# The economic case for prevention of population vitamin D deficiency

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# The economic case for prevention of population vitamin D deficiency: a modelling study using data from England and Wales

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## Abstract

**Background:** Vitamin D deficiency (VDD) affects the health and wellbeing of millions worldwide. In high latitude countries such as the United Kigdom (UK), severe complications disproportionally affect ethnic minority groups.

**Objective:** To develop a decision-analytic model to estimate the cost-effectiveness of population strategies to prevent VDD.

**Methods**: An individual-level simulation model was used to compare: (I) wheat flour fortification; (II) supplementation of at-risk groups; and (III) combined flour fortification and supplementation; with (IV) a 'no additional intervention' scenario, reflecting the current Vitamin D policy in the UK. We simulated the whole population over 90 years. Data from national nutrition surveys were used to estimate the risk of deficiency under the alternative scenarios. Costs incurred by the health care sector, the government, local authorities, and the general public were considered. Results were expressed as total cost and effect of each strategy, and as the cost per 'prevented case of VDD' and the 'cost per Quality Adjusted Life Year (QALY)'.

**Results**: Wheat flour fortification was cost-saving as its costs were more than offset by the cost-savings from preventing VDD. The combination of supplementation and fortification was cost-effective (£9.5 per QALY gained). The model estimated that wheat flour fortification alone would result in 25% fewer cases of VDD, while the combined strategy would reduce the number of cases by a further 8%.

**Conclusion:** There is a strong economic case for fortifying wheat flour with Vitamin D, alone or in combination with targeted vitamin D3 supplementation.

## Introduction

Vitamin D helps to maintain adequate levels of calcium and phosphorus in the body, playing a fundamental role in bone and muscle health (1). The main source of Vitamin D is sunlight exposure and many behavioural, cultural or environmental factors increase the risk of VDD by limiting the skin's direct exposure to sunlight. Risk factors for VDD include, for example, sun screen use, air pollution, indoors lifestyles, full body clothing, and living in high latitude settings (2,3). People with dark pigmented skin who live in setting with limited sunlight, such as high latitude countries are also at a higher risk for VDD, as well as older adults, particularly if institutionalised. VDD can lead to poor health and its symptoms manifest as osteomalacia, bone pain, muscle weakness and consequent increased risk of falls. In children, severe VDD additionally causes hypocalcaemia (low levels of calcium in the blood), which is associated with seizures, tetany and heart failure (4,5), and rickets with osteomalacic leg bowing, muscle weakness and delayed infant development. Morbidity from VDD is predominantly found in individuals from Black and Asian Minority Ethnic (BAME) groups living in high-latitude countries, including in the UK (6,7), the US (8), Canada (9), Scandinavian countries (10–13) and Australia (8,14). Nonetheless, VDD is common in many populations across the world, regardless of ethnicity.

In response, most countries have adopted policies to increase the populations' intake of vitamin D, which generally consist of a combination of supplementation and food fortification strategies (15). In the UK, multivitamin supplements containing vitamin D are recommended to all infants and children up to the age of four, as well as to pregnant women and breastfeeding mothers (16). These vitamins are provided free-of-charge to those in low-income households. In addition, infant formulas and spreadable fats are mandatorily fortified, while other foods including breakfast cereals and milk substitutes are voluntarily fortified. While both supplements and fortified foods are important sources of vitamin D for the UK population, evidence suggests supplementation polices are not working (7,17) and the mean daily vitamin D intake is still below the Reference Nutritional Intake (RNI) of 400 IU per day (2,18). Therefore, rickets and hypocalcemic complications remain a serious health issue and cause of death in infants, particularly in the BAME group (4,7,19,20). Evidence shows that vitamin D status, which is measured through the blood concentration of a Vitamin D metabolite, the 25-hydroxyvitamin D [25(OH)D], is suboptimal in 13% of the European population (21). In the UK population, 20% of adults and 16% of children aged between 11 and 18 years are estimated to be VDD (2), with the BAME group being, by far, the most affected (10,12,22–25).

So far, the economic evidence needed to inform and underpin VDD prevention policies has been limited (26). To the best of the authors' knowledge', there is no evidence on the cost-effectiveness of preventing population VDD through food fortification or a combination of food fortification and supplementation, even though the latter is the approach taken in most countries (15). This study estimates the cost-effectiveness of preventing VDD using the population of England and Wales as a simulated cohort and compares the strategies of supplementation of at-risk groups, wheat flour fortification, and a combination of the two approaches.

## Methods

An individual-level state-transition model was developed to compare four different strategies to prevent population VDD. A state transition model was chosen to allow recurrence of VDD over the life course, and individual-level simulation was used to make the most efficient use of available data on risk heterogeneity for VDD in the population, as well as to account for individual pathways across the model's time horizon (27,28). The model used a one-year cycle length, and both costs and benefits were discounted at 3.5% per year, as recommended by the UK National Institute for Health and Care Excellence (NICE) (29). The base case analysis was done from a societal perspective and results reported using incremental cost effectiveness ratios (ICER) in the form of cost per additional quality-adjusted life year (QALY) gained, and cost per prevented case of VDD. The model was built in TreeAge Pro 2016 software, and followed modelling (28,30) and reporting (31) guidelines for good practice.

The model comprised three main health states (**Figure 1**). These health states were mutually exclusive and represent clinically relevant stages:

1) Vitamin D deficient (VDD): all children with serum 25(OH)D concentrations below 30nmol/L (3) and adults with serum 25(OH)D below 50 nmol/L (32).

2) Vitamin D sufficient (VDS): all children with serum 25(OH)D concentrations above 30nmol/L (3) and adults with serum 25(OH)D above 50 nmol/L (32).

3) Dead: based on all-cause mortality and naturally treated as an absorbing state.

**[Figure 1]**

The majority of the VDD population were assumed to be asymptomatic. Within the model, asymptomatic individuals followed a pathway with the possibility of remaining deficient or becoming sufficient over time. For the deficient population who become symptomatic, children were assigned a risk of developing rickets and hypocalcemic complications, and adults a risk of developing osteomalacia. Younger adults aged between 19-64 years old who acquire osteomalacia suffer from diffuse pain and muscle weakness. Older adults with osteomalacia had a modest increased risk of falls due to pain and muscle weakness. The full model structure depicting the clinical pathways for children and adults with symptomatic VDD can be found in the supplementary material (Figure S1 and Figure S2).

The starting cohort within the model was simulated based on the population of England and Wales, according to its age, sex and ethnicity distributions (33). The following four alternative strategies were compared: (I) wheat flour fortification at 400IU of Vitamin D per 100 g of wheat flour; (II) free supplementation to all at-risk groups; (III) a combination of flour fortification and supplementation; and (IV) no additional intervention, i.e. maintaining the current fortification and supplementation policy of providing supplements to young children, pregnant women and breastfeeding mothers within low-income households, and fortifying certain food groups. Wheat flour was chosen as the most appropriate food for fortification since, contrary to milk and spreadable fats, flour is a staple food across multiple ethnic groups, including Asian, African, Caribbean, and white ethnic groups, and therefore will potentially reach multiple at-risk groups. Evidence from Scandinavian countries shows that milk supplementation is not as effective in reaching ethnic minority groups as it is in reaching white ethnic groups (15). Regarding safety, a UK study that compared vitamin D fortification of milk, flour and a combination of both showed that flour fortification alone presented the lowest risk of toxicity in the population (34). Wheat flour is already fortified in the UK, and addition of vitamin D to the mix of added nutrients is likely to carry lower implementation barriers than targeting an industry that has no fortification infrastructure, in place, such as milk in the UK.  The baseline risk of VDD was estimated using individual-level intake data reported from the National Diet and Nutrition Survey (NDNS) (18,35). The intake of vitamin D included all food sources (natural and fortified foods, including voluntarily fortified). Differences in intake by age group and sex were considered.

The effectiveness of wheat flour fortification in reducing the risk of being VDD by sex was derived from Allen et al.'s nutrition model (34,36). Ethnicity specific effects were not available and therefore the same effect was assumed for white and BAME populations. The full list of the transition probabilities used in the model for the current UK policy and wheat flour fortification is presented in the supplementary material (Table S1.A. and Table S1.B.). The effect of the supplementation programme was based on data provided by a local government organization in London, UK (37), which recorded the uptake of free vitamin D supplements using an electronic card system. In this Local Authority, all children up to 4 years old, pregnant women and breastfeeding mothers were eligible to receive free Vitamin D supplements. In our model, supplements were provided to all sub-populations at risk of symptomatic VDD including all infants and young children up to 18 years old; individuals of all ages from BAME backgrounds; and all individuals aged over 65 years. In the absence of data on the uptake of supplements by adults and older children (>4 years old), we assumed the same uptakes in older and younger children to that of children <4 years, and the adult uptake to be the same as that of pregnant and breastfeeding women. The model assumed a supplement dosage of 400IU per day for all groups except for the elderly, who received 800IU per day as per the recommended minimum dose to prevent falls (38). The effectiveness of the combined scenario (wheat flour fortification plus supplementation of at-risk groups) was estimated as the additive effectiveness of each strategy alone.

**Outcomes**

Preventing VDD in the population reduces the risk of poor bone and muscle health. The outcome unit used for the cost-effectiveness analysis was the number of cases of VDD prevented. For the cost-utility analysis, the health-related quality of life (HRQoL) for a given health state was combined with the time spent in that health state to formulate QALYs. The preference-based quality of life values (i.e. utilities) applied to estimate QALYs were sourced from two HRQoL studies, published elsewhere (39), one focusing on VDD in children, and the other in adults (supplementary material, table S2).

**Costs**

Cost data were derived from multiple sources (supplementary material, table S3). For the wheat flour fortification strategy, the price of dried vitamin D was obtained from a UK commercial flour supplier of the food industry (LFI (UK) Ltd). The costs of re-labelling packages, used in a sensitivity analysis, and the public sector costs of enforcing mandatory fortification were sourced from the Food Standards Agency‘s study of wheat flour fortification with folic acid (40). The cost structure of the supplementation programme was based on the Local Authority’s supplementation programme (37), which was pharmacy-led. It was assumed that supplements would be supplied through community pharmacies, which would receive an initial financial incentive for participating in the programme and reimbursements for the cost of the supplements dispensed. An additional incentive would be provided for each supplement dispensed to encourage sustained adherence to the programme.

**Uncertainty and sensitivity analyses**

Several sensitivity analyses were conducted to determine how sensitive the model results were to the assumptions made (Table 1). First, the time horizon was varied to 5 and 10 years. Second, the discount rate for both costs and benefits was set to 1.5%. Third, the perspective was altered to include only public sector costs, therefore eliminating all private costs borne by the food industry. Fourth, following the Food Stardards Agency report on the cost of fortifying flour with folic acid in the UK (40), the model included a conservative estimate for the food industry costs of relabelling flour packages, and all products containing flour, such as cakes and biscuits. Fifth, the model assumed no disutility from asymptomatic VDD. Sixth, the starting cohort was altered to include a higher proportion of BAME individuals, reflecting the population mix of many large UK cities (33). Finally, a probabilistic sensitivity analysis was conducted based on 10,000 iterations of a Monte Carlo simulation, using the model parameter distributions listed in the supplementary material (Tables S4-S11). All analyses was conducted in TreeAge Pro 2017, R1.

**[Table 1]**

**Results**

The model base case analysis showed that wheat flour fortification was cost-saving, which means that it led to fewer costs and more benefits when compared to the current national policy in England and Wales, and is therefore described as dominant (Table 2). All other strategies were found to be superior to the current national policy in terms of cases of VDD prevented.

The model estimated that if the current VDD policy is kept in place, there will be almost 40 million new cases of VDD – asymptomatic and symptomatic - over the next 90 years. Introducing wheat flour fortification would result in a 25% reduction in this number, and if that is combined with an additional supplementation programme then a further 8% would be prevented (33% in total). The model estimated that wheat flour fortification would lead to an increased expenditure of £0.12 per person per year based on consumption estimates that include common flour based products such as cakes and biscuits (41). The model found the strategy of flour fortification to be cost-saving, saving approximately £65 million over a 90-year time horizon. If food fortification is combined with supplementation, then this would lead to an additional cost of nearly £2 per case of VDD prevented but more cases of VDD would be prevented when compared to fortification alone.

**[Table 2]**

The analysis showed that wheat flour fortification at 400IU per 100g of flour combined with targeted supplementation at 400IU for children up to 18 years old and all individuals from BAME backgrounds and 800IU for all individuals older than 65 years old is cost-effective. The intervention costs on average £0·38 per person across the whole population (total costs over the 90 years modelled is 250 million) and leads to an average gain of 0·04 QALYs, resulting in an ICER of £9·50 per QALY gained (table 3). Under commonly applied UK thresholds of willingness to pay per QALY, this represents a highly cost-effective use of resources.

**[Table 3]**

The sensitivity analyses showed the model results were not sensitive to the majority of the assumptions made. Consistently, with each subsequent sensitivity analysis, the model showed the flour fortification strategy to be dominant and the combined strategy to impose a small cost but to be highly cost-effective. Evidence from the literature suggests that asymptomatic VDD – (serum concentrations of 25(OH)D levels below the deficiency threshold, but no overt symptoms), if coexisting with limited dietary calcium, are regarded as a pre-clinical health risk state, with diffuse pain (1), muscle weakness and fatigue (42), and thus likely to impact on quality of life. In the base case analysis, a detrimental impact on HRQoL was assumed based on an expert elicitation study (39). We tested this assumption in a sensitivity analysis and noted that when it is assumed that the asymptomatic VDD health state results in the same quality of life as being vitamin D sufficient, then the combined strategy has no additional benefit (supplementation material, appendix 4).

Finally, the probabilistic sensitivity analysis (**Figure 2**) showed that for willingness to pay values of up to £200 per QALY, wheat flour fortification is the recommended option. For values above £200 per QALY, a combination of wheat flour fortification and supplementation of all-at risk groups is the optimal strategy.

**[Figure 2]**

**Discussion**

Our model found that implementing strategies to prevent VDD is likely to be cost-effective and wheat flour fortification to be cost-saving as compared to the current policy in England and Wales. The costs of implementing and running the fortification scheme were more than compensated for by the health care savings from preventing more cases of VDD. Alternatively, the combined strategy of adding Vitamin D to wheat flour and extending the coverage of supplementation to all at-risk groups would be highly cost-effective strategy. Therefore, for an additional cost, the combined strategy prevents more cases of VDD when compared to fortification alone and under conventional decision-making rules(43), this additional cost would be regarded as a highly cost-effective use of public resources.

These results of our study are in line with published economic evaluations of food fortification programmes for other micronutrients, such as folic acid (44–46), which have found food fortification to be cost-saving, in pre- and post-implementation studies. The economic advantage of food fortification lies in the wide-coverage and shared costs across the private sector, consumers and the government. Food fortification has the potential to target hard-to-reach populations, overcoming some of the problems with low uptake of supplementation programmes. Moreover, fortification has a far lower burden on the health care budget than supplementation alternatives, as most costs of the food fortification programme are borne by the food industry, and passed on to the consumer. However, a combined strategy offers both a nutritional safety net to the population by fortifying the food chain, and a targeted supplementation scheme to those who are most in need.

We have included children, BAME groups and individuals aged over 65 years old in the at-risk group of the population. Even though most severe cases of VDD have been reported in BAME mothers and their new-borns, overall pregnant women benefit from adequate levels of 25OHD. Most vitamin D supplementation policies around the world already target pregnant women and infants. When considering new public health approaches to reach at-risk and vulnerable groups, pregnant women should continue to be a target group for the strategy of supplementation.

The analysis presented here is based on hypothetical scenarios with conservative assumptions applied to increase confidence in the results. For example, potential savings in primary care associated with consultation of general practitioners and testing were not included, such as the economic burden from routine 25(OH)D testing. In children alone, these costs were estimated to be £1·7 million (at 2014 prices) (47). As new and more expensive diagnostic tests are introduced, the economic burden is likely to increase. Furthermore, conservative estimates regarding the modelling of VDD-related falls in the elderly were also applied, based on a recent economic evaluation study by Poole et al (2015) (48).

We have focused on the benefits of vitamin D to bone and muscle health. The emerging evidence of potential wider benefits of maintaining a healthy vitamin D status such as prevention of cancer and cardiovascular disease (49,50), acute respiratory infections, (51) and other illnesses (52), suggests that the impact of public health measures to tackle vitamin D deficiency might be even stronger than that reported in this study. A recent meta-analysis using individual patient data from over 10,000 individuals found that vitamin D supplements reduced the risk of acute respiratory infections, such as colds and the flu, which have a tremendous burden in population health and health systems (51). As more robust evidence on non-musculoskeletal effects of vitamin D from interventional studies become available, there is potential for future models to incorporate these additional benefits. If the same public health measures compared in our model are able to prevent other diseases, the cost-effectiveness results will be even more favourable that the ones we present here.

One of the strengths of the model is that it was informed by direct communication with stakeholders, including clinical experts, local UK public health organisations, established researchers with experience in economic evaluation of micronutrient interventions, and expert investigators in the economics of food fortification. Moreover, this is the first model to compare supplementation and food fortification with vitamin D independently, as well as the combination of both in the same analysis, which is a more meaningful way of representing the relevant alternatives for policy makers to consider. Our findings were robust when tested under a number of deterministic sensitivity analyses and a probabilistic sensitivity analysis.

The model has some limitations. Data on the costs and uptake of the supplementation programme were sourced from a Local Authority, and were extrapolated to a nation-wide scenario. Regarding the costs, for example, purchases at the national level might achieve economies of scale and result in lower costs. To account for this uncertainty, each relevant model input (eg. cost estimates) was assigned a wide distribution within the probabilistic sensitivity analysis. There was a lack of data on the uptake of supplements by ethnic groups who have different risk profiles for developing VDD. In the absence of uptake data by ethnic group, equivalent levels were applied to all ethnic groups. Furthermore, the cost and effectiveness of the combined strategy was assumed to be the sum of the costs and effectiveness of the flour fortification and supplementation strategies combined. In reality, if implemented simultaneously, interactions between the two strategies are likely, although it is unknown in which direction. Finally, the model only included the health-related benefits from preventing VDD and any other benefits beyond health were not included. Economic evaluation requires that the relevant benefits and costs of each of the policy alternatives are quantifiable. This is the greatest challenge when applying standard economic evaluation methods to the prevention of micronutrient deficiencies. The benefits from reducing the prevalence of vitamin and mineral deficiencies are wide but hard to measure (53). Nutrition, including vitamin D status, impacts human development from conception until the later stages of life (54–56). Moreover, poor nutrition affects socioeconomically disadvantaged groups of the population, and tackling it would have a wider economic benefit by addressing health and social inequalities (57). For example, there would be a clear social benefit from reducing the prevalence of VDD in minority ethnic groups, as it would reduce any stigma associated with rickets in children (58).

The effectiveness of any fortification programme depends on a number of programme design choices, for example, the food chosen needs to be consumed by the targeted population, and the price increase of the final product should be kept low, so that no access barriers based on income are not created (53,59). These features of a programme are particularly important in the context of VDD since BAME groups are at a higher risk. Other studies have highlighted that there is a need to collect data on the diet and nutritional status of BAME populations in the UK (60). We corroborate such needs. To date, nutritional data from the NDNS have not been reported by ethnic group. Doing so would facilitate implementation of food fortification programmes, the effectiveness of which could be monitored using the existing structures, as done in other countries such as Finland (21). Fortifying flour would ensure that population serum 25(OH)D concentrations are raised to safe levels with supplementation used to target subgroups that the fortification programme may not reach effectively.

VDD is wide-spread in the population, it has a negative impact on HRQoL with a burden of disease that is much larger than rickets and osteomalacia. VDD and its complications are preventable and well-planned public health strategies can be highly cost-effective and even cost-saving. Biological, environmental, cultural, historical, and economic factors influence how VDD affects the population, as well as the cost and effectiveness of alternative strategies. Therefore, tackling population VDD in England and Wales requires efforts from multidisciplinary professionals, such as clinicians, nutritionists, health economists, public health professionals, and policy makers.

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**Conflict of interest**

None declared

**Author Contributions**

All authors contributed to designing the research. MA conducted the research and analyzed data supervised by LA, MP, WH and EF. All authors contributed substantially to writing the paper, while MA and EF had primary responsibility for final content. All authors have read and approved the final manuscript.

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**Figures legends**

Figure 1 – Illustration of the model structure

Figure 2 – Cost-effectiveness acceptability curve (CEAC) showing the probability of alternatives to prevent VDD being cost-effective at increasing acceptability thresholds