered (via freeze-drying and grinding) and included in appropriate food products e.g., breads amongst others. 	<ul style="list-style-type: none"> • The stability of vitamin D₂ in foods made from the powdered UVB-exposed mushrooms is unclear • Will increased consumption of D₂-enhanced mushrooms, and associated food products, reduce serum 25(OH)D₃ concentration? 	<p>An artificial UV-B dose of 0.53 J/cm² raised the mushroom vitamin D₂ content to much higher levels of 67.1 ± 9.9 µg/g dry weight (DW) than sun exposure (3.9 ± 0.8 µg/g DW), and both much higher than normal mushroom levels(see opposite). https://www.ncbi.nlm.nih.gov/pubmed/26314311 https://www.ncbi.nlm.nih.gov/pubmed/27323764</p> <p>A systematic review and meta-analysis of responses of serum 25(OH)D₂ and 25(OH)D₃ to consumption of UV-exposed mushrooms by healthy participants shows that, while variable, their consumption may increase serum total 25(OH)D when baseline vitamin D status is low via an increase in 25(OH)D₂ and despite a concomitant but relatively smaller reduction in 25(OH)D₃. When baseline vitamin D status is high, the increase in 25(OH)D₂ and a relatively similar reduction in 25(OH)D₃ may explain the lack of effect overall. This needs to be confirmed experimentally. https://www.ncbi.nlm.nih.gov/pubmed/26865648</p>
Bread 	<5% of the Mean Daily Intake of vitamin D [MDI]	<ul style="list-style-type: none"> • Vitamin D baker's yeast (using UVB light to enhance its vitamin D₂) has been approved by the US FDA. Thus, by its inclusion in breads and other appropriate baked products, this could be an important product in improving vitamin D status. 	<ul style="list-style-type: none"> • The bioavailability of the vitamin D₂ from the yeast in bakery products is unclear. • Will increased consumption of D₂-enhanced breads reduce serum 25(OH)D₃ concentration? 	<p>The efficacy of biofortified yeast as a source of vitamin D₂ was evaluated using a single-blind, randomised, placebo-controlled RCT conducted over wintertime in adult women in Finland.</p> <p>Vitamin D₂ from UV-irradiated yeast in bread (confirmed by HPLC after baking) was not bioavailable in humans. https://www.ncbi.nlm.nih.gov/pubmed/26864127. Bread with vit D₂ added, while increasing serum 25(OH)D₂, it reduced 25(OH)D₃.</p>
Fish 	Fish [combined] 14% MDI: Wild salmon 25 µg/100 g v. Farmed salmon 6 µg/100 g	<ul style="list-style-type: none"> • Article 9t (b) of Council Directive 70/524/EEC allows a max. content of 3000 IU vit D₃/kg feed for fish. • Micro and macro-algae has been suggested as a natural form for use in vitamin D bio-fortification of fish. • HyD[®] is commercially available. 	<ul style="list-style-type: none"> • Levels of vitamin D₃ and 25-hydroxyvitamin D achieved in farmed fish with these various feeding approaches are not clear. • The feasibility of use of micro- and macro-algae for vitamin D biofortification purposes in fish has not be assessed, and has not compared with more traditional approaches of addition of synthetic vitamin D₃ to fish feeds. 	<p>A dose-related vitamin D feeding trial in cultured salmon showed that at a high dietary level (57,600 IU/kg diet), the salmon fillet contained 10.2 µg total vitamin D activity/100 g. Lower levels of dietary inclusion were less effective.</p> <p>UV treatment of micro-algae dramatically increased their vitamin D₂ content, but this is not well utilised by fish. Micro-algae used to microencapsulate vitamin D₃ was tested in feeding trials with cultured seabream and trout, and was found to be no more effective than traditional fortification of feeds with vit D₃ or HyD[®] (all at 3000 IU/kg); and none showed major benefit over the usual addition level (1200 IU/kg).</p>

<p>Eggs</p> 	<p>9% MDI</p>	<ul style="list-style-type: none"> • Article 9t (b) of Council Directive 70/524/EEC allows a maximum content of 3000 IU vitamin D₃/kg feed for poultry. • 25-hydroxyvitamin D (HyD[®]) is commercially available for poultry feeds. • Irradiation of chickens with UVB light has been shown to replace the need for vitamin D in feed. 	<ul style="list-style-type: none"> • Levels of vitamin D₃ and 25-hydroxyvitamin D achieved in eggs with these feed-based approaches are not clear. • The bioavailability of vitamin D₃ and 25-hydroxyvitamin D from eggs in humans is unclear. • Irradiation of hens with UVB light may be able to dramatically increase the content of egg but this has not been tested. 	<p>A hen feeding trial with vitamin D₃ or HyD[®] showed that HyD[®] (3000 IU/kg equiv) had the highest total vitamin D egg yolk content (5.1 µg/egg) compared to 3000 IU/kg vit D₃. https://www.sciencedirect.com/science/article/pii/S1466856416305604</p> <p>A RCT investigating the effect of the consumption of vitamin D-enhanced eggs (produced by feeding hens at the maximum concentration of vitamin D₃ or HyD[®] lawfully allowed in feed) on winter serum 25(OH)D in healthy adults showed that weekly consumption of 7 vitamin D-enhanced eggs has an important impact on winter vitamin D status in adults. https://www.ncbi.nlm.nih.gov/pubmed/27488236</p> <p>While it is technically feasible to increase the egg vitamin D content by exposing hens to UVB light, the UVB dosage/exposure at which there is no accompanying adverse effect on hens needs to be further investigated.</p>
<p>Meat: <i>Beef</i></p>  <p><i>Pork</i></p> 	<p>26% MDI [as combined food group]</p>	<ul style="list-style-type: none"> • Article 9t (b) of Council Directive 70/524/EEC allows a maximum content of vitamin D/kg of feed: <ul style="list-style-type: none"> - 4000 IU vit D₂ or D₃/kg for cattle. - 2000 IU vit D₂ or D₃/kg for pigs. • HyD[®] is commercially available for use in animal feeds. • The UVB-exposed mushroom powder (above) is also suitable for use in animal feedstuffs. • Irradiation of pigs with UVB light has been suggested as a possible mechanism for enhancing the vitamin D content of pig meat. 	<ul style="list-style-type: none"> • Data to suggest that vitamin D₂ and D₃ in feeds for pigs and cattle are equivalent is lacking. • The impact of HyD[®] (plus/minus vitamin D) in animal feedstuffs on vitamin D₃ and 25-hydroxyvitamin D in beef, pig meat is not clear. • Impact of UV light treatment of pigs and resulting pig meat vitamin D content is not clear. 	<p>A feeding trial showed that supplementation of beef heifer diets with vit D₃ yielded higher (<i>P</i><0.001) beef total vitamin D activity (by 30-49%; <i>P</i><0.05) [1.4 µg/100 g] and serum total 25(OH)D (by 26-36%; <i>P</i><0.05), compared to that from Vit D₂ and Mushroom D₂ (all 4000 IU/kg) supplemented animals; no significant differences (<i>P</i>>0.05) in the latter 2 groups. https://www.sciencedirect.com/science/article/pii/S0308814618303364</p> <p>A feeding trial showed that supplementation of pig diets with vit D₃ yielded higher (by ~40%; <i>P</i><0.05) pork total vitamin D activity [0.8 µg/100 g] compared to that from Vit D₂ and Mushroom D₂ (all 2000 IU/kg) supplemented animals; no significant differences (<i>P</i>>0.05) in the latter 2 groups. (<i>in press in Meat Science</i>)</p> <p>HyD[®] is not as yet permitted for use in cattle in Europe, but is allowed for pigs and in a feeding trial was shown to have greatest effect on raising serum 25(OH)D and pork total vitamin D activity [1.3 µg/100 g] compared to D₃ and/or D₂.</p> <p>UV treatment of pigs using UV emitting LEDs, at a dose which did not induce erythema, led to a total vitamin D activity level in pork comparable to that achieved with the HyD[®] - supplemented diet.</p>

Work package 6: *Proof of effectiveness of food-based solutions to prevent vitamin D deficiency*

A systematic review and meta-analysis from the *Cork Centre for Vitamin D and Nutrition Research* of RCTs using vitamin D-fortified foods concluded that while fortified foods increase serum 25(OH)D, the evidence from the limited number of trials to date is too fragmented to confirm proof of efficacy of food-based solutions to prevent deficiency. Thus, building on data from WPs 2 and 5, the main objectives of WP6 were to deliver this proof of efficacy and safety by focussing the research effort on EU-resident adults who are most at risk of vitamin D deficiency either due to skin colour, sun exposure practices or dietary habits, in two ways: firstly, by carrying out a food-based RCT in white and South Asian women in Copenhagen and secondly, by completing a new trial- and individual participant data (IPD)-level meta-analysis and meta-regression of food-based RCTs conducted by WP6 participants within and outside of ODIN. As mentioned above under WP4 for ease, WP6 also had the vitamin D requirement RCT in ethnic versus white adult women.

WP6 was completed on schedule (month 44) and the data from both tasks are in preparation for publication. The aim of the WP6 food-based RCT was to investigate the efficiency and safety of relatively low-dose vitamin D fortification of four different foods (designed to collectively deliver an extra 10-20 µg vitamin D/d) to prevent vitamin D deficiency (serum 25(OH)D <30 nmol/L) in white and South Asian women at high risk of vitamin D deficiency in Copenhagen during 3 months of winter. The mean baseline serum 25(OH)D in the Danish and the Pakistani groups was ~50 nmol/L. Inclusion of the four vitamin D-fortified foods contributed to a median vitamin D intake of 30 µg/day, and when given over 12 weeks of winter was effective in increasing the mean serum 25(OH)D in both groups of women living in Denmark. The Danish women had a greater response to the vitamin D-fortified foods than did the Pakistani women. None of the Danish women and only 3% of the Pakistani women consuming the vitamin D-fortified foods had serum 25(OH)D <30 nmol/L at endpoint, whereas 13 and 20% of Danish and Pakistani women receiving the placebo, non-fortified foods, respectively, had serum 25(OH)D <30 nmol/L at endpoint of the 3-month, winter-based RCT. This work is currently in preparation for peer review and the full data and findings will be made publically available after publication.

The aims of the new WP6 trial- and IPD-level meta-analysis and meta-regression of food-based RCTs conducted by WP6 participants were firstly, to evaluate the impact of food fortification interventions on reducing the prevalence of vitamin D deficiency and secondly, using the approach developed under WP4 (above) to conduct the first-ever IPD-level meta-regression analyses of the response of winter serum 25(OH)D to increased vitamin D intake, again in a European-based RCT setting but in this WP, the increased vitamin D intake arose from consumption of vitamin D-fortified/enhanced foods. A total of five winter-based RCTs with vitamin D-fortified/enhanced foods conducted in Europe were identified – two RCTs were from ODIN, one was ODIN associated (but funded by the Irish government) and two other RCTs were from ODIN partners but funded nationally (UK and Denmark). An *a priori* criteria was that the RCTs were limited to those of only white adults and with foods with enhanced vitamin D₃ content. With combined data from the five food-based vitamin D RCTs (784 participants; 390 treated and 394 controls), a random effects meta-analysis showed a highly significant ($P < 0.00001$) treatment effect on serum total 25(OH)D concentration. While there was a high degree of heterogeneity across the five RCTs ($I^2 = 99\%$; $P < 0.00001$), and thus

warranting some caution in the interpretation of the treatment effect, the point estimates for all RCTs showed a statistically significant effect of vitamin D-fortified/enhanced food consumption on serum total 25(OH)D. Meta-analysis of the five RCTs also showed that the odds of vitamin D deficiency in winter was dramatically lower ($P < 0.00001$) for those participants consuming vitamin D-fortified/enhanced foods compared to those not consuming such foods. This work will be presented for peer review once the above WP6 food-based RCT paper is published, and the full data and findings will be made publically available after publication.

Based on a 2-step non-linear IPD meta-regression model of these food-based vitamin D RCTs (as per WP4 IPD meta-regression analysis of supplemental vitamin D), the vitamin D intake estimates required to maintain serum 25(OH)D concentrations above the various thresholds used by the various regulatory agencies were very similar to those derived from our earlier IPD analysis.

Overall, the new WP6 food-based RCT as well as the IPD meta-regression analyses of five food-based vitamin D RCTs, the first of its kind, shows how an increased vitamin D intake would keep most people above the proposed thresholds below which the risk of clinical vitamin D deficiency increases. The constituent RCTs used in our IPD analyses highlight the feasibility by which inclusion of the vitamin D-fortified/enhanced foods in the diet can allow for such intakes to be achieved as well as also demonstrating the lack of technological and consumer acceptability barriers to the production of vitamin D-fortified/enhanced foods.

Work package 7: *Vitamin D and health outcomes in pregnancy and early life*

The potential role of vitamin D in supporting a healthy pregnancy and promoting optimal growth and development remains unresolved. Conflicting results in these life stages are due to a number of factors, primarily the dearth of prospectively collected, clinically validated data on health outcomes, inadequate subject phenotyping and analytical differences in quantifying 25(OH)D. Accordingly, the main objectives of WP7 were to examine proposed associations between vitamin D status and perinatal and infant outcomes. Maternal determinants of circulating serum 25(OH)D in neonates at delivery and factors that influence the vitamin D composition of human milk were to be described. WP7 would examine the interactions between vitamin D status during pregnancy and infancy and skeletal development and body composition in children. In addition, an analysis to elucidate the vitamin D hypothesis with respect to atopic disorders, including eczema and asthma, would be conducted. These objectives were to be realized using the strategy adopted throughout ODIN, which is to partner with ongoing and existing projects to achieve critical mass both in the quality of the biobanks and datasets employed and to enlist the specialist expertise required to address the question of vitamin D and health in these vulnerable and neglected life stages.

WP7 was successfully completed during the course of ODIN. We published the first report of CDC-accredited 25(OH)D data and pregnancy outcomes from a clinically validated prospective pregnancy cohort study of 1786 primiparous women based in Cork. This paper was published in the *American Journal of Clinical Nutrition* (available under open access at: <https://www.ncbi.nlm.nih.gov/pubmed/27357092>) and described a 36% reduction in risk of uteroplacental dysfunction, indicated by a composite outcome of small for gestational age

birth and pre-eclampsia, among women who had circulating 25(OH)D concentrations of at least 75 nmol/L. We also explored the concept of functional vitamin D deficiency and calcium metabolic stress in the SCOPE pregnancy cohort, by analysing intact parathyroid hormone in 1800 women at 15 weeks of gestation, and conducting a stratified analysis to examine the differential effects of low vitamin D status concomitant with high PTH, on perinatal outcomes. The data, currently under review, showed that the risk of elevated mean arterial pressure and SGA birth were elevated with functional vitamin D deficiency, suggesting that trials to determine the effects of vitamin D on perinatal health should consider the effects of calcium nutrition in the study design.

We went on to apply the validated protocols developed in the Vitamin D Standardization Programme to two additional commensurate prospective pregnancy cohort studies in the UK (Southampton Women's Study, SWS) and Sweden (GraviD), giving a total sample size of 5928, and described the distribution of 25(OH)D across the cohorts and the prevalence of low vitamin D status, using a number of internationally recognized thresholds. Our analysis showed that the standardised prevalence of 25(OH)D concentrations below the IOM threshold indicating increased risk of vitamin D deficiency ranged from 5% in the SWS cohort, in late pregnancy to 17% in SCOPE Ireland cohort in Cork. The overall prevalence of vitamin D deficiency among this sample of almost 6000 women in early pregnancy in the UK, Sweden and Ireland was 14.7%, or 1 in 7 women. In early pregnancy, 38-49% had 25(OH)D <50 nmol/L, with an average prevalence of 43.6% across the three cohorts and 75-88% of women had 25(OH)D < 75nmol/L in early pregnancy. This study, which is the first to extend the VDSP protocols to perinatal cohorts, describe the only commensurate pregnancy cohorts that have standardised 25(OH)D data, and thus represent the largest source of reliable information on vitamin D status in early pregnancy to date. Extension of the VDSP to additional contemporary cohorts with well-curated and biobanked species is of crucial importance to understand the extent of the vitamin D deficiency problem and its implications for perinatal health. The study is being prepared for peer review during 2018.

In our analysis of infant health outcomes, WP7 started by completing an IPD analysis of 3 existing studies of maternal-infant pairs in Denmark and Ireland to describe the early life predictors of neonatal and infant vitamin D status. The data showed that at birth, a high proportion of infants had 25(OH)D < 50 nmol/L when mothers were unsupplemented during pregnancy, particularly infants born during wintertime. In early life, a daily vitamin D supplement of 10 µg seemed to assure replete vitamin D status without causing risk of excessive 25(OH)D concentrations among partially breastfed or weaned infants who also received vitamin D from infant formula. In a large prospective birth cohort in Cork, we published the first CDC-accredited data on 25(OH)D, as well as the 3-epimer of 25(OH)D₃, in 1050 umbilical cords (open access the *Journal of Steroid Biochemistry and Molecular Biology* at <https://www.sciencedirect.com/science/article/pii/S0960076016303454?via%3Dihub>).

Overall, 35% of cords (50% during winter) had 25(OH)D <25 nmol/L, 46% were <30 nmol/L and 80% were <50 nmol/L. In this predominantly white cohort, the main predictor of cord 25(OH)D was summer delivery. Maternal smoking during pregnancy (9% prevalence) was negatively associated with cord 25(OH)D and there were no associations between cord 25(OH)D and birth weight or any anthropometric measures at birth. Despite the high prevalence of vitamin D deficiency at birth, there were no documented musculoskeletal complications during infancy, which was likely due to widespread supplementation with vitamin D. The proportion of 25(OH)D as 3-epi-25(OH)D₃ was 11.2% and cord 3-epi-25(OH)D₃

concentrations were strongly associated with cord 25(OH)D₃. For the first time, we reported a negative association of 3-epi-25(OH)D₃ with gestational age and maternal age. These data provided further evidence of very low vitamin D status among infants born to un-supplemented mothers.

Analysis of the vitamin D content of 750 bio-banked human milk samples was conducted using the Aarhus LC-MS/MS platform for human milk analysis in four separate studies of lactation that were carried out in Ireland, Denmark (2 studies) and the Gambia. The vitamin D content of milk ranged from 1.3 to 3.7 µg of total vitamin D activity/L.

We estimated that an exclusively breastfed infant whose mother had adequate vitamin D status would receive ~2 µg /day of vitamin D, assuming an average consumption of milk of ~750 ml/day (up to 6 months of age). This is 20% of the adequate intake (AI) of 10 µg. Factors that were important influencers of the vitamin D content of human milk were maternal vitamin D status, milk its fat content and the number of days postpartum when the sample was collected. Maternal BMI had a negative association with milk vitamin D content in the Cork study, as did circulating parathyroid hormone.

As the evidence for a relationship between *in utero* vitamin D exposure and atopic disease has been inconsistent, we sought to interrogate two extensively characterised, disease-specific maternal-infant cohorts with gold standard analysis of antenatal and umbilical cord vitamin D status and clinically validated atopic outcomes, to investigate the potential role of intrauterine vitamin D exposure in the development of atopic disease. We undertook a comprehensive evaluation of the relationship between intrauterine vitamin D exposure and the development of eczema, food allergies, asthma and other atopic disorders using data from the Cork BASELINE Birth Cohort (BASELINE) and the Manchester Asthma and Allergy Study (MAAS). Serum 25(OH)D and vitamin D metabolite concentrations for 1035 infants in BASELINE and 458 infants in MAAS were analysed at University College Cork. The BASELINE and MAAS cohorts differed in terms of the (self-reported) inherited risk of atopy. In BASELINE, 49% of mothers and 37% of fathers reported a previous history of atopy; both parents reported atopic history in 19% of children. In MAAS, 72% of infants were categorised as high-risk, with atopy in both parents and 18% of infants were categorised as low risk, with no parental history. Analysis of the BASELINE cohort did not show any significant independent association between intrauterine vitamin D exposures and clinically validated atopic disease outcomes. In MAAS, umbilical cord 25(OH)D was associated with atopy. A per 10nmol/L increment was positively associated with a 27% and 30% greater likelihood of a positive skin prick test (SPT) response for pollen at 3 years and for grass at 8 years, respectively. Each 10nmol/L increase in cord 25(OH)D was associated with a 36, 40 and 45% increase in likelihood of serum IgE-defined sensitivity to grass at 5 and 8 years and for peanut at 8 years, respectively. Cord vitamin D concentrations (per 10nmol/L) were also significantly associated with increased odds of allergic rhinitis at 11 years [OR (95%CI): 1.17 (1.00, 1.38)], but not with asthma at 5 years. These data are currently under review.

With regard to infant growth and bone mineral density, the question of whether increasing maternal vitamin D status during in pregnancy might improve offspring bone development remains unresolved. In particular, there is a paucity of data relating to long-term follow-up of children. Interpretation of this data is also limited by variability in 25-hydroxyvitamin D (25(OH)D) analysis, sampling and population differences. In WP7, we conducted a meta-analysis using data from two commensurate mother-offspring observational birth cohort

studies: The Southampton Women's Survey (SWS) and the SCOPE-BASELINE Cork Birth Cohort Study. Serum 25(OH)D at 11 and 34 weeks in SWS and at 15 and in umbilical cord samples in BASELINE were analysed. At 6 years of age, children in SWS underwent a whole body and lumbar spine DXA scan. Whole body and lumbar spine DXA assessments were carried out in BASELINE children at 5 years of age. Maternal 25(OH)D assessments were grouped into early and late pregnancy/cord and associations with bone mineralisation were investigated with 25(OH)D as a continuous and binary predictor. Early pregnancy 25(OH)D and childhood DXA data were available for 879 and 440 mother-offspring pairs in SWS and SCOPE-BASELINE, respectively. 1,004 and 321 mother-offspring pairs from SWS and SCOPE-BASELINE, respectively, were included in the analysis of late pregnancy/cord 25(OH)D and offspring bone mass. There were no significant associations with early pregnancy 25(OH)D and either whole body less head (WBLH) or lumbar spine (LS) bone mineral content (BMC), bone area, bone mineral density (BMD) or size adjusted BMD in univariate or adjusted analyses. Children of mothers above a threshold of 25 nmol/L for early pregnancy 25(OH)D had significantly greater whole body BMD and trended towards higher BMC. While there were no significant associations between late pregnancy/cord 25(OH)D and offspring WBLH bone mineralisation, a positive association was identified between 25(OH)D and LS bone area and a trending association with LS BMC, which remained statistically significant in multivariate analyses. Late pregnancy/cord blood 25(OH)D > 25 nmol/l was associated with greater WBLH BMC and BMD and LS BMC and bone area, which persisted in multivariate analysis. In summary, this meta-analysis demonstrated that low maternal 25(OH)D in both early and late pregnancy and at delivery is associated with reduced bone mineralisation in early childhood.

Work package 8: *Vitamin D and health outcomes in adults: mortality and CVD*

Vitamin D deficiency is a significant predictor of all-cause mortality, cardiovascular disease (CVD) and metabolic risk factors including elevated blood pressure, impaired glucose homeostasis, dyslipidemia and systemic inflammation. Challenges in interpreting cohort and RCT data are complicated by various classifications of serum 25(OH)D concentrations, clinical outcome definitions and statistical approaches. Thus, the key objectives of WP8 were, using a standardized analytical method for 25(OH)D (as per WP1) and harmonized clinical endpoint classification, to conduct an IPD meta-analysis of seven large cohort studies and a separate IPD analysis of 11 current or completed vitamin D RCTs to elucidate associations of circulating 25(OH)D and major clinical non-skeletal outcomes, namely, overall mortality, CVD mortality, cardiovascular events, stroke, cancer, and incidence of type 2 diabetes. In addition to considering the effects of lifestyle, adiposity and diet, WP8 aimed to explore the potentially significant role for genetics (single nucleotide polymorphisms [SNP] in genes involved in the vitamin D synthesis or metabolic pathways) in determining vitamin D status and its association with clinical outcomes by performing Mendelian Randomization studies in a subset of the 8 cohorts for which SNP data was available, and which elucidate the independent effects of genotype on 25(OH)D concentration variability. These WP8 objectives were to be realized using the strategy adopted throughout ODIN mentioned above under WP7, namely to partner with ongoing and existing projects to achieve critical mass both in the quality of the biobanks and datasets employed and to enlist the specialist expertise required to address the question of vitamin D and our prioritized adult health outcomes.

WP8 was successfully completed in 2017 and the data have been, or are in preparation, for publication (see below). WP8 published the first IPD meta-analysis using standardized 25(OH)D data in *PLoS One* in 2017 (available under open access at: <https://www.ncbi.nlm.nih.gov/pubmed/28207791>). In almost 27,000 participants (median age 61.6 years, 58% females) with a median circulating 25(OH)D concentration of 53.8 nmol/L, we reported adjusted hazard ratios (with 95% confidence interval) for mortality in the 25(OH)D groups with 40 to 49.99, 30 to 39.99, and <30 nmol/L of 1.15 (1.00–1.29), 1.33 (1.16–1.51), and 1.67 (1.44–1.89), respectively, compared to participants with circulating 25(OH)D concentrations of 75 to 99.99 nmol/L, over a median follow-up time of 10.5 years (see Figure below). We observed similar results for cardiovascular mortality, but there was no significant association between 25(OH)D and cancer mortality. On the basis of this association between low circulating 25(OH)D and increased risk of all-cause mortality, it is of public health interest to evaluate whether treatment of vitamin D deficiency prevents premature deaths. Of note, the paper was included in the ‘The Top 12 Vitamin D Papers for 2017’ (source: Orthomolecular Medicine News Service, January 12, 2018).

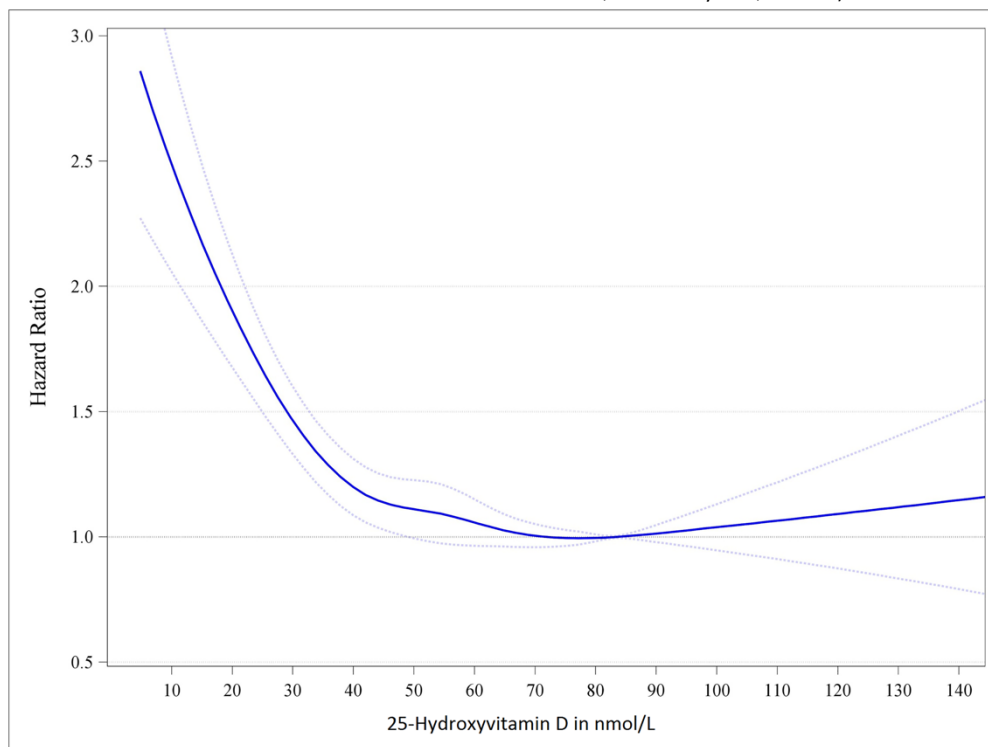


Fig 1. Dose-response trend of hazard ratios of death from all causes by standardized 25 hydroxyvitamin D. [PLoS One. 2017 Feb 16;12(2):e0170791.]

Other findings of WP8:

- The results of the Mendelian Randomization studies in three of the cohorts may argue in favour of a causal relationship between vitamin D deficiency and all-cause mortality, but with a large uncertainty in the effect size. These findings on vitamin D and mortality deserve further study and consideration in the public health discussion regarding the value of the vitamin D status of the general population. This work is currently undergoing peer review and the data and findings will be made publically available after publication.

- An IPD meta-analysis of 12 vitamin D RCTs, to study whether there are beneficial or harmful effects of vitamin D₃ supplementation according to subgroups of re-measured serum 25(OH)D on cardiovascular and gluco-metabolic surrogate markers, showed that besides its effect on parathyroid hormone, vitamin D supplementation might have a beneficial effect on low density lipoprotein cholesterol concentrations, particularly when the achieved 25(OH)D concentrations remain <125 nmol/L. Other outcomes (such as blood pressure, high density lipoprotein and total cholesterol, triglycerides, glycated haemoglobin (HbA1c), fasting glucose, insulin and C-peptide, and 2-h glucose) were unaffected by vitamin D₃ supplementation in this pooled analyses. This work is currently in press at *The American Journal of Clinical Nutrition* and the data and findings will be made publically available after publication.
- We also performed a systematic quantitative review on characteristics of RCTs included in meta-analyses on non-skeletal effects of vitamin D supplementation, published in *PLoS One* in 2017 (available under open access at: <https://www.ncbi.nlm.nih.gov/pubmed/28686645>). We identified 54 SRs including data from 210 RCTs (see below).

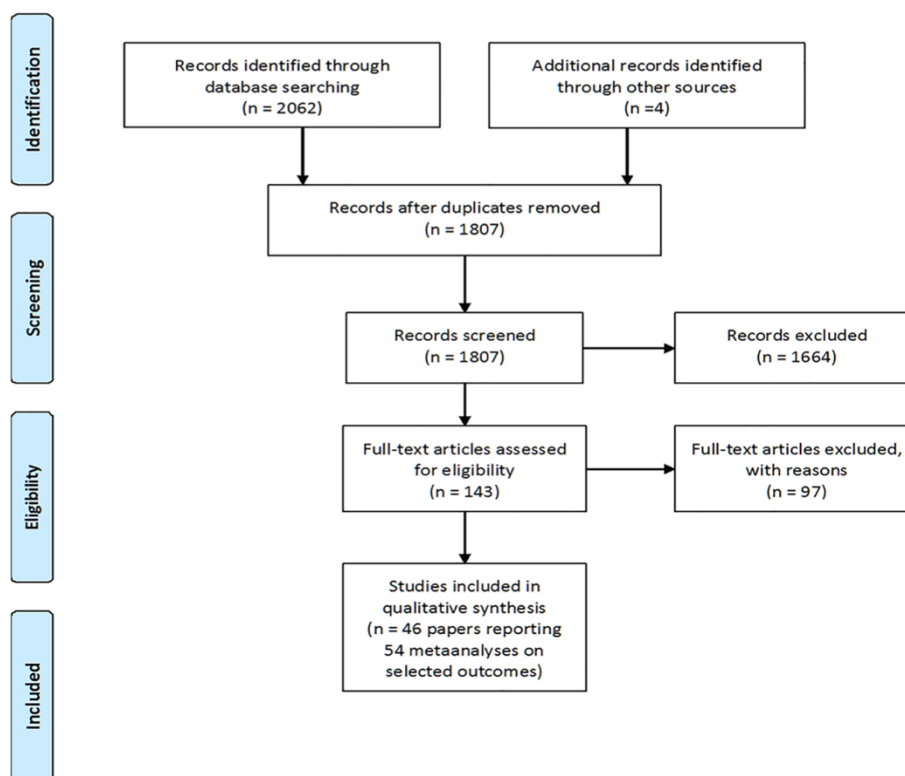


Fig 1. PRISMA flow diagram.

- Most meta-analyses as well as the individual RCTs reported null-findings on risk of cardiovascular diseases, type 2 diabetes, weight-loss, and malignant diseases. Beneficial effects of vitamin D supplementation was reported in 1 of 4 meta-analyses on depression, 2 of 9 meta-analyses on blood pressure, 3 of 7 meta-analyses on respiratory tract infections, and 8 of 12 meta-analyses on mortality. Most RCTs have primarily been performed to determine skeletal outcomes, whereas non-skeletal

effects have been assessed as secondary outcomes. Only one-third of the RCTs had low level of 25(OH)D as a criterion for inclusion and a mean baseline 25(OH)D level below 50 nmol/L was only present in less than half of the analyses. Published RCTs have mostly been performed in populations without low circulating 25(OH)D levels. The fact that most meta-analyses on results from RCTs did not show a beneficial effect does not disprove the hypothesis suggested by observational findings on adverse health outcomes of low circulating 25(OH)D levels.

Work package 9: *Safety considerations in relation to increasing vitamin D intake and serum 25(OH)D concentrations*

The main objective of WP9 was to integrate data from WPs 1-8 and compile a dossier to document all safety issues across the project. The ODIN safety dossier was to include information arising from the project on the following:

- Dietary intakes of vitamin D above the EFSA Tolerable Upper Level (50-100 µg/d; age-dependent, 2012)
- Prevalence of high serum 25(OH)D concentrations (>125 nmol/L)
- Information on adverse health effects of sustained high concentrations of serum 25(OH)D
- Animal safety issues related to increasing the vitamin D content of animal produce/foods via dietary or UVB light means (biofortification).

The risk of excessive intakes of vitamin D are close to zero following application of the fortification and bio-fortification strategies proposed in ODIN to 10 nationally representative dietary surveys of adults and children in four EU countries. Risks of excessive intakes among children and adults were attributable to vitamin D supplementation at doses of 25 µg and 50 µg/day in children and adults, respectively, using current usage of supplementation products. High serum 25(OH)D concentrations were rare in cohort studies and no adverse effects of high 25(OH)D were detected. The prevalence of serum 25(OH)D >125 nmol/L increased according to treatment dose in intervention studies, particularly >~70 µg/day. Lower doses of supplements or food-based interventions for increasing vitamin D intake were minimally associated with high 25(OH)D concentrations. Overall, out of 3,419 participants who either took part in ODIN RCTs or had previously enrolled in RCTs re-analyzed by ODIN, a total of 322 (9.4%) individuals had serum 25(OH)D >125 nmol/L and 30 (<1%) had elevated serum calcium. There were no documented adverse effects or serious adverse events associated with any of the interventions. Analysis of data from the ODIN intervention studies as well as adult, pregnancy and birth cohorts showed no evidence of adverse health effects associated with vitamin D intake, supplementation (at modest doses) or high serum 25(OH)D concentrations. This work is currently in preparation for peer review and the full data and findings will be made publically available after publication.

This summary of S&T results arising from the 9 RTD WPs were made possible not only by excellent collaboration among the partners within the ODIN consortium but also by excellent management and coordination which was effected through a highly experienced *Project Executive Management Board*, project manager and a dedicated management WP. These findings have been widely communicated and disseminated to a variety of stakeholders (see Section 4.2A below), a testament to the commitment of the project partners to publication and dissemination activities.

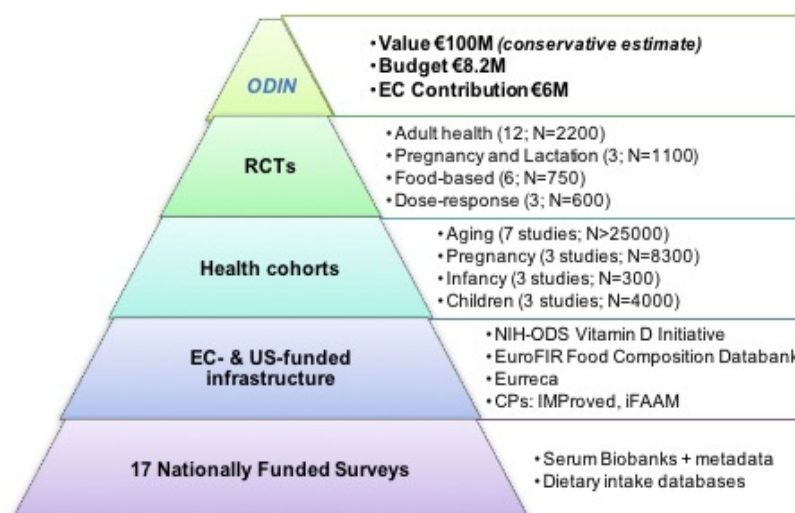
D. Impact section and dissemination/exploitation of results

The potential impact of the ODIN project's key findings

ODIN driving excellence in vitamin D research while ensuring value for money to European taxpayers

The research undertaken within ODIN which led to the project's key results, as outlined in Section C above, provided the European taxpayer with added-value to the worth of around €100M (see Figure below), as a conservative estimate. ODIN by utilizing its broad collaborative network took advantage of existing randomized controlled trials, cohorts, national health and nutrition surveys and other infrastructural capacities, including:

- 17 National nutrition (or Health) surveys/cohorts of children and adults;
- 9 Food consumption and nutrition surveys;
- 3 previous RCTs defining dietary vitamin D requirements;
- 3 previous or ongoing food-based RCTs with vitamin D in terms improving status;
- 7 large cohort studies of European adults to elucidate associations of serum 25OHD and major clinical non-skeletal outcomes;
- 11 eleven current or completed RCTs to test the effect of major clinical non-skeletal outcomes;
- 4 pregnancy and birth cohorts and 4 lactation studies;
- as well as the significant contribution of the *Vitamin D Standardization Program (VDSP)* led by the NIH, Office of Dietary Supplements, on a *pro-bono* basis.



Through its creative programme of research that incorporated and built upon these existing resource and infrastructure, ODIN was able to strategically mobilise the €6M available from the EC for the project, to deliver its priority objectives, as outlined above in Section B, and also to avoid any potential duplication. Thus, ODIN maximized national and EU resources to drive excellence in research and provide value for money to taxpayers in a challenging economic environment. This was a powerful representation of the potential to maximize national and international investment for public health and private sector gain.

Societal and associated financial implications of ODIN's findings

ODIN highlights the magnitude of the public health problem of vitamin D deficiency in Europe

By utilizing data and biobanked blood samples from 14 of the above-mentioned National nutrition (or Health) surveys/cohorts of children and adults, together with statistical resources of the VDSP, ODIN produced the first internationally comparable dataset of vitamin D status and prevalence of vitamin D deficiency in Europe. This work led to an overall pooled estimate (irrespective of age group, ethnic mix, and latitude of study populations) of 13% of the total sample size of 55,844 European individuals with serum 25(OH)D concentrations <30 nmol/L. Of note, dark-skinned ethnic subgroups had much higher (3- to 71-fold) prevalence of serum 25(OH)D <30 nmol/L than did white populations. According to an alternate suggested definition of vitamin D deficiency (serum 25(OH)D <50 nmol/L), the prevalence was 40%. Extension of the VDSP protocols into perinatal cohorts, established a prevalence of vitamin D deficiency of 15% (or 1 in 7) women in early pregnancy in the UK, Ireland and Sweden, with 44% <50 nmol/L of 25(OH)D. Thus, ODIN definitively showed that vitamin D deficiency is evident throughout the European population at prevalence rates that are concerning and that requires action from a public health perspective. These vitamin D status data form the bedrock on which to base scientific judgments, and ODIN has now provided this high-quality, priority data for Europe. This new data, which has been widely disseminated and is being highly cited already, has also raised awareness among the scientific community, policy makers, food industry as well as the general public.

Implications of these findings for disease burden

It is generally agreed that prevention of vitamin D deficiency (as defined by the conservative serum 25(OH)D threshold of <30 nmol/L) is a public health priority, for prevention of nutritional rickets and osteomalacia, which have severe and lasting consequences for bone growth and skeletal integrity throughout life. Thus, it is of great concern that even a crude estimation, based on the magnitude of European population coupled with the ODIN prevalence estimate for vitamin D deficiency, suggests something in the region of 96 million individuals deficient in Europe.

While data showing associations between vitamin D status and non-skeletal disorders are also abundant, the evidence-base is currently less robust than that for bone health. Nevertheless, many investigators in the vitamin D field concur with a serum 25(OH)D threshold of <50 nmol/L to designate vitamin D deficiency for protection of skeletal and non-skeletal health. ODIN again utilized its broad collaborative network and, by accessing 8 cohort studies in European adults and older adults and utilizing the VDSP protocols, was able to undertake the first individual participant data (IPD) meta-analysis using standardized serum 25(OH)D data. In almost 27,000 participants (median age 61.6 years, 58% females) with a median 25(OH)D concentration of 53.8 nmol/L, ODIN reported adjusted hazard ratios (with 95% confidence interval) for mortality in the 25(OH)D groups with 40 to 49.99, 30 to 39.99, and <30 nmol/L of 1.15 (1.00–1.29), 1.33 (1.16–1.51), and 1.67 (1.44–1.89), respectively, compared to participants with 25(OH)D concentrations of 75 to 99.99 nmol/L, over a median follow-up time of 10.5 years. ODIN observed similar results for cardiovascular mortality, but there was no significant association between 25(OH)D and cancer mortality. These important observational findings suggest a 67% higher risk of death from all causes in

those with serum 25(OH)D <30 nmol/L. In our investigation of perinatal and infant health outcomes in WP7, ODIN showed that having high vitamin D status during pregnancy was associated with reduced risk of small for gestational age birth and pre-eclampsia. Our analysis of neonatal vitamin D status indicated a very high prevalence of deficiency, particularly among infants born to mothers who did not receive antenatal nutritional supplementation. In children in the North of England with high inherited risk of atopy, ODIN observed a positive association of cord 25(OH)D and skin prick test- and IgE-defined sensitivity to pollen and grass throughout childhood, as well as IgE-mediated sensitivity to peanut and allergic rhinitis in later childhood. Our analysis also indicated an association of low maternal 25(OH)D in both early and late pregnancy and at delivery with reduced bone mineralisation in early childhood.

While these findings do not provide direct evidence of cause and effect for vitamin D deficiency, of note, a recent IPD of 25 eligible vitamin D supplementation RCTs (total 10933 participants, aged 0 to 95 years) showed that vitamin D supplementation reduced the risk of acute respiratory tract infection by 12% among all participants. Sub-group analyses showed that among those receiving daily or weekly vitamin D, protective effects were stronger in those with baseline serum 25(OH)D levels <25 nmol/L (aOR 0.30) than in those with 25(OH)D levels ≥25 nmol/L (aOR 0.75) (Matineau *et al.* 2017).

At the outset of the project, the ODIN consortium chose to prioritize a low threshold for serum 25(OH)D of 30 nmol/L, as a reasonable and feasible public health target for deficiency prevention. The data described here underpin our assertion that in the European context, this target is a valid and meaningful first priority from a public health perspective.

Potential impact in relation to reducing the economic burden of disease in Europe

The cost of non-communicable diet-related disease is subject to various colossal estimates, in the realm of trillions, but a consistent finding is that budget allocations to disease prevention are much lower than to treatment of chronic disorders, typically by pharmaceutical or surgical interventions, that are lifestyle or dietary in origin. As mentioned above, the role of vitamin D in prevention of metabolic bone disease is undisputed, and the evidence base of benefits of vitamin D in terms of some non-skeletal disease is strengthening.

Estimates from a Europe-wide study put the direct and indirect costs of inadequate vitamin D status at €187 Billion for the region's 363 million people in 2007 [now in excess of 500 million] (Grant *et al.* 2009). While these estimates are based on a serum 25(OH)D concentration of <100 nmol/L defining inadequate vitamin D status, it is clear that vitamin D deficiency using the more evidence-based lower serum 25(OH)D thresholds (as outlined above) still represents a significant burden to Europe's health-care budgets. A recent study of vitamin D and health care costs in the general population of North-Eastern Germany showed that those with serum 25(OH)D of 25 nmol/L had a 13% higher relative risk of hospitalization compared to those with serum 25(OH)D of 50 nmol/L, which was associated with 51% higher inpatient costs (Hannemann *et al.* 2017).

ODIN's findings highlight the benefit from a societal and economic perspective of a food first approach towards tackling vitamin D deficiency

ODIN was able to model the ultraviolet B (UVB) availability for synthesis of vitamin D in skin for the same European sites included in the estimation of vitamin D deficiency prevalence exercise, and this highlighted that such potential for endogenous synthesis is limited for a number of months (i.e. the vitamin D winter) in each of the included European countries. Increased summer sun exposure as a strategy of increasing vitamin D status carries the public health risk of skin damage and cancer. Vitamin D intakes are typically low, as it occurs naturally in few foods and in low concentrations, and the dietary supply is currently unable to offset the seasonal UVB sunshine deficit. Thus, as per ODIN's *a priori* key objective, focus was placed squarely on development of 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 <30nmol/L. Development of sustainable food-based solutions aimed at increasing serum 25(OH)D in European citizen's represents an economically sound approach to lowering the economic burden of disease in Europe, but in addition could increase competitiveness of the European food industry through the development of new food products (see below). A competitive food industry is critically important to the economy of Europe, and in line with EC policy.

In terms of a 'food first' approach towards tackling vitamin D deficiency, a number of key information gaps existed, and ODIN successfully addressed several of these gaps which it had prioritized. Nationally representative data on habitual vitamin D intakes and food sources, including the contributions from fortified foods and nutritional supplements, were required for Europe so as to clarify the distribution of vitamin D intake in Europe. This is the starting point in terms of devising evidence-based strategies which use food to tackle inadequate intake of vitamin D and thus lower the prevalence of vitamin D deficiency in Europe.

While representative data on vitamin D intakes in several EU countries exist, data from European national nutrition and food consumption surveys were fragmented and used various methods of food consumption data collection, analysis and reporting, making meaningful comparison problematic. In addition, more comprehensive coverage of the vitamin D content, including 25(OH)D, of staple foods was required within food composition 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. ODIN, together with EuroFIR, constructed an 'ODIN-EUROFIR vitamin D food composition database' using analytical data that have been quality assessed using EuroFIR standards, including fortified foods and nutritional supplements. ODIN also developed approaches to analysing intake data, including the contributions from recipes and composite foods, which were standardised and estimates calculated using a single data analysis platform to deliver harmonised vitamin D intake data from the base diet, fortified products and nutritional supplements in four countries in 10 methodologically comparable national survey systems.

Following these enabling developments, ODIN described the first harmonised, validated vitamin D intake data in 10 nationally representative surveys from 4 EU countries and

reported intakes of 3-5 µg/d in the UK, Denmark, the Netherlands and Ireland, with 77-100% of people at risk of inadequate vitamin D intakes. Some traditional sources of vitamin D, such as eggs, were still important, while others such as oily fish, made a limited contribution due to low consumption levels in most countries, particularly among children.

After establishing this base priority, ODIN moved to addressing a number of other key areas of critical importance along the pathway towards a food first approach to addressing the vitamin D deficiency problem. The ODIN concept is based on the premise that increasing vitamin D intake moderately across the population intake distribution, using a combination of biofortification (through eggs, meat and fish, and mushrooms) and nutrient addition, will generate increases in serum 25(OH)D concentrations across the status distribution that are sufficient to ensure a minimal prevalence of vitamin D deficiency. This commodity-based strategy, including both fresh and processed foods in several food groups, will ensure widespread coverage of the population and minimize the risk of excessive exposure at the top end of the intake distribution.

The findings from ODIN's three human intervention trials and animal/fish feeding trials (in WP5 and WP6) highlighted how technological advances in food production and animal nutrition could be harnessed to increase vitamin D in the food supply with consideration for dietary diversity and local preferences. Of note, the three ODIN human intervention studies with vitamin D-enhanced foods tested and illustrated the efficacy of these food-based solutions for preventing vitamin D deficiency in diverse population groups. The findings from these 3 studies were also combined with data from 3 existing non-ODIN, food-based RCTs (but from partners within the consortium) to provide the first IPD-level evidence of the potential of vitamin D fortified/enhanced foods, some of which were products developed during the project, for protecting winter vitamin D status of free-living persons, both persons of European origin resident at Northern and Southern latitudes and dark-skinned South Asian immigrants. This research was only feasible by partnering with nationally funded projects and harnessing prior expertise in implementing challenging food-based RCTs in the community. These new data are key in terms of supporting the underpinning evidence base for a food first approach.

In terms of population-level evidence, ODIN used the updated food analytical vitamin D data from ODIN's human and animal food intervention trials in its novel and bespoke dietary modelling to answer the question of how will increasing vitamin D in the food supply affect this distribution and reduce the prevalence of inadequate intakes in European populations, particularly after confirming their relatively low base. The novel and validated ODIN system for progressing step-wise dietary modelling of evidence-based food fortification scenarios in the same 10 nationally representative surveys in 4 EU countries showed that proposed combination ODIN fortification and enhancement strategies, including milk, eggs, cheese and meat could achieve desired population intakes and distributions of vitamin D, relative to the Estimated Average Requirement of 10 µg/day, without increasing the risk of excessive intakes. These findings highlighting not only the potential for addressing inadequacy of vitamin D intake, but also the excellent safety profile of a food first approach.

Of key note, the research within ODIN in relation to food first approach towards tackling vitamin D deficiency was only feasible on the back of a meaningful research partnership between academic scientists and the food industry, including the SME sector. It underscores

the conclusion of a US Institute of Medicine workshop on the topic of Building Public-Private Partnerships in Food and Nutrition, which suggested that many of today's public health challenges would be well served by public-private partnership approaches, with all stakeholders engaged. Successful implementation of the research in relation to food-based solutions for vitamin D deficiency element within ODIN was contingent upon the strength of the public-private collaboration. ODIN scientists in academia and research partnered with agri-food producers, industry and SMEs to devise new technologies and food products to increase the vitamin D content of food that are inclusive and affordable and mindful of the requirements of food policy and regulatory bodies.

The findings in relation to the vitamin D food-based solutions has been of major interest to the European food industry sector, and is ripe to be translated into NPD, with potential for increased competitiveness. As one example, during the later stages of the ODIN project, one of our industry partners secured approval from their national food regulatory agency to launch UVB-treated mushrooms. This was facilitated by research undertaken within ODIN in relation to their safety and efficacy. A number of Europe's major food industry players have interacted with ODIN principle investigators to develop their strategy in relation to vitamin D-enhanced products. These interactions extend well beyond dairy, and include cereals, agri-food producers and ingredients suppliers.

ODINs findings to underpin European public health nutrition policy

ODIN considered it one of its core obligations to provide reliable evidence on which the EC, EFSA and other national regulatory authorities within Europe can base decisions, and which will have direct benefits for European citizens and enable the authorities and the industry to progress safely with implementing strategies for vitamin D deficiency prevention.

A serious challenge that has existed for regulatory authorities charged with setting recommendations for dietary intakes of vitamin D and issuing regulations for the safe addition of vitamins to foods and feeds, as well as the agri-food producers and industry who work within this framework to feed the population, is the persistence of fundamental knowledge gaps throughout the vitamin D field, which have contributed to the risk of unreliable recommendations and lack of clarity in the evidence on which decisions are made. ODIN has contributed core data on prevalence of vitamin D deficiency as well as on inadequacy of vitamin D intake across Europe, which were the most obvious knowledge gaps. These highlight the need for action from a public health perspective. Global vitamin D supplementation and blood testing are widely advocated, at huge cost, with alleged benefits to individuals and society that over-reach the currently available proof. The momentum generated by calls to action and impassioned pleas for political intervention have produced a chaotic range of recommendations for vitamin D from various agencies and institutes representing clinical specialties. Notwithstanding that vitamin D supplementation is required among certain high-risk groups, the uptake and dosing levels are highly variable. Supplements only benefit those who use them, which nullifies the concept of global supplementation among free-living individuals who exercise personal choice. The ODIN consortium, having provided leadership and guidance on evidence-based practice in implementing safe and sustainable strategies to prevent vitamin D deficiency with concomitant public health benefits across the European population, urges regulatory

authorities and the Industry to adopt a step-wise approach to modifying vitamin D intakes in the population.

Revised dietary recommendations for vitamin D for the EU population and regulations governing the maximum allowable addition of vitamin D to foods and feeds have the potential to directly impact nutritional status and health in >500 million EU citizens and would indirectly influence global recommendations going forward. ODIN, through its four dose-response RCTs, has provided experimental evidence on vitamin D requirements to formulate intake recommendations for pregnant women, infants, children, adolescents and ethnic immigrant people resident at Northern latitudes from specifically designed RCTs, which were almost completely absent prior to the implementation of the project. This lack of evidence had been widely acknowledged by expert authorities and agencies briefed with established new recommendations for vitamin D. ODIN has also pioneered the application of an IPD approach to estimation of the dietary requirements for vitamin D, an area which is receiving focussed attention by the agencies as they move forward and look towards future iterations of their Dietary Reference Values (DRVs) for vitamin D. ODIN again capitalized on existing extensive research infrastructure in Europe by assembling the largest critical mass of prospective adult, pregnancy and birth cohort studies to date and conducting a series of collaborative trial and IPD-level meta-analyses which provided new insight into the associations between vitamin D and perinatal outcomes, childhood [allergic disease, bone growth and development and body composition] and ageing adults [premature mortality, cardiovascular disease], also with a view to the next iteration to DRVs.

Also of critical importance from a regulatory perspective, ODIN has maintained a watching safety brief over all its activities with respect to exposure, status and health outcomes. Over its life-time, ODIN monitored the risk of exceeding tolerable upper intake levels (ULs) for vitamin D, of generating serum 25(OH)D concentrations above thresholds (125 nmol/L) considered to be potentially associated with increased risk, of adverse health consequences of low and high serum 25(OH)D concentrations and actively monitored the occurrence of any adverse effects from the seven RCTs stipulated within its work-plan. This must underpin any implementation of recommendations in relation to food-based solutions and safeguard human health by minimizing the dual risk of nutritional deficiency and excess in a step-wise, controlled approach governed by the principles of risk assessment and risk management.

ODIN leading the way globally in relation to collaborative vitamin D research

As part of its work, a recent analysis of World-wide research architecture of vitamin D research examined collaborative efforts in the area of vitamin D. Of the ~26,000 vitamin D articles included in their exercise (spanning 1900 to 2014), 3,467 articles were a result of an international collaboration – of which 2,821 were of a bilateral nature (Brüggmann *et al.* 2018). Only 436 were trilateral collaborations, while 99 publications were issued by authors from four countries working together. The numbers of publications were quite low (29, 23, 14, and 18) when one looks at researchers working in collaborative efforts from five, six, seven and eight countries, respectively. An analysis of ODIN's publications arising from direct project funding (see Section 4.2A below) shows that to date all of these papers were collaborative efforts and bar one bilateral collaboration, the remainder of the papers were at a

minimum trilateral and up to inclusion of authors from 11 countries. ODIN's two papers included in 'The Top Vitamin D Papers' for 2015/16 and 2017 had researchers, in some cases more than one research group per country, from 11 and 8 countries, respectively. Using Ireland as the ODIN coordinating centre and as a case-study for the ODIN consortium overall, the study by Brüggmann *et al.* (2018) showed that the ratio of number of collaborations to total vitamin D publications by that country was 0.48:1 as compared to the US and Japan (having the greatest and 2nd greatest number of vitamin D articles, respectively) which had ratios of 0.21:1 and 0.16:1, respectively. These metrics highlight the collaborative nature of ODIN's research, and show-case the European model of collaborative projects.

Detailed information in relation to other societal implications are also provided in section 4.3 below.

Dissemination activities and exploitation of ODIN project's key findings

The ODIN consortium was highly committed to and active in their dissemination of the project results. ODIN's full array of dissemination activities were in addition to its communication actions to promote the project by providing targeted information to multiple audiences beyond the scientific and medical communities, including the public and food industry sector.

Dissemination was through the following means (additional details are provided in Section 4.3 below):

- The ODIN website (www.vitd-odin.eu) through its *News feed* section has provided updates on ODIN research findings that were published and also presented at various conferences and workshops; through its *Publications* section providing a list of scientific papers including summaries for a number of these publications, as well as the three ODIN newsletters and press releases. The website also includes a link to the user-friendly and interactive *European Vitamin D deficiency map* (<http://www.odin-vitd.eu/public/7-european-vitamin-d-deficiency-map/>) and the *Vitamin D winter map*, based on data and publications arising from WP 1 and 3, respectively. The ODIN website has been extensively updated over the course of the project with a view towards its key role as a dissemination channel.
- *Peer reviewed publications*: To date, ODIN partners have published 75 peer-reviewed vitamin D-related papers in high-impact international journals (See Section 4.2A below where papers presented by WP). These publications are based either directly on new research findings in ODIN (the majority of which are available under open access) or were enabled by ODIN's research activities. The publication of ODIN research will also continue post-project, as some of the research was conducted towards the end of the funding window. Two of ODIN's papers have been included in the Top Vitamin D Papers, one paper in 'The Top 18 Vitamin D Papers in 2015-2016' and another in 'The Top 12 Vitamin D Papers for 2017' (source: Orthomolecular Medicine News Service).
- *Three ODIN newsletters* were distributed electronically to those who subscribed through the ODIN website. While the 1st newsletter focused on the ODIN project overview and its overall aims, the 2nd and 3rd newsletter focused on key project findings and associated papers as well as highlighting dissemination events at which ODIN results were shared. ODIN also employed the various social media channels (42 Facebook posts, 117 tweets and re-tweets) to disseminate information on the project findings and related news.
- *Presentation at key scientific conferences*: ODIN partners attended a variety of scientific meetings, such as symposia, congresses, conferences and workshops, where they communicated ODIN outcomes and results (See Section 4.2 below). Of particular note, there were 135 oral presentations by ODIN principle investigators or junior scientists on the project's findings, many of which were keynote/invited presentations. The conferences at which these were delivered represented a blend of European, North American as well as those further afield, highlighting the reach of ODIN's dissemination of its key results. As can be seen in Section 4.2 below, there were also many conference poster presentations, print newspaper articles, online newspaper and magazine articles aimed at health professionals and media pieces on online food industry magazines, TV interviews and radio interviews. In all, there have been 253 dissemination activities.

- *Two targeted stakeholder ODIN workshops:* ODIN organised and hosted two very successful one-day dissemination events at the European Commission buildings in Brussels to which more than 60 invited participants from European Commission regulatory bodies, European food, health and consumer agencies and relevant food companies participated at each event. The first workshop 'One-day symposium to outline the implications of new research data on vitamin D from the ODIN project for public health policy and food innovation in Europe' on March 3rd, 2016 disseminated data from ODIN's research on vitamin D status, intake and food-based solutions. The second workshop 'Dietary Requirements for Vitamin D in Children, Adolescents, Black-skinned adults and pregnant women in Europe' on March 24th, 2017 disseminated data on the project's research on vitamin D dietary requirements in various under-researched population subgroups. Both events received extremely positive feedback from attendees and there was a very high level of audience engagement and interaction.
- *The ODIN international vitamin D conference:* The ODIN coordinators hosted an International Scientific Conference *Vitamin D & Health in Europe: Current and Future Perspectives* on the 5th & 6th September, 2017 at University College Cork, Ireland. The conference programme focused on presenting the exciting findings that have emerged from the ODIN project as well as learning from internationally-renowned scientists and their research into vitamin D and health (<http://www.vitaminconference.eu/page/6-programme/>). The conference had four plenary sessions and a special workshop which covered topics ranging from dietary requirements for vitamin D, food strategies and novel food solutions for tackling inadequacy of vitamin D intake and status, vitamin D in relation to adult health as well as infant and maternal health outcomes. In addition to the plenary invited speakers, there were a number of promoted abstract oral presentations and an impressive collection of poster presentations which addressed various vitamin D-related topics. The extremely positive feedback on the conference from participants and delegates (>150) suggested that the event provided a supportive forum for the exchange of knowledge and ideas between researchers, policy makers and the food sector. This was a hope for the conference, as ODIN believed this was necessary to support and stimulate innovative solutions for public health. The conference was acknowledged at the Cork Convention Bureau awards.
- ODIN was invited to host a dedicated session of the 3rd *International Conference "Vitamin D - minimum, maximum, optimum"* in Warsaw, Poland September 22-23rd, 2017. Research findings and highlights from ODIN were presented by four of ODIN's principle investigators (including the co-coordinators), followed by a very interactive question and answer session.



- ODIN and its findings featured in the European Commission's *Horizon2020* website as an example of some of the best research currently being carried out (https://ec.europa.eu/programmes/horizon2020/en/news/s_hining-light-vitamin-d-deficiency-europe). This was followed by three EC updated news articles on ODIN.

- ODIN was presented as an exemplar of the EC model of research and sustainable food first approaches as part of the highly subscribed *Sustainable and Healthy Nutrition* session at the FOOD2030 conference in Brussels, October 2017,

- ODIN hosted a dedicated session as part of the International Union of Nutrition Sciences congress, in Buenos Aires in October 2016, called VITAMIN D STATUS AROUND THE WORLD: EPIDEMIOLOGICAL DATA AND DIAGNOSIS.
- Beyond its commitment to dissemination activities in relation to key results of the ODIN project, the consortium was also highly committed to their translation and exploitation. Exploitation is important to convert the knowledge gained from ODIN into socio-economic benefits for Europe and its citizens. As mentioned above, ODIN by fostering the existing, and forging new, links between public research organisations and industry, have created an environment for knowledge spill over. Commercialisation and transfer of knowledge are two mainstream channels for exploitation of public research results.

ODIN has taken the following established measures aimed at ensuring ‘exploitation’ of its results (and additional details are provided in Part B2):

Using the findings in further research activities (outside the action):

- The standardized serum 25(OH)D, generated during the ODIN project, has been used in research activities outside the action, which had been identified as a means of exploitation of these new data.
- The know-how generated within ODIN, particularly in relation to food-based solutions and certain health and metabolism outcomes, have been used by several partners in new vitamin D research project proposals in response to national funding calls.
- The findings from ODIN will also be used in collaborative initiatives going forward – these will range from individual participant data analyses, to informing nutrition policies and practices in relation to vitamin D status in low and middle income countries.
- Currently, the EC, the UN Sustainable Development Goals and many governmental agencies and NGOs are deliberating the potential of using food-first strategies for micronutrient deficiency prevention. The GAIN alliance, the Micronutrient initiative, the Bill and Melinda Gates Foundation and the SUN Movement are actively seeking approaches to address the ‘Hidden Hunger’ of micronutrient deficiency. The validated ODIN model of using agri-food production and food technology approaches to enrich foods with vitamin D, supported by a dietary modelling framework that demonstrates safe and effective levels of addition to the food supply, is a transferable model that could be applied to other micronutrients that are weakly supplied in the modern diet.

Developing, creating or marketing a product or process:

- The outcomes of ODIN’s WP5 RCT in relation to poor bioavailability of vitamin D₂ from bread made with UV-treated yeast was followed up with an industry-commission research contract to undertake further study of the impact of the form of yeast on bioavailability of vitamin D₂.
- The ODIN bioavailability trial with the vitamin D₃-enriched low-fat cheese has generated additional knowledge in relation to optimal enrichment of low-fat cheese with vitamin D. This process may turn into down-stream market opportunities.
- The research undertaken in ODIN in relation to the safety and efficacy of UV-exposed mushrooms facilitated one of our industry partners securing approval from their national food regulatory agency to launch UVB-treated mushrooms.
- The underpinning science behind the process of biofortification of eggs, red meats and cultured fish, and of vitamin D enhanced pork achieved through a novel process of UV-

treatment of the animals in the pens have contributed to the scope for increasing markets for such vitamin D-enriched animal foods with benefits for human vitamin D nutrition.

- Major food companies and regulatory authorities have requested and will facilitate conversion of ODIN data to concise documents for use in food labelling and to advocate for updates to the food labelling regulations (specifically the outdated EC RDA).
- Collectively, the view of a global science-based company active in health, nutrition and materials was that the ODIN project had set a new bar for achievement within the context of EC funded research, in the cognate areas of SC1 and SC2.

Creating and providing a service(s) – potential for spin-off using ODIN IP

The standardization of existing serum 25(OH)D data-sets from strategically important population studies/surveys has been undertaken outside the ODIN action as a service to interested parties, including industry. This service has been undertaken as external research contracts. The online *ODIN vitamin D deficiency map* has raised awareness of the approach and its application. There is also scope to offer associated service in which the UVB availability of certain locations can be modelled using the approach used in ODIN and illustrated in its *Vitamin D winter map*. In line with this, the innovative and validated ODIN system for conducting dietary modelling of the vitamin D food supply, is of commercial interest. Finally, there is scope to offer a service which takes the data from modelled UVB-availability and the modelled changes in vitamin D intake arising from a vitamin D-enhanced food(s) and predicts the impact on the population serum 25(OH)D and prevalence of vitamin D deficiency.

Transfer of knowledge to relevant agencies briefed with protecting public health:

Beyond ODIN's productive dissemination of its research findings, ODIN also sought to maximise its data and results to the benefit of society by offering raw data from our ODIN's RCTs and IPD analyses available to the European Food Safety Authority (EFSA) in relation to their recent DRV exercise for vitamin D. ODIN, through its joint coordinators, has also had direct communications with and knowledge transfer to the Scientific Advisory Committee on Nutrition (SACN) in the UK in relation to their recent exercise on DRV for vitamin D as well as with the Health Council of the Netherlands (Committee on Nutrition), who are currently re-evaluating their vitamin D recommendations. This continues upon a strong tradition of the ODIN joint coordinators sharing data with the Institute of Medicine for their 2011 vitamin D exercise. The ODIN coordinators had dialogue with the Nutrition Unit at EFSA in relation to information and knowledge exchange on the use of IPD approach to estimation of dietary vitamin D requirement estimates and possible between-individual surrogates that might be applied within more standard meta-regression approaches. The coordinators have also met with the Office of Dietary Supplements at NIH in relation to the potential and application of the IPD approach to future dietary reference intake exercises for vitamin D. There is scope to offer a service to relevant governmental stakeholders which utilises the IPD approach to estimation of vitamin D requirements.

ODIN has also shared as yet unpublished findings with the EFSA Working Group on Amino Acids and Vitamins of the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP Panel) in response to an initiative to collect data on vitamin D₃ in fish flesh and/or in fish feed (EFSA-Q-2014-00604, FAD-2014-0035). This was in support of the EFSA preparing an opinion on the safety of vitamin D₃ addition to feeding stuffs for fish.

E. Project website and contact details



The ODIN project website is available at: <http://www.odin-vitd.eu>

The ODIN website will be maintained beyond the lifetime of the project by the *Cork Centre for Vitamin D and Nutrition Research* at University College Cork, either as an independent website, or as a microsite, for a minimum of three years.

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