DECISION ANALYTIC MODELLING OF THE PREVENTION OF VITAMIN D DEFICIENCY IN ENGLAND AND WALES

by

MAGDA FRANCISCA CALÁS OLIVEIRA CARVALHO AGUIAR

A thesis submitted to the University of Birmingham for the degree of

DOCTOR OF PHILOSOPHY

Health Economics Unit

Institute of Applied Health Research

College of Medical and Dental Sciences

University of Birmingham

September 2017

ABSTRACT

Vitamin D deficiency (VDD) is widespread in England and Wales, affecting both children and adults by increasing their risk of poor bone health. In order to inform public decisions on the prevention of VDD, a decision analytic model was developed to compare four alternatives to prevent population VDD: wheat flour fortification, supplementation of at-risk groups, a combination of wheat flour and supplementation, and no intervention. Methods used to inform the model development stage included literature reviews, expert consultation, and preference-based questionnaires to elicit proxy utility values. An individual-level simulation Markov model was chosen to simulate the costs and benefits of each alternative. A cost-effectiveness and cost-utility analysis were undertaken for the base case analysis, using a 90-year time horizon. A societal perspective was chosen to account for private and public costs of implementing each of the alternatives. Parameter uncertainty was tested through deterministic and probabilistic sensitivity analyses. Moreover, in order to inform decisions under uncertainty, a value of information analysis was undertaken. The model results support the decision to implement interventions to prevent VDD, namely a combined strategy of at-risk groups supplementation and wheat flour fortification. Furthermore, this thesis contributes evidence on methodological considerations for modelling micronutrient interventions.

ACKNOWLEDGEMENTS

I thank my supervisors Emma Frew, Lazaros Andronis, Miranda Pallan and Wolfgang Högler for the continuous guidance, support and encouragement. I am grateful to Emma for bringing together such a great supervisory team, for the uplifting chats, and for tirelessly making sure I enjoyed my experience as a PhD student.

I gratefully acknowledge the PhD funding from the College of Medical and Dental Sciences, and the travel scholarship to visit the University of Melbourne from Universitas 21.

I thank Kim Dalziel for supervising me during my visit to the University of Melbourne, and for facilitating my visit to CHERE, in Sydney; Phil Haywood and Stephen Goodall for the valuable feedback; Eleanor McGee, Gwenda Scott and Smita Hanciles for sharing data and valuable insights. I extend my gratitude to participants of the Rickets Consensus meeting, the 2nd EuHEA PhD student-supervisor conference, the seminars at the Health Economic Unit (HEU), the University of Melbourne and the CHERE, the Health Economics Study Group (UK) Manchester and Birmingham, and the 12th iHEA congress for helpful suggestions and conversations.

I thank the HEU staff for the cheering and stimulating environment; particularly those who shared tips on modelling - Tosin and Mark - and those who read drafts of this thesis - Kate, Katie, Carol, and Karen.

I thank my old friends in Portugal and my new friends in the UK for keeping my spirits up throughout these years.

Finally, I am very grateful to my grandparents, my parents, and my sister. I thank you for the immediate presence despite the distance. I am also grateful to Attilio for the daily support, partnership, and for the magic helping hand in formatting this thesis.

To Di, Ana and José Aguiar

“The complexity of things - the things within things - just seems to be endless. I mean nothing is easy, nothing is simple.”

Alice Munro

“(...) the height of sophistication is simplicity”

Clare Boothe Luce

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ABBREVIATION	EXPLANATION
25(OH)D	25-hydroxyVitamin D
BAME	British and Asian Minority Ethnic Minorities
CBA	Cost-benefit analysis
CDC	Center for Disease Control
CEA	Cost-effective analysis
CEAC	Cost-effectiveness Acceptability Curve
CHU9D	Child Health Utility 9 Dimensions questionnaire
CUA	Cost-utility analysis
DALYs	Disability Adjusted Life Years
EQ5D	Euro QoL 5 Dimensions questionnaire
EVPI	Expected Value of Perfect Information
FFI	Food Fortification Initiative
FSA	Food Standard Agency
FSANZ	Food Standards Australia and New Zealand
HRQoL	Health Related Quality of Life
HS	Health State
HTA	Health Technology Assessment
HUI	Health Utility Inc. questionnaire
ICER	Incremental Cost effectiveness Ratio
IoM	Institute of Medicine
LACORS	Local Authorities Coordinators of Regulatory Services
MNDs	Micronutrient Deficiency

NABIM	National Association of British and Irish Millers
NICE	The National Institute for Health and Care Excellence
NMB	Net Monetary Benefit
nmol/L	Nano moles Per Litre
NDNS	National Diet and Nutrition Survey
OECD	Organisation for Economic Co-operation and Development
PCTs	Primary Care Trusts
PedsQoL	Paediatrics Quality of Life survey
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic Sensitivity Analysis
QALY	Quality Adjust Life Years
RNI	Reference Nutrition Intake
SKU	Stock Keeping Unit
SG	Standard Gamble
SPF	Sun Protection Factor
TP	Transition Probability
TTO	Time Trade Off
UL	Upper Limit
UV-B	Ultraviolet light B
VDD	Vitamin D Deficiency
VoI	Value of Information
WHO	World Health Organisation
WTP	Willigness to pay

LIST OF FIGURES

LIST OF TABLES

DISSEMINATION

PUBLICATIONS

1. Aguiar, M., Andronis, L., Pallan, M., Högler, W., Frew, E. (2017) Preventing Vitamin D deficiency (VDD): a systematic review of economic evaluations. Eur J Public Health ckw270. doi: 10.1093/eurpub/ckw270

ORAL PRESENTATION

1. Modelling complex public health nutrition interventions: an individual-level simulation model for the prevention of population Vitamin D deficiency. (2017, October). National congress of the Portuguese Association of Health Economists, Coimbra, Portugal.
2. Modelling complex public health nutrition interventions: an individual-level simulation model for the prevention of population Vitamin D deficiency. (2017, July). iHEA Congress, Boston, MA, USA.
3. Health economics and nutrition – modelling the prevention of Vitamin D deficiency in the UK, (2017, February). Centre for Health Policy Seminar Series, University of Melbourne, Melbourne, Australia.
4. Use of expert knowledge in evaluating benefits of population Vitamin D deficiency programmes (2017, January) Health Economics Study Group (HESG) conference, Birmingham, UK.

5. An economic framework for evaluating a complex nutrition intervention to prevent Vitamin D deficiency in the UK. (2016, January) Health Economics Study Group (HESG) conference, Manchester, UK.

POSTER PRESENTATION:

1. Modelling complex public health nutrition interventions: a microsimulation model for the prevention of population Vitamin D deficiency (VDD), (May, 2017), College of Medical and Dental Sciences Graduate School Festival of Graduate Research, University of Birmingham, Birmingham, UK.
2. Economic evaluation of food fortification to prevent population Vitamin D deficiency – The case of wheat flour fortification. (2015, September) PhD-Supervisor conference of the European Association of Health Economics, Paris, France.

INTRODUCTION

This thesis aims to contribute with evidence to reduce the burden of Vitamin D deficiency (VDD) and help public health decision making in the UK, by estimating the cost-effectiveness of preventing population VDD using a decision analytic model.. This introductory section summarises the background behind the research question and provides a summary of each chapter within the thesis.

Vitamin D deficiency

VDD is a cause of concern for several stakeholders within the UK. Data from the National Diet and Nutrition Survey (NDNS) rolling programme, a continuous cross-sectional survey of the UK population's diet and nutritional status, has continuously highlighted, in its several reports that the mean daily dietary intake of Vitamin D is below recommended levels (1, 2). The 2014 NDNS report states that around 7.5 % of children and 20 % of adults are Vitamin D deficient (1). In the UK, and other mid- and high-latitude settings, dark skinned populations are at a higher risk for VDD, explaining why symptomatic VDD has been observed mainly in Black, Asian and Minority Ethnic (BAME) groups. This has raised concerns among the clinical community that the current national policies are failing to protect these groups of the population (3, 4). Moreover, VDD is also of interest to the public, as it is commonly mentioned in the media, often with contradictory messages about the benefits of limiting or eradicating it (5).

Vitamin D has an important role in the body in maintaining optimal bone and muscle health. VDD refers to insufficient Vitamin D in the body, and its diagnosis is made through a blood test. The term ‘Vitamin D’ is in fact a generic term that encompasses two analogue molecules, the most well-known cholecalciferol (also known as Vitamin D3), and ergocalciferol (Vitamin D2). The diagnostic test detects a hydroxylated Vitamin D metabolite that circulates in the blood serum, the 25-hydroxyVitamin D [25(OH)D], which is used as an indicator of Vitamin D status. In this thesis the term ‘Vitamin D’ is used to refer to both Vitamin D2 and D3, while ‘25(OH)D’ is used to refer to the Vitamin D status indicator.

The policy making context

In the UK, reports of high prevalence of VDD and cases of rickets have prompted decision makers to re-evaluate the national preventive strategy. Since 2005, a national programme, the ‘Healthy Start’, has been running with the aim to improve nutritional status of vulnerable groups, namely pregnant women, children up to the age of five years, and mothers of infants up to one year. This programme covers families receiving tax or income benefits, and offers them vouchers that mothers can trade for healthy food and multivitamin supplements, which include Vitamin D.

In 2014, the National Institute for Health and Care Excellence (NICE) called for economic evaluations on the most cost-effective way of providing supplements (6). In detail, the guidance calls for research on the effectiveness and cost-effectiveness of interventions to increase access to Vitamin D, improve uptake and adherence rates, and improve Vitamin D status in at-risk groups.

Thesis outline

The thesis is divided into three-parts: background research; research to inform the parameters for the decision analytic model; and development and analysis of the decision analytic modelling.

The first part, background research, comprises the first four chapters and provides: 1) a background regarding the clinical context; 2) the methodological foundations for the work developed within this thesis; and 3) the background and methodological guidance from previously published economic evaluations and model based analyses.

Chapter one explores the clinical and public health context of VDD in the UK by defining Vitamin D deficiency, the risk factors, the population at risk and potential ways of tackling it. Chapter two provides a summary for the theoretical and practical basis for decision-analytic models, and describes the most appropriate model types for addressing the research question posed in this thesis. The chapter moves on to describe value of information analysis and its application within economic evaluations of public health interventions. Chapter three presents a systematic review of the literature with the aim of exploring the methods used to estimate the costs and benefits of population strategies to prevent VDD. Finally, chapter four broadens the scope of the literature review presented in chapter three, by reviewing economic evaluations, with an emphasis on model-based analysis, of strategies to prevent micronutrient deficiencies (MNDs) other than VDD.

The second part of the thesis describes the empirical work to inform parameters for the model. In chapter five, the methods and results of two surveys developed for the estimation of health state (HS) utility values of VDD in children and adults are presented. The surveys used preference-based multi-attribute questionnaires, to elicit utility values from clinical experts.

The third and final part of the thesis presents the methods to build the decision analytic model and reports its findings in terms of the expected costs and benefits of different alternatives. Chapter six presents the methods to estimate the costs and benefits of preventing VDD. The chapter describes the data sources for the population inputs, as well as the costs and effectiveness parameters, and explains the model structure and its main characteristics. The methods for the base case analysis, as well as the deterministic and probabilistic sensitivity analyses are also presented. Furthermore, a value of information analysis (VoI) is described. In Chapter 7, the results of the base case analysis and the uncertainty analyses are presented, following, where applicable, the appropriate guidelines for good reporting standards (7).

Finally, chapter eight discusses the findings of the thesis. The results of the literature reviews, the empirical research, and the model are summarised and put in context within existing research. This chapter also ponders the strengths and limitations of the thesis and, concludes by elaborating on the implications of the research undertaken for future research and policymaking.

CHAPTER 1

VITAMIN D DEFICIENCY

Introduction

Vitamin D refers to a group of steroid hormones with an important role in maintaining bone health and in the cell life cycle (8). Vitamin D3 is produced when the skin is exposed to sunlight (9). Although sunlight, namely the ultraviolet B (UV-B) light, is Vitamin D's main source, it can also be sourced from foods and for this reason, Vitamin D is also known as a nutrient. Foods rich in Vitamin D include cod liver oil, fatty fish such as salmon and sardines, eggs, and sun-dried mushrooms (10).

The most well-known role of Vitamin D in the human body is to regulate the intestinal absorption of calcium and phosphorus. In the late 1800s and the early 1900s, it was discovered that nutritional rickets was cured when children were subjected to UV light and when they were treated with Vitamin D. This discovery led to food fortification with Vitamin D which in some countries resulted in the eradication of rickets (11). The more recent history of Vitamin D includes the discovery of Vitamin D receptors in a variety of tissues in the body, besides those related to bone metabolism, which has triggered new research to determine the potential role of Vitamin D in the cardiovascular system, dental health, insulin and glucose metabolism, the immune system, and cancer (11-13). To date, the main known complications of VDD are rickets, osteomalacia, hypocalcaemia and their complications.

VDD is defined by the concentration of one of Vitamin D's metabolite, 25-hydroxycholecalciferol [25(OH)D], in the blood serum. There have been different interpretations on the optimal level of 25(OH)D (SACN, 14). Among different clinical areas, different cut-offs have been suggested (15, 16). In the context of preventing rickets in children, recent consensus was achieved with respect to the definition of Vitamin D status based on 25(OH)D levels (17):

- Vitamin D deficiency: 25(OH)D <30nmol/L
- Vitamin D Insufficiency: 25(OH)D between 50-30nmol/L
- Vitamin D sufficiency: 25(OH)D >50nmol/L

This definition means that at concentrations of 25(OH)D <30nmol/L, there is a higher risk for developing rickets (17). In the UK, the Department of Health (18) defined VDD as serum 25(OH)D <25nmol/L, a threshold that is still in use nowadays (14). In the context of bone health, the Institute of Medicine (IOM) (19) states that 'individuals are at risk of deficiency at serum 25(OH)D concentrations < 30 nmol/L; some, but not all, individuals are potentially at risk for inadequacy at serum 25(OH)D concentrations from 30 up to 50 nmol/L; and practically all individuals are sufficient at concentrations of 50 nmol/L and above.' The IOM specified Vitamin a threshold of 50 nmol/L as consistent with the requirements of 97.5% of individuals aged >1 year for maintenance of bone and overall health (19). In turn, the Endocrine Society Task Force on Vitamin D (10) stated that 'individuals should be diagnosed as Vitamin D deficient at a cut-off level of 50 nmol/L serum 25(OH)D' and 'to maximise the effect of Vitamin D on calcium, bone, and muscle metabolism', serum 25(OH)D concentration 'should exceed 75 nmol/L' (10).

Thresholds between 50-100 nmol/L have been proposed for other non-skeletal outcomes (16, 20), but to date causality has not yet been established and such recommendations are not supported by the Global Consensus Group, IOM, SACN or the Endocrinology Society.

Historical background

The discovery of Vitamin D is closely linked with research into the cure for rickets. The compound was first mentioned in the literature by McCollum et al., 1922, named as the calcium depositing factor and was defined as a "Vitamin with the specific property of regulating bone metabolism" (21). After it was noticed that cod liver oil was able to treat rickets, and as a result of McCollum's experiment, Vitamin D was identified as the molecule present in cod liver oil that was responsible for the rickets remission (21). That compound became known as an essential nutrient and was named Vitamin D and followed the discoveries of Vitamins A, B and C (11).

Some hundred years before, in 1822, Sniadecki observed a higher incidence of rickets in children living in Warsaw compared to those living in rural areas (22). He correctly associated rickets with scarce sunlight and advocated adequate sunbathing as a healthy habit. In 1890, Palm T. came to a similar conclusion when he compared the incidence of rickets among several European countries, as well as India, China, Japan, the West Indies and the United States (23). These findings triggered more research and, in 1919, Huldschinsky was the first to provide evidence of curing rickets through UV light exposure, in an experiment using a mercury vapour lamp (24). These new discoveries prompted the beginning of a healthy sunshine era, where adverts would promote outdoor physical activities and mothers were encouraged to sunbathe their children, or to give them cod liver oil, "the bottled sun" (25). The first published work on the biological active forms of Vitamin D dates from 1967 (26).

Sources of Vitamin D

The major source of Vitamin D is its synthesis in the skin. The skin contains contain 7-dehydrocholesterol (also known as provitamin D3) which, in the presence of (UV-B) photons from the wavelength between 290–315nm, converts into pre-vitamin D3 (24, 27). The latter is then transformed into Vitamin D3 in the liver. If the skin is exposed to UV light for a long period of time, pre-vitamin D is converted into inactive forms of Vitamin D. This means that there is no risk of Vitamin D toxicity caused by prolonged sun light exposure (15). Experiments have shown that, in optimal conditions, the production of Vitamin D by sunlight exposure is equivalent to a daily dose of up to 10,000 International Units (IU)[1] of Vitamin D, i.e., 100 times the recommended daily adult intake (28). It is worth mentioning that this process is not constant and depends on the amount of UV-B that reaches the skin, as well as on the amount of pro-vitamin D available in the skin (19). Similarly, to Vitamin D, melanin, the pigment present in the skin, is produced by the action of UV-B. Melanin competes with pro-vitamin D for UV-B light and therefore, those with darker skin tones produce less Vitamin D.

Vitamin Food

Vitamin D can be found in a limited number of foods, and most of it is retained in the food even after being subjected to high temperatures (29). It is produced by irradiation of UV light in plants/fungi (Vitamin D2) and in the animals' skin (Vitamin D3). Due to its fat-soluble nature, animals are able to store greater amounts of Vitamin D in their adipose tissue, and subsequently provide humans with it through the diet. The main dietary sources of Vitamin D include cod liver oil, fatty fish (such as salmon, mackerel, halibut and herring) and dairy (SACN, 14). The amount of Vitamin D3 in fish is not constant, even within the same species, and it varies largely according to its source (wild or aquaculture) and other factors (27). The UK NDNS reports that meat and meat products were the major contributor to Vitamin D intake for all age groups, except children aged 1.5 to 3 years, providing 23-35% of intake. Milk and milk products were the major contributor to Vitamin D intake for children aged 1.5 to 3 years, providing 24%.

Fortified foods

Vitamin D can be found in various fortified foods but the amounts vary according to national policies and cultures. Food can be fortified with either Vitamin D2 or Vitamin D3. The choice of which compound to use depends on several factors such as chemical properties (for example Vitamin D3 has better stability when dried to be added to flour) (30), and on the market targeted (Vitamin D2 is more attractive to vegetarians due to its vegetable origin).

Under UK statutory regulations, the addition of Vitamin D is mandatory for spreadable fats (40-100IU/ 100 kCal) and infant formula (320IU/100g) (31-35). Additionally, most breakfast cereals are voluntarily fortified with Vitamin D. According to the NDNS, spreadable fats contributed 19-21% to Vitamin D intake across all age groups, while ‘cereal and cereal products’ provided 13-20% of intake (1).

In the United States, for example, fortification provides roughly three-quarters of the Vitamin D intake from the diet. Under US regulation, it is mandatory to add Vitamin D to fortified milks (36). The fortification of other foods such as cereals, flour, pasta, rice, beverages, regular milk and dairy is optional and the maximum allowed is defined by law (36). In Europe, milk is fortified in Scandinavian countries (37). In Finland, food fortification has been gradually implemented: butter, spreadable fats and milk were fortified in 2003. A subsequent dietary survey showed that there were still groups of the population with insufficient Vitamin D intake and therefore the policy was revised to increase the amount of Vitamin D added. The latest survey (2012) showed most groups achieved adequate daily intake, except older women (37).

Supplementation

Vitamin D can be found in several supplement preparations alone, in multi-vitamin preparations or in combination with calcium. Although there is no official data on how many individuals in the UK take Vitamin D supplements, the NDNS found that 22% of adults aged between 19-64 years and 41% of adults aged 65 years and over had taken at least one supplement during the study period. In children, supplement use was most common in the 4-10 years’ age group (16%) (1). The study also found that the most common type of supplements were fish oils, including cod liver oil, and multi-nutrient supplements. In older adults aged 65 and over, 24% took cod liver oil and other fish oils during the whole study period.

Most European countries have supplementation programmes, specially to cover infants up to one year (37). In Sweden, children aged 0-2 years have access to free Vitamin D supplements of 400 IU per day through child welfare centres. Daily supplementation is also recommended for those with dark skin, with limited sunlight exposure including people wearing fully concealing clothing, those who are institutionalised, and for pregnant women (37).

Risk factors for VDD

VDD is mainly caused by restricted sun exposure and, to a lesser extent, to low dietary Vitamin D intakes. The intake of Vitamin D is compromised in some diets (milk allergy, lactose intolerance, ovo-vegetarianism and veganism), and when the absorption of Vitamin D in the intestine is inadequate, such as in malabsorptive conditions or Crohn's disease (38). Conditions that affect the normal function of the liver or kidney are also associated with low levels of serum 25(OH)D (19). Several lifestyle and environmental factors constitute barriers to UV reaching the skin and therefore increase the risk of VDD (SACN, 14):

- Winter season in higher latitude regions, when the angle of sun light is such that, at latitudes above 50^0, there is no sufficient sun light;
- Spending most of the time indoors and behind window glass;
- Use of clothing that covers the whole body, such as winter attire and some religious clothing;
- Use of sunscreen that blocks UV-B, particularly when the sun protection factor (SPF) is >8 (15);

- Being in areas that are in shadow, as well as cloudy days, air pollution and smog (39);

Latitude is an important limitation to sunlight availability. In low latitude settings, the tropics and subtropical regions have optimal UV light available throughout the year, and Vitamin D can be produced year-round (Figure 1). The number of months with adequate sunlight exposure decreases with increasing latitude. In the mid-latitudes, roughly between 35^0 and 50^0, Vitamin D synthesis is optimal during five months (May to September). In high latitudes, above 52º, which in the UK means north of Cambridge, the season for optimal Vitamin D is restricted to four months (mid-May to mid-September) (40). Hence, in mid- and high-latitude settings, there is marked seasonal variation in the prevalence of VDD. In the UK, it has been found that serum 25(OH)D is highest in September, at the end of the summer, and lowest in February.

Interestingly, VDD is not confined to high latitude settings. Several countries are now concerned with a high prevalence of VDD, which can be associated with the usage of full body clothing, mainly by women in some cultures, sun avoidance behaviour in response to very hot weather, sunscreen usage due to risk of skin cancer, and pollution, among others (41-44).

Moreover, obese individuals have, on average, lower serum 25(OH)D levels. Since Vitamin D is a fat-soluble molecule, it is likely that it is deposited in fat tissues, reducing its bioavailability (45).

Besides the environmental and geographical factors, the skin's capacity to produce Vitamin D varies. As stated previously, those with melanin-rich skin produce lower amounts of Vitamin D when exposed to sunlight. Dark skinned populations are at high risk of VDD, especially when living in high latitude countries since in these settings, the year-round availability of sunlight does not meet their needs for optimal exposure (SACN, 14). The skin's ability to produce Vitamin D is also compromised in older adults. Moreover, elderly individuals are more likely to be confined to indoor environments, due to illness or lack of independence.

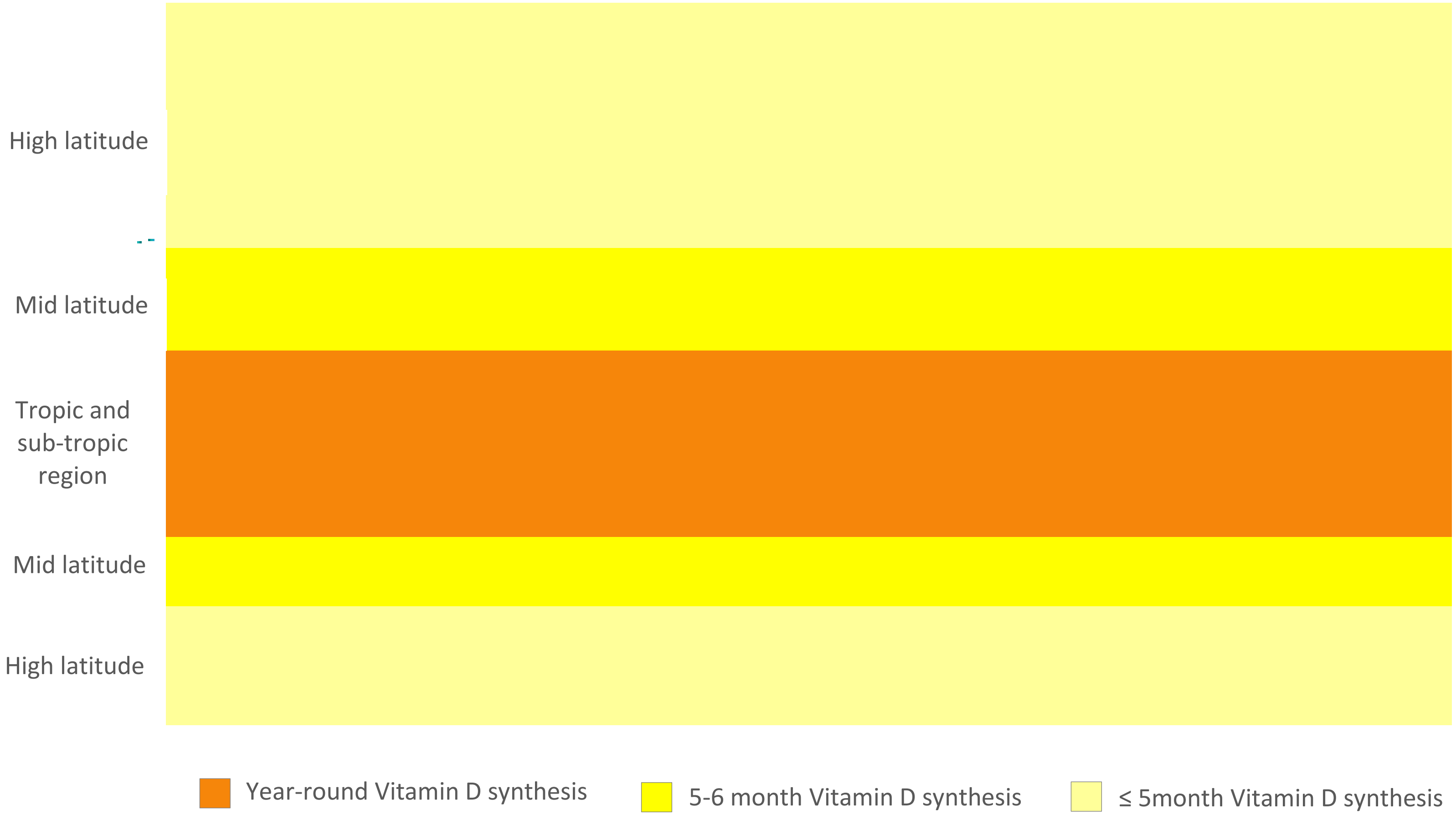


FIGURE 1 - VITAMIN D SYNTHESIS ACCORDING TO LATITUDE

Reference nutrition intake (RNI) of Vitamin D in the UK

NICE defines RNI as “the amount of a nutrient required to meet the needs of around 97% of individuals within a group” (46). The RNI/Safe intakes have been developed to ensure that the majority of the UK population has a satisfactory Vitamin D status throughout the year, in order to protect musculoskeletal health (14). Until 2016, the RNI for Vitamin D was only defined for children and older adults. In 2016, SACN published new Vitamin D recommendations in which the RNI was defined for the wider population. SACN recommends an RNI of 400IU/day, throughout the year, for everyone in the general UK population aged four years and above. Although insufficient data was found for younger ages, the new guidelines recommend a safe intake of 380-400 IU/day for infants up to one year and of 400IU/day for young children aged between 1-4 years..

The last report of the NDNS found that mean intakes of Vitamin D from food sources were markedly below the RNI in both children and elderly participants (27% and 33% respectively) (1). Inclusion of intakes from dietary supplements brought the mean intake up to 32% of the RNI for children aged 1.5-3 years old and 51% for adults >65 years old.

Prevalence of VDD

The literature reports VDD to be widespread in children and adults around the world (10, 47) but reported estimates vary. The use of different 25(OH)D cut-offs to define

VDD, the season in which blood samples are collected and the type of assay used may influence the results.

Cashman et al. 2016 combined data from 14 studies set in several European countries, including Austria, Denmark, Greece, Ireland and the UK to estimate the prevalence of VDD in Europe. The study pooled individual data from over 5,000 individuals and found that the prevalence of VDD in Europe is 13.0%, defined as serum 25(OH)D < 30 nmol/L (47).

The comparison of prevalence of VDD across settings is hindered by the use of different cut-offs, differences in the study designs, the influence of the latitude and month in which the blood is collected, and differences in laboratory methods used to analyse the samples (37).

Countries with wider fortification policies have managed to eliminate the latitude effect in their population's VDD risk. For instance, Sweden reports higher mean population serum 25(OH)D than countries in southern Europe. Besides the strong fortification policies, the high intake of fatty fish and the high proportion of white ethnic groups are factors that contribute to the Vitamin D status of the Swedish population (37, 48). Importantly, there is evidence that dark skin populations do not have sufficient milk intake in order to achieve adequate Vitamin D intake (49, 50).

United Kingdom

Data from NDNS revealed that year-round the proportion of children with serum 25(OH)D < 25nmol/L was 7.5% in those aged 1.5 to 3 years; 12.3% in boys aged 4 to 10 years; 19.7% in boys aged 11 to 18 years; 15.6% in girls aged 4 to 10 years; and 24.4% in girls aged 11 to 18 years Figure 2. The proportion of adults who had a 25(OH)D concentration below 25nmol/L was 24.0% of men aged 19 to 64 years; 16.9% of men aged 65 years and over; 21.7% of women aged 19 to 64 years; and 24.1% of women aged 65 years and over (1).

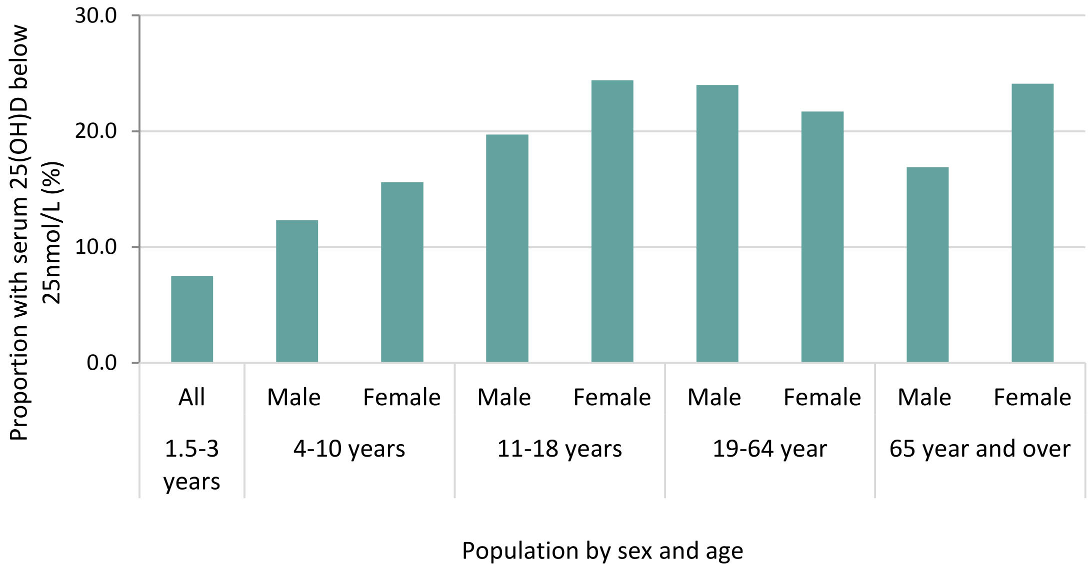
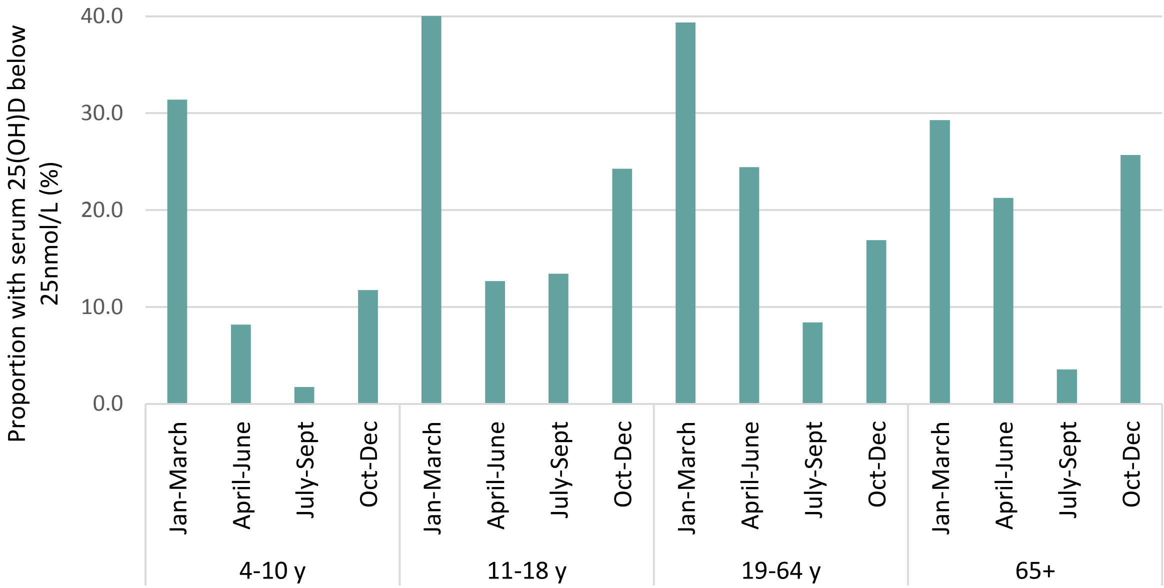


FIGURE 2 – YEAR-ROUND PROPORTION OF THE UK POPULATION WITH SERUM 25(OH)D BELOW 25NMOL/L.

A cohort study including 7,437 white adults aged 45 years old found that 15.5% had serum 25(OH)D below 25nmol/L and 46.6% had levels below 40 nmol/L (51). The NDNS (1)also reports the seasonal variation in the prevalence of VDD in the UK (Figure 3), and the proportion of deficient individuals is at a maximum in the winter, and minimum at the end of the summer.



.

FIGURE 3 – SEASONAL VARIATION OF THE PREVALENCE OF VDD IN THE UK

None of the studies above provide data on ethnic minority groups. Although no population data is available, several studies found lower serum 25(OH)D in Black and Asian minorities (52-54). Additionally, it has been found that, unlike in the white ethnic groups, there is no seasonal variation in the prevalence of VDD in BAME groups (55).

Clinical outcomes

As mentioned before in this chapter, VDD leads to poor bone mineralisation. Children with prolonged and severe VDD may develop rickets and osteomalacia, which can result in bone deformities such as bowed legs and widened wrists and ankles, muscle weakness and hypocalcemic complications (seizures, cardiomyopathy) (4, 17, 56). In adults, chronic VDD leads to osteomalacia, which is also characterised by poor bone mineralisation. Osteomalacia in adults may result in bone pain and muscle weakness (57, 58).

The link between Vitamin D status and chronic diseases such as cancer, cardiovascular disease, autoimmune disorders, tuberculosis, multiple sclerosis and type 1 diabetes has been hypothesised. Due to the poor quality of the evidence available so far, the IOM considered the role of Vitamin D in these diseases as 'hypotheses of emerging interest'(19). Other than bone health, the committee concluded that there was no convincing or adequate evidence of cause or effect for Vitamin D playing a role in disease risk (19).

Children

A. HYPOCALCAEMIA

Hypocalcaemia is a metabolic complication of VDD that poses a life-threatening risk. Symptoms include seizures, tetany and severe cardiac disorders. VDD is the most common cause of hypocalcaemia diagnosed in primary care in the UK (4, 58).

Cardiac disorders due to hypocalcaemia include dilated cardiomyopathy, congestive cardiac failure and left ventricular dysfunction (59-63). A retrospective study undertaken between 2000 and 2006 in a paediatric cardiology unit in Southeast England (64) found 16 cases of cases hypocalcemic heart failure caused by VDD, all within infants from a BAME background (10 of Afro-Caribbean ethnicity and six South Asians). This resulted in an estimated incidence of 2.7 cases per year. All patients required admission to the intensive care unit and respiratory and cardiovascular support. Of the 16 cases, three patients died and six needed to be resuscitated. Two patients received extracorporeal membrane oxygenation support (one for seven days and the other for 13 days). One case of neurological damage was reported, although no further details were provided (64). Brown et al. reviewed records of hypocalcemic dilated cardiomyopathy in a hospital in Washington, U.S. All four cases identified were Afro-

Americans infants who had been exclusively breastfed (65). Although apparently rare, cardiac disorders have high direct and indirect costs (66)

Another severe event resulting from hypocalcaemia is hypocalcemic seizures. Several reports from Turkey, Pakistan, India, the U.S. and the UK (67-72) show that hypocalcemic seizure can be caused by VDD. A study by Julies et al. in two hospitals in London estimated an incidence of 6/10,000. All cases were in Asian ethnic groups and in infants up to one year. The same study highlights the risk of hypocalcemic seizures being misdiagnosed as (more common) febrile convulsions (73). If this is the case, no blood test is performed and severe VDD remains under reported. Basatemur and Sutcliffe (70) reviewed hospital records of hypocalcemic seizures caused by VDD in the UK and Ireland. The study estimated an incidence of 3.49 per million in children aged between 0 and 15 years. The majority of the cases (88%) occurred in children from Asian and black ethnicities. Almost all children (98%) were admitted to the hospital with a median duration of stay of three days. Treatment included intravenous calcitriol in 78% of the children and intravenous calcium gluconate in 44% of the children. Half of the patients, 51%, were given anti-convulsive therapy (Benzodiazepine, Phenobarbitone or Phenytoin). No deaths were registered. One patient suffered burns due to the extravasation of intravenous calcium gluconate (70).

A study undertaken in two Turkish hospitals reviewed the records of infants with less than 3 months of age admitted to hospital and diagnosed with VDD (71). Of the 42 cases identified, 33 presented with seizures and seven with severe respiratory symptoms. Of 126 children with rickets in an Australian study, 33% presented with hypocalcemic seizures (74)

From the available evidence, it is clear that hypocalcemic seizures and cardiac disorders caused by VDD pose severe health consequences and require medical attention, including hospitalisation.

B. RICKETS AND OSTEOMALACIA

Causality between VDD and rickets/osteomalacia is well established, however the epidemiological burden of rickets is challenging to assess (56). Rickets is a condition affecting the growth plates (new bone) and osteomalacia stands for bone softness of existing bone (old bone). One of the reasons is that studies use different definitions and diagnosis criteria, which make studies non-comparable. Another obstacle is the environmental changes over time, e.g. pollution and nutrient availability translates into highly variable incidence over time. The prevalence of rickets was reportedly as high as 98% in high latitude regions between the 1920s and the 1930s (75). Recently reported incidence rates indicate rickets is a rare disease in most high-income countries (less than five cases in 10,000 of the general population, as defined by the European Union (Table 1).

TABLE 1 – INCIDENCE OF RICKETS IN SOME HIGH-INCOME COUNTRIES

Study	Country	Population	Rate
Ward et al. (76)	Canada	General population	2.9/100,000
Munns et al. (77)	Australia	General population	4.9/100,000
Callaghan et al. (3)	UK	General population	7.5/100,000
Callaghan et al. (3)	UK	African Caribbean	9.5/10,000
Callaghan et al. (3)	UK	Asian	3.8/10,000
Ashraf et al. (78)	UK	Non-Caucasian	1.6 / 100

Although incidence rates of rickets have historically decreased in high-income countries throughout the last century, the opposite phenomenon is reported for the hospitalisation rates for rickets (79). Hospitalisation rates were low in the 1960s and declined until the 1990s. Rates were lowest in 1991-96, 0.34 children per 100 000 under 15 years (95% CI 0.13-0.55) and highest in 2007-11, 1.78 children per 100 000 (95% CI 1.27-2.29). The same study provides the individual-base rate (3.16 children per 100 000) and the episode-based rate (4.78 children per 100 000) for England. The majority of the children were < 5 years. Regarding ethnicity, 32% of the cases occurred in white children, 33% in south Asian, 33% black, and 2% other non-white.

Adults

A. OSTEOMALACIA

Osteomalacia, which means “soft bone”, (poor bone mineralisation), affects children and adults, causing symmetrical, non-radiating pain and in the back and legs, spreading later to the arms (57). Osteomalacia and associated hypocalcemia due to VDD leads to muscle weakness, creating difficulties in climbing stairs and getting up from a squatting position (80).

A meta-analysis by Annweiler et al. (81) reports that 25(OH)D serum levels are lower in older adults that suffer a fall, when compared to non-fallers, and notes that the link between low serum 25(OH)D and falling persists, even when rates are adjusted for several confounding factors such as age, gender, body mass index, comorbidities, polypharmacy, depression, cognitive decline, muscular strength and visual acuity (81). The underlying cause for the falls is muscle weakness, and aging.

The evidence from effectiveness studies is in line with such a statement, and the direct and indirect effect of Vitamin D supplementation in preventing falls in the elderly population has been estimated in two Cochrane reviews (82, 83). The reviews considered both community and residential care home settings, and concluded that Vitamin D supplementation is effective in preventing falls in individuals who are Vitamin D deficient (82, 83). Supplementation was effective in reducing the rate of falls (0.57, 95% CI 0.37 to 0.89) and the risk of falling (0.70, 95% CI 0.56 to 0.87) (82).

A meta-analysis of eight RCTs found that Vitamin D supplementation reduced the risk of falls (RR, 0.78; 95% CI, 0.64-0.94), if the dose was 700 IU/d or greater, and the serum 25(OH)D was at least 62.4 nmol/mL. The benefit of Vitamin D could have been limited to those with unrecognized osteomalacia, which is associated with proximal muscle weakness and gait instability.

Falls have been reported to have an economic impact, not only on the health budget but on society, as they translate in high morbidity and mortality rates to the patient and require informal carer resources. The WHO Global report on falls prevention in the elderly population states that falls are the underlying cause of 10%-15% of all emergency department visits (84). Falls are also a leading cause of traumatic brain injury and fractures. The largest share of direct costs related to falls consists of inpatient costs. Additionally, falling may result in a post-fall syndrome that includes loss of autonomy, confusion, immobilization and depression. The societal cost of a fall includes loss of productivity if a relative takes time off-work to care for the patient (84).

The cost of falls in the UK was estimated to be £581 million to the National Health Service (NHS) and £400 million to the Personal Social Services (PSS) in 1999 (85). The burden goes beyond the public sector, as those who fall incur monetary costs, as well as a decrease in quality of life due to injuries or post-fall trauma (86).

Prevention strategies for Vitamin D deficiency

Since VDD emerged as an area of importance within the public health agenda, countries worldwide have adopted different strategies to prevent it. Possible interventions include supplementation of targeted groups and food fortification (12).

Supplementation

Supplements are a vehicle to provide micronutrients and/or minerals, alone or in combination, to targeted groups of the population. The available concentration of the micronutrient is generally large and presented in the pharmaceutical dosage of pills, capsules or syrups. The supply is optimised as nutrients are delivered in their highest absorbable forms and marketed dosages take into account the reference intake values. When mild micronutrient deficiency is diagnosed, supplementation is an effective way to rapidly restore the optimal status (12).

The production costs for supplements can be high, depending on the price of the micronutrients included and the level of complexity of the dosage form chosen. The effectiveness of supplements depends widely on an effective distribution system and optimal consumer adherence. The latter is critical for supplements that require long-term compliance, as is the case for Vitamin D supplements (12).

In the UK, a national supplementation strategy exists, within the Healthy Start scheme, to provide essential nutrients, including Vitamin D, to children up to four years old, pregnant women and breastfeeding mothers. The programme targets low income families and free supplements are available to families in receipt of Income Support, Income-based Jobseeker's Allowance, Income-related Employment and Support Allowance, or Child Tax Credit and an annual family income of £16,190 or less (87).

Food Fortification

Food fortification can be used as a public health measure that results in the addition of an essential micronutrient – Vitamin or mineral - to a food with the aim to improve the nutritional quality of the food supply (12). Vitamin D is a fat-soluble compound that can be added to vegetable oil, margarine, milk and dairy products, as well as to wheat flour and maize flour.

Fortification of foods is implemented through statutory processes, and national regulations will determine what foods can be fortified, as well as the minimum amount of nutrient required and the maximum permitted. Fortification can be mandatory, where all food suppliers are required to comply with the regulation, or voluntary, when only those wishing to fortify will do so, following the maximum amounts.

Several countries have Vitamin D fortification policies in place. In the UK, it has been mandatory to fortify margarines since the 1930s. In other high latitude countries, such as Canada, the United States and Scandinavian countries, milk is a vehicle for Vitamin D fortification (37). Wheat flour fortification initiatives have more recently started in Jordan and the Gulf Countries.

Toxicity

Toxicity due to high levels of Vitamin D is rare, and manifests as hypercalcemia or hypercalciuria, i.e., increased serum or urine calcium concentrations. To avoid toxicity, authorities have stipulated a Tolerable Upper Intake Level (UL) of Vitamin D, which is the highest safe level of Vitamin D intake for almost all individuals in the general population. Intakes above the UL increase the risk of adverse effects (14). The UL for all adults, including pregnant women, and children above nine years, is 4,000 IU/day. Lower ULs were set for younger children and infants: 1,000 IU/day for infants 0-6 months, 1,520 IU/day for infants aged 6-12 months, 2,000 IU/day for children aged 1-3 years and 3,000 IU/day for children aged 4-8 years.

Vitamin D and calcium

It is challenging to isolate the effects of Vitamin D due to its synergetic function with calcium (the formed being the supplier to the body of the latter). Moreover, supplements available to adults are commonly combined preparations containing both Vitamin D and calcium. Studies investigating the prevention of bone related outcomes commonly study interventions of both Vitamin D and calcium. The rickets consensus (17) clarified those individuals with low serum 25OH Vitamin D are not at risk for nutritional rickets if their dietary calcium intake is optimal. Vice versa, calcium-deficiency rickets can occur in the presence of normal 25OH Vitamin D concentrations, in areas or ethnic communities with very low dietary calcium content. The NDNS reports that the majority of the UK population have adequate calcium intake, except for teenage girls (1). Policies on dietary calcium are outside the scope of this thesis and will not be considered hereafter.

IMPORTANT MESSAGES FROM THIS CHAPTER

- The main source of Vitamin D is cutaneous via UV-B (sunlight) exposure; Vitamin D can also be sourced from some foods, although in smaller amounts;
- VDD is widespread in some regions due to high latitude (no UV-B containing sunlight for part of the year), and/or insufficient time exposed to the sun – this is caused by lifestyle and environmental factors such as full-body clothing, pollution or long working hours indoors;
- VDD leads to hypocalcemia and poor bone mineralisation in children and adults, of all age groups;
- Those at higher risk for VDD are the elderly, infants and BAME groups living especially in high latitude countries.
- Year round, approximately 7.5% of the children and around 20% of the adults in the UK general population are VDD.
- Strategies to prevent VDD include supplementation of groups at-risk and food fortification.

CHAPTER 2

DECISION ANALYTIC MODELLING TO INFORM PUBLIC HEALTH DECISIONS

Introduction

Public health has been defined as 'the science and art of promoting and protecting health and well-being, preventing ill-health and prolonging life through the organised efforts of society' (88). This definition conveys the idea that all individuals in society are committed to achieving and preserving good health and well-being. To do so, public health goes beyond the health care sector, acting across several fronts such as education, environment and housing. Indeed, the prevention of ill-health and its treatment are two different things: the latter is concerned with modifying aspects of existing disease, by alleviating and/or eliminating them, while the former aims to modify conditions that expose individuals to higher risk of disease, such as pollution, and smoking. The benefit of public health programmes lies in reducing the risk of illness or premature death. In turn, how benefits are valued depends on the initial risk, the reduction in risk achieved, and the time it takes for this reduction to happen.

Public health decision makers need to answer complex resource allocation questions, where they are having to constantly trade-off between scarce resources and the delivery of effective interventions. In England, as in most countries in the world, public health is primarily under jurisdiction of the government, and decisions can be made at a local or national level. Decisions about resource allocation rely more and more on economic evaluations, including model based analysis, as a way to evaluate the costs and benefits of competing programmes. The NICE methodological recommendation on producing guidance includes methods for incorporating economic evaluations and draws a clear distinction between economic evaluation conducted to inform Health Technology Assessment (HTA) reports and guidance on interventions with health and non-health outcomes in the public sector and other sectors (89).

From an economic perspective, the government intervention in the health care market is justified by the presence of market failures. If we accept the neoclassical economics assumption that individuals make rational decisions with the aim of maximising their utility, the problem with the health care market relates to, among others (90):

1. Information failures, i.e., individuals are not informed about unhealthy lifestyles, advertising of unhealthy goods;
2. Uncertainty regarding outcomes.

It is therefore assumed that individuals do not always act as their best agents when it comes to preventing illness. Hence, the government intervenes, acting as their agent by promoting lifestyles that are more likely to result in the absence of illness and longer life. This is seen as a paternalistic intervention, where the state interferes in the individual’s choice, acting in their best interests and promoting choices that the individual would not otherwise consider (90).

This chapter describes the theoretical and empirical foundations of economic evaluation and model based analysis in the context of health care and public health. The chapter starts with the distinction between the concepts of positive and normative economics, to contextualise economic evaluation into the normative economics framework. Next, the main theoretical basis for economic evaluation in health is outlined, followed by a description of the main types of economic evaluation. The chapter continues by describing the main characteristics of model based analyses and finishes by outlining methods to deal with decision uncertainty, namely probabilistic sensitivity analysis (PSA) and Value of Information (VoI) analysis.

Theoretical Background

Normative economics and decision making in health care

Economics is divided into two main streams: positive and normative economics. While positive economics answers objective and verifiable questions, by using available evidence to explore the relationship between economic variables (91), normative economics is a subjective approach that relies on value judgements to answer questions about how things should be (91). For example, positive economics would determine the relationship between user charges and the demand for care, while normative economics would be concerned with the desirability of such a relationship. The latter is subjective and context specific and judgement on the desirability would take factors, such as equity and efficiency, into consideration (91).

Although summarising available data on costs and benefits to influence future policy implications may intuitively seem a task that fits within positive economics, economic evaluations are normative in their nature (91) since there is a fundamental normative stage of deciding what costs and consequences should be considered within the analysis (92), how benefits are valued and what is regarded as the optimal option. All these considerations require value judgements and are therefore normative (91). The two main normative approaches used in health economics are welfarism and extra-welfarism, which are explained below.

Welfarism and the Pareto principle

Welfare economics is "defined as the systematic analysis of the social desirability of any set of goods or states of the world, solely in terms of the utility obtained by individual people" (91).

Welfare economics aims to provide a framework to allow the ordering of states of the world according to social preferences (93). The framework is normative and based on four principles (94):

1) The expected utility principle, which states that individuals are able to rationally maximise their welfare by ordering different options and choosing the preferred one – the one that results in higher expected utility;
2) Individualism, i.e. each person is the best judge of their own welfare;
3) Consequentialism, i.e., utility is obtained only as a consequence of the consumption of goods;
4) Welfarism, which determines that the desirability of a state of the world is judged by, and only by, the utility of the individuals in that state.

Hence, welfarism provides the evaluative space in which decisions are made (93) and the combination of the four principles tells us that policies ought to be evaluated in terms of utility only, and this utility is the sum of the self-assessed individual utilities (94). In order to identify efficient resource allocations, economists use the Pareto principle, which determines that a policy change is socially desirable if everyone is made better off (weak Pareto improvement) or at least some are made better off while no one else is made worse off (strong Pareto improvement) (95), according to their own judgement. The former is referred to as a weak Pareto improvement as it is formed by a weak value judgement, i.e., one that gathers consensus, while the latter is a strong Pareto improvement because it is based on a strong value judgement, i.e., a less consensual and therefore a more debatable judgement (91). Pareto optimality states that the community becomes better off if one individual becomes better off and no one becomes worse off.

The Pareto principle is not without criticism. Firstly, as Tsuchiya and Williams (96) noted, there are hardly any Pareto Improvements in the real world, meaning that all policies require a trade-off that will make some better off, at the expense of some being made worse off. Secondly, the Pareto rule is blind to whose utility is being increased (96) thereby ignoring distributional aspects of the potential changes to the states of the world. Finally, Pareto optimality does not guide the social decision about what bundle of goods, or what policies, considered optimal under the Pareto rule, should be adopted, as it is not possible to make comparisons among different points involving trade-offs (91). Pareto Welfare Economics does not offer a theory for social choice (95), hence why the concept of Potential Pareto Improvements was developed. First suggested by Kaldor (97) and Hicks (98), this concept introduces the compensation principle, whereby a potential Pareto improvement requires the losers to be compensated and, if after compensation, the gainers are still better-off, the change is desirable (99). This is more easily understood if gains and losses are expressed in monetary terms. If moving from A to B would make an individual gain £500 and another lose £100, the winner could compensate the loser and still gain £400. It is clear that, if seen as a whole, the transaction constitutes an overall gain to the societal welfare, i.e., there is the potential for a Pareto Improvement. An obvious problem of this approach is that individuals are not compensated in practice and, therefore, real losses occur that may not be acceptable (100). Moreover, compensation in social and health markets would require that losses are valued in monetary terms, and we would know exactly how much each person would require as compensation (96), which is hard to achieve. Nonetheless, Potential Pareto improvements are still used in economic evaluations in several fields, including health economics, as they underpin the method referred to as cost-benefit analysis (CBA).

Extra-welfarism

The extra-welfarist approach has had been widely used among health economists as an alternative to welfarism. Although it has weaker roots in economic theory, it assumes a more pragmatic view of the decision problem that has proved helpful within the health care context.

Extra-welfarism has its foundations is seeded in the critique of welfarism, namely in its limitations in capturing wellbeing meaningfully. Sen (101) argued that self-assessed utility is affected by the individual's physical condition and the individual's economic circumstances, aspects that are not considered in welfare economics. Sen (101) called the former the physical 'condition neglect', and the latter the 'valuation neglect'. Information regarding these characteristics should be incorporated in the process of comparing health states (HSs) because the individual's characteristics, including functioning and freedoms of choice (capabilities), are likely to determine how they assess their wellbeing. The notion of adding these extra aspects to the social welfare function became known as extra-welfarism (91).

Further criticism of the application of welfare economics to health includes questions around the application of market based theories to the health care market, that is dominated by market failures itself (96). Moreover, the consequentialist principle of welfare economics does not allow the inclusion of community values into the social welfare function (102, 103). In communities, individuals may reveal preferences towards common goods, which lower their own utility (91).

Sen's work was particularly relevant to the health sector, and the idea of considering the characteristics of people in health care decision making was strongly advocated (104) and permeated to what is nowadays the most widely used methodology in economic evaluation of health policies. Extra-welfarism applied to health care defends the maximisation of heath, as opposed to utility, as health is seen as the means to increase utility, by reducing deprivation (104). Brouwer et al. (2008) asserts that extra-welfarism adds four extra components to welfarism, as 'it permits the use of outcomes other than utility, it permits the use of sources of valuation other than the affected individuals, it permits the weighting of outcomes (whether utility or not) according to principles that need not be preference-based, and it permits interpersonal comparisons of wellbeing in a variety of dimensions' (93).

Extra-welfarism is the prevailing basis of economic evaluation in health care in the UK and internationally (105, 106) and offers a pragmatic approach that is seen to fit well with decision makers' goals. Nonetheless, some authors criticise extra-welfarism for being too narrow in only considering health as the relevant outcome in economic evaluations (94, 106). Hurley (94) argues that extra-welfarism is limited by its consequentialist view that utility arises only from the consumption of health, neglecting aspects that are potentially important, such as ethical and distributional concerns (106).

Economic Evaluation in health care

Economic evaluations are a systematic approach to analyse the available evidence to support decisions. Data on costs, benefits and disease pathways are combined with the aim of improving decisions about the allocation of resources in terms of maximising allocative efficiency.

Drummond et al. (2005), describes the advantages of choosing such an approach in health care decision-making:

1. Systematic analysis of all relevant alternatives;
2. Provision of independent evaluation by analysing costs and outcomes from a viewpoint other than that of the decision maker's;
3. Information on the value of the benefits that have been forgone by investing in a given programme instead of another, using an 'opportunity cost' approach that aims to reach a decision resulting in the most value, under scarce resource conditions.

Cost-benefit analysis

Rooted in welfarist economics, cost-benefit analysis (CBA) was the first type of economic evaluation to be applied to health care. Although still used, other types of analysis, namely cost-effectiveness and cost-utility analysis are more frequently used in health care. Nonetheless, CBAs are still the preferred type of evaluation in other sectors such as the environment (107, 108) and transport (108). Indeed, one of the advantages of using CBA in health care is the comparability of alternatives across different public sectors, to identify those with higher benefit. CBA is seen as applied welfare economics with the aim of identifying Pareto improvements or Potential Pareto improvements, in order to increase social welfare. Because it takes a societal perspective, CBA is regarded as an independent tool that can be used by decision makers to assess different alternatives (91).

CBA values all costs, resources used and benefits in the same unit - monetary terms. The calculations involved are relatively simple. The complexity of CBA arises from the difficulty in valuing health outcomes in monetary units. The most widely used method, contingent valuation (CV) involve eliciting individuals' valuation of health outcomes in terms of hypothetical payment to receive a benefit or compensation to accept an undesirable outcome (91).

Practical and ethical limitations of valuing health in monetary terms have led to other types of evaluation becoming preferred to CBA, namely cost-effectiveness and cost-utility analysis. One commonly cited limitation is that the results of the valuation exercises are likely to be influenced by the individual's income. In practice, those with a lower income will state a lower WTP, which may not mean that they value attributes less, but rather that they place a higher marginal value on one monetary unit. Moreover, some raise ethical concerns about placing a monetary value on health and health care.

Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) originates from operations and management research, and assumes the goal of maximisation under conditions of constraint, which has been applied to health care and defined as 'Technical efficiency' - producing the most output (health) with the use of the available resources (91). CEA draws from extra-welfarism in that it adds to the social welfare function, which is defined through utility maximisation in terms of money, health and other relevant outcomes. While costs and resources used are considered in monetary terms, benefits are measured in natural units, for example blood pressure or weight. CEA is therefore useful to compare interventions targeting the same health condition and is particularly useful in a clinical setting. However, CEA has important limitations for decision makers, as it does not allow comparison of cost-effectiveness across a range of different health conditions, which limits the usefulness of CEA in informing budget allocation decisions, since these decisions need, at a national and local level, to consider a variety of interventions in different areas of health and social care.

Cost-utility analysis

Cost-utility analysis (CUA) has the same foundations as CEA, and it is regarded in some literature as a type of CEA. Instead of using natural units, CUA uses a single generic measure of benefit, which overcomes the problem of comparability across different health conditions. The most widely used measure of benefit is the quality-adjusted life-year (QALY) (91), which combines quality of life and length of life into one single measure. QALYs are obtained through preference-based questionnaires that can elicit preferences in relation to a HS from the patients themselves, or proxies, such as members of the general public.

The use of QALYs in economic evaluations of public health interventions has been criticised, partly for considering health as the only relevant outcome, whereby ignoring the production of wider benefits that are not captured in the QALY. Additionally, the QALY does not incorporate any equity weights and the same value is assumed, regardless of who is gaining it (or losing it). Moreover, changes in QALYs are the same, regardless of where in the scale they occur, meaning that it would theoretically be as good to invest in the improvement of 0.1 QALYs in a population with 0.7 QALYs as it would be in a population with 0.2 QALYs. Application of QALYs is blind to focusing on improving health and life of those who are worse off in society, which clashes with one of the public health's core aims, the reduction of inequalities (109).

Decision rules in economic evaluation

Results of economic evaluations are considered in terms of the costs and benefits, following standard decision rules (110). If one of the alternatives costs less and produces more benefits than the others, it is unequivocally considered cost-effective. More commonly, alternatives generate gains at additional costs and under these conditions, can still be cost-effective. A ratio is calculated, the Incremental Cost Effectiveness Ratio (ICER), in terms of cost per additional unit of benefit. If a decision needs to be made between two options, "a" and "b", the ICER is calculated by firstly estimating the costs and effects of both options. The ICER is then given by the ratio of the incremental costs and effects, as shown below:

$$ICER = \frac{Cost_a - Cost_b}{Effect_a - Effect_b} = \frac{\Delta Cost}{\Delta Effect}$$

In economic evaluations, the ICER is frequently represented using the cost-effectiveness (CE) plane (Figure 4), a graphical representation of the two dimensions of the cost-effectiveness analysis - costs and effects. In the graph, the incremental cost and the incremental effect of a new intervention are plotted versus a comparator. The x-axis represents the incremental effect of the new intervention in relation to the comparator and the y-axis the incremental cost of the new intervention in relation to the comparator (111).

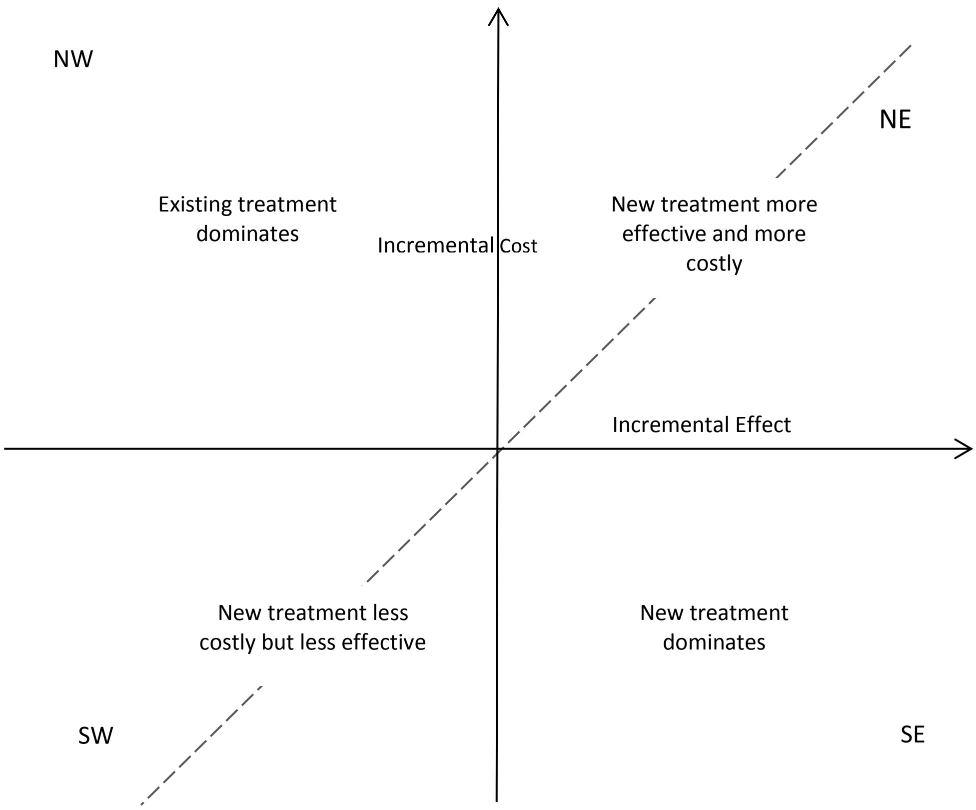


FIGURE 4 – THE COST-EFFECTIVENESS PLANE. ADAPTED FROM BLACK (1990)

The origin of the graph represents the point of comparison. The new intervention can be more or less effective and more or less costly than the comparator, and the combination of the two dimensions results in a different graph location.

If a new intervention is less costly and more effective than the comparator, it is located in the south--east (SE) quadrant. If this is the case, the intervention dominates the comparator and the cost-effectiveness analysis results are favourable to the adoption of the new intervention. If the new intervention is less effective and more costly than the comparator, the new treatment is in the north-west quadrant (NW). In this case, it can be said that the new treatment is dominated by the comparator, which means it should be rejected. Both SE and NW results can be translated to straightforward decision rules. However, it is more common for the results to lie in the northeast (NE) and south-west (SW) quadrants, where the decision implies a trade-off between effect and cost: either additional health gains can be achieved at higher costs (NE quadrant) or lower expenditure can be achieved at the detriment of some health benefits (SW quadrant). Not all trade-offs are acceptable, meaning that there is a maximum amount of health gain that the decision maker is willing to forgo, the case of the new intervention being in the SW quadrant, and a limit to how much the decision maker is willing to pay for the additional health gains, when the result lies in the NE quadrant. The dashed line in figure 3 represents this decision maker threshold, which is typically stipulated for a WTP threshold in terms of cost per additional unit of benefit, which supports decision making when results fall in the NW quadrant.

Decision analytic modelling has been applied to economic evaluation in health care to improve the capacity to answer resource allocation questions. Models are mathematical tools that are used to systematically inform decisions under uncertainty (Raiffa, 1968) in (110). Models compare alternatives through a series of mathematical relationships that allow them to predict costs and consequences over time.

Decision analytic models

Modelling for economic evaluation of public health interventions has numerous advantages. Models are able to combine evidence from several sources, which is generally required in public health, where trials are less common and evidence on costs and effectiveness are reported within a number of studies. Moreover, models can predict outcomes over a long period of time, overcoming the difficulties of the long follow up periods that are needed in public health effectiveness studies. They can compare current practice with hypothetical scenarios, which allows all relevant comparators to be analysed, even if real world data are not fully available. Models rely on the available evidence, as well as on a set of reasonable assumptions to make predictions, which go beyond trials or observational follow-up periods and overcome sample size limitations.

Type of models

Most decision models focus on the average patient and therefore create simulations for cohort models (110). The most common types of cohort model structures are decision trees and Markov models.

1.1.1. Decision trees

Decision trees are a commonly used, simple model structure in decision analytic modelling (91). Decisions trees start with a decision node (the square node in Figure 5), which indicates a decision point between the relevant alternatives. The tree divides from the decision node into each of the alternative's branch, where chance nodes (circle nodes in Figure 5) represent points where two or more events can occur. At a chance node, each event has a probability of occurring. Depending on what events occur throughout the decision tree, mutually exclusive pathways are defined - in the hypothetical example in Figure 5 there are four possible pathways, A-D. Pathways are mutually exclusive, which means that a given individual can only follow one of the pathways, and exhaustive, i.e., the simulated individual must follow one of the pathways (92, 110). Each pathway is assigned costs and benefits. The cost-effectiveness results of a decision tree are estimated by the rollback method to sum all costs and benefits of each alternative. Despite being a useful method to compare the cost-effectiveness of different alternatives, decision trees have some important limitations. Firstly, they do not specifically integrate time variables, meaning that time-dependent events can be hard to incorporate (92). Secondly, when modelling chronic diseases over a long time period, with multiple possible pathways, decision trees can become hard to handle as several mutually exclusive pathways are added (92).

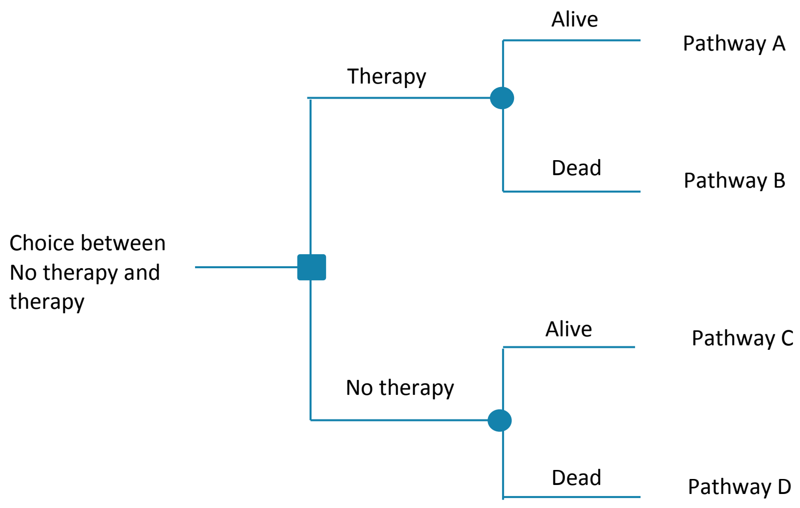


FIGURE 5 – EXAMPLE OF A DECISION TREE STRUCTURE

1.1.1. Markov models

Markov models are a more complex type of model and widely used in economic evaluation, partly to overcome the limitations of decision trees (92). Instead of pathways, Markov models are divided into mutually exclusive HSs (eg. 'well', 'sick' and 'dead' in Figure 6). Individuals stay in one of the HSs for a pre-determined period (cycle length) and have a probability (transition probability) of moving to a different HS, or remain in their initial HS, for the next cycle. Costs and effectiveness measures are assigned to each HS and the resulting cost-effectiveness of each alternative depends on the time spent in each HS. Markov models have the advantage of allowing time variables and complex pathways, while still keeping a relatively simple structure (112). Moreover, recurrence, which is an important aspect of illness, particularly chronic conditions, can be easily simulated in Markov model designs.

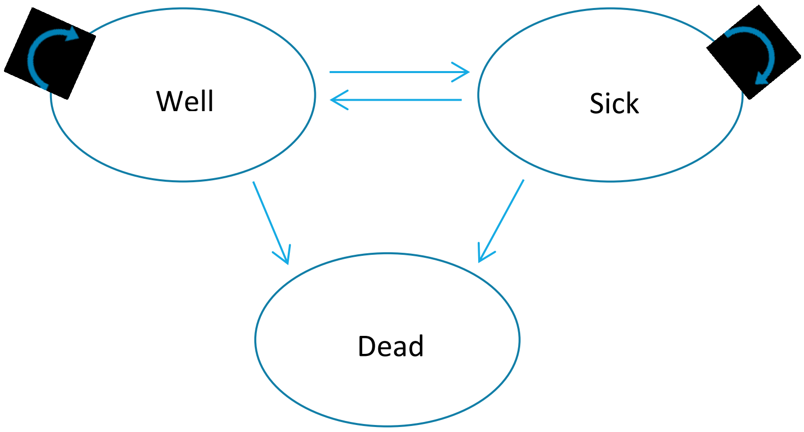


FIGURE 6 – EXAMPLE OF MARKOV MODEL STRUCTURE

Although Markov models allow great flexibility, they have also some restrictions, particularly related to what is known as the Markovian assumption, which means that after a hypothetical individual moves from one state to another, the model will have 'no memory' regarding the individual's previous states and the timing of the transitions. In health, a patient's history and timing are two very important factors affecting risks, and consequently costs and benefits of interventions (92).

1.1.1. Individual-level simulation models

Individual-level simulation models, also known as microsimulation models, can be applied to decision trees and Markov models, and can be used instead of the traditional cohort simulations (110).

Modelling the progression of individual patients through the models has two main advantages: incorporating population's heterogeneity without increasing the complexity of the model structure; and overcoming the Markovian assumption by tracking the individual's pathway throughout the model. The history of the patient can then be used to update risks, costs and benefits in the model, providing a more realistic cost-effectiveness result. Individual patient simulations also have restrictions in terms of data, and computation demands. Microsimulation models require that detailed data on individuals are available. Moreover, simulating one individual at a time translates into more analysis time, and total model run times depend on the power of the machines used. Uncertainty analysis can be limited by time constraints.

Discounting

One important feature that models need to incorporate is the ability to model costs and benefits that occur in the future, which raises the question of how future parameters should be introduced (92). Most methodological guidelines recommend both costs and benefits to be discounted (89, 113). The rationale for discounting costs and benefits in an economic evaluation is based on the positive time preference phenomenon. Positive time preferences mean that individuals prefer to incur costs later and enjoy benefits now. It is therefore necessary to include this non-indifference relating to time as a parameter in the economic evaluation comparing alternatives, particularly when the alternatives differ in not only the associated costs and benefits, but also in regards to when these occur.

Preventive interventions typically will require costs to be incurred in the present for benefits to be enjoyed in later stages of life. For example, interventions to support smokers to quit will result in a lower risk of lung cancer that will be experienced later in life. As it is, discounting may negatively impact cost-effectiveness of preventive programmes, when compared to treatment programmes, whose benefits occur in the present. NICE guidelines for economic evaluation of public health interventions recommend the use of a 3.5% discount rate for both costs and benefits, and the same is recommended in economic evaluations of health technologies (89).

Uncertainty

Even though decision analytic models are used to reduce uncertainty around resource allocation decisions, uncertainty is part of their definition, as described at the beginning of this section. The advantage of using models to deal with decision uncertainty is that they provide a systematic approach to deal with it, by identifying the type of uncertainty, quantifying it and exploring its sources. In practice, models provide answers not only about what is known, but also about what is not known and how that is likely to affect the decision.

The types of uncertainty within a model have been classified as methodological uncertainty, parameter uncertainty and structural uncertainty (114). Methodological uncertainty refers to the analytic methods used within the models, parameter uncertainty refers to the appropriateness and accuracy of the data inputs that inform the model, and structural uncertainty is concerned with the chosen model structure, and with whether the appropriate methodology to combine inputs was followed. All types of uncertainty can be addressed using sensitivity analyses (114, 115).

One-way sensitivity analysis deals with one parameter at a time and aims to explore how sensitive cost-effectiveness results are to changes in that parameter. One-way sensitivity analyses are justified for critical parameters to which analysts are unsure of the true value, and have the potential to affect results. Risk, transition probabilities and costs are generally good candidates for one-way sensitivity analyses. After testing the parameter, if the cost-effectiveness results stay the same, it can be concluded that the decision is not sensitive to that individual parameter. If the results change with variation in that parameter, results are sensitive to it and threshold analyses can be performed, which determines the maximum (or minimum) value the parameter needs to be for the intervention to be cost-effective (91). In a multi-way sensitivity analysis, more than one parameter is tested at the same time, creating a scenario analysis; commonly best/worst case analysis, which tests results under extreme conditions.

Parameter uncertainty is tested through a probabilistic sensitivity (PSA). In a PSA, inputs such as transition probabilities, effectiveness and costs are defined as probability distributions. The simulation is then repeated a number of times and for each repetition, a different value parameter is drawn from the distribution assigned. PSA gives a joint distribution of costs and benefit pairs, which then can be used to plot cost-effectiveness acceptability curves (CEACs) which show the probability of each intervention being cost-effective, at different WTP values.

Expected Value of Perfect Information

Beyond providing a systematic approach to summarizing evidence and evaluating interventions, models can inform research planning through value of information (VoI) analysis (116). Considering that a decision based on the current available evidence is made under uncertainty, there is a probability that the decision made is ‘wrong’.

The results of models, in particular the results of the PSA, can be used to quantify the value of additional information to reduce uncertainty (117), so decision makers may decide to postpone a decision until more evidence is available. VOI represents the difference between the expected utility of the optimal action given new information and the expected utility of the optimal action given information available prior to collecting additional information (118). The result is the expected value of perfect information. If the cost of new research to eliminate uncertainty exceeds the EVPI, the research is not considered cost-effective. In turn, if the EVPI is greater than the cost of research, funding the research may be considered by the decision maker.

VoI analyses are gaining popularity among decision makers in health care (91), as they provide a framework to prioritise competing research and health interventions.

Policy making in Public Health

Economic evaluations are useful to inform budget allocation decisions and some national policy decision-making bodies have published methodological guidelines for submissions of economic evaluations to adhere to. The UK reference case for NICE Public Health evaluations is a commonly used example, but there are many others (119). The American Centre for Disease and Dissemination (CDC) explicitly states that they use Public Health Economics to assess the costs and benefits of preventative programmes (120). Furthermore, umbrella international organisations, such as the Organisation for Economic Co-operation and Development (OECD), the World Health Organisation (WHO) and the World Bank have published reports on the use of economics to inform public health decisions (119).

Public Health priorities vary from country to country, but also from region to region.

In 2013, the Department of Health introduced fundamental structural changes to the public health system, which included the creation of Public Health England as the new national public health agency, and the transfer of the responsibility for health improvement from the Primary Care Trusts (PCTs) to local government -Local

Authorities (LAs). These changes have resulted in the involvement of multiple organisations in the commissioning and delivery of public health programmes, and thus more complex decision making and commissioning processes.

At a national level, NICE public health guidelines state a threshold decision rule for cost-effectiveness in public health, with authorities hypothetical willing to pay £20,000 -£30,000 per QALY gained (121)

Conclusion

This chapter provided a background to the development of decision analytic modelling that is the main aim of this thesis. It has explored the foundations of economic evaluation in health care, described the types of analyses used, and highlighted model based evaluation as a widely used and powerful instrument to predict the expected cost-effectiveness of interventions. This chapter describes different types of economic evaluations and model structures, presenting the possible applications and limitations of each methodology.

Model based analyses are particularly relevant to the evaluation of public health interventions for two main reasons:

1) The ability to simulate the costs and effectiveness of interventions over long periods of time;
2) The ability to model all relevant alternatives, even hypothetical programmes that have not yet been implemented, since assumptions can be made regarding its potential impacts, and sensitivity analysis can test the robustness of such assumptions.

In addition to information on the expected value of the cost-effectiveness of prevention studies, models have the potential to inform us how uncertainty affects those decisions and how much decision makers should be willing to pay for future research to reduce this uncertainty.

There is no 'gold standard' method to apply to evaluate public health interventions, although in the UK, NICE recommends cost-utility analyses reported in terms of cost/QALY gained. The following chapter presents a systematic review of economic evaluations of strategies to prevent Vitamin D deficiency.

CHAPTER 3

A SYSTEMATIC REVIEW OF ECONOMIC EVALUATIONS OF STRATEGIES TO PREVENT VITAMIN D DEFICIENCY

Introduction

As it has been shown in chapter 1, most countries have adopted public health policies to prevent VDD in at-risk groups of the population (37), opting for either 1) mandatory fortification of staple foods such as milk in Finland (122) or voluntary fortification, such as breakfast cereals in the UK (37), and 2) supplementation programmes for pregnant and breastfeeding women, and infants (37). Despite these initiatives, VDD still persists as a serious public health concern (47). A recent study conducted in Europe pooled estimates from 55,844 individuals and found that VDD, defined as serum 25OHD concentrations below 30nmol/L, affects 13% of the European population (47). The evidence is robust about the much higher prevalence of VDD in dark-skinned populations, highlighting the inadequacy of the current policies in Europe to protect the at-risk groups (3, 47, 123).

The work presented in this chapter aims to systematically review economic evaluations of preventing population VDD and identify the evidence gaps to inform the development of a decision analytic model to prevent population VDD in England and Wales.

In addition, it aims to:

- Determine the cost-effectiveness of population strategies;
- Identify whether cost-effectiveness varies by population subgroup and country setting and, if possible, what are the source of such variations;
- Identify and appraise alternative modelling structures for measuring the cost effectiveness of population strategies;
- Determine the methods used for measuring the outcomes of strategies to prevent VDD.

A systematic review is a widely used methodology, supported by numerous research groups and policy-makers, and generally placed at the top of hierarchy of evidence for effectiveness studies. It is robust and replicable, producing highly reliable results (124).

Methods

Search Strategy

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology (125) where applicable. Literature searches were conducted in January 2015 and updated in April 2016 and in September 2017. The search strategy included terms relating to VDD and economic evaluation (full search strategy provided in Appendix 1. The following bibliographic databases were searched: MEDLINE, EMBASE, Econlit, NHS EED, CEA registry and RepEC. Additionally, the reference lists of the included articles were searched. The screening was conducted by the main reviewer (Magda Aguiar, MA) and the second reviewer (Emma Frew, EF) screened 10% of the titles and abstracts.

Inclusion/exclusion criteria

All full economic evaluations, defined as a consideration of both costs and outcomes, were included, namely cost-consequence, cost-effectiveness, cost-utility and cost-benefit analyses. The interventions of interest were those aiming to prevent VDD, including supplementation, food fortification and public health campaigns. Interventions were included if administering Vitamin D alone, Vitamin D in combination with calcium or multi-Vitamin supplements containing Vitamin D. Studies where VDD occurred as secondary to other health conditions, such as liver disease or malabsorption, were excluded. There were no language restrictions although inclusion was limited to the availability of a translator.

Data extraction and quality assessment

The relevant characteristics of each study in relation to the methods used and the main results reported were extracted. The data extracted included: population and setting; intervention and comparators; type of economic evaluation; analytical methods used; the perspective adopted; clinical outcomes and measure of benefits used; and the main results reported.

Drummond's checklist (126) was chosen to assess the quality of the included studies because it is a widely used quality tool that allows assessment of different types of economic evaluations including cost-effectiveness, cost-utility and cost-benefit analysis, as well as any analytic method - model-based and trial-based analysis, allowing us to use the same tool for all included studies. Studies were not excluded from the analysis on the basis of the quality assessment results, rather, the quality of the studies was considered when drawing conclusions from the synthesised data.

Data Synthesis

First, the results were categorised by type of prevention strategy being evaluated, as shown in Figure 7. Second, the studies were grouped by type of intervention analysed. High heterogeneity was expected across studies due to the variation in costs and resources used both between countries and within the same country. Therefore, pooled estimates were not considered appropriate to summarise the evidence.

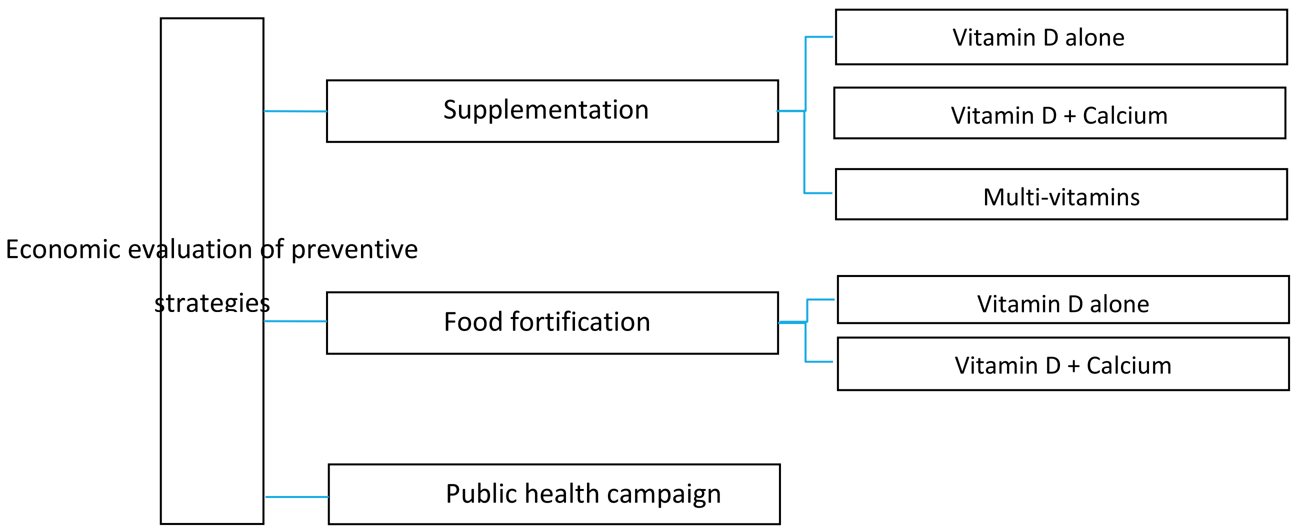


FIGURE 7 – DIAGRAM SHOWING POSSIBLE INTERVENTIONS

Results

The search strategy generated 2552 references after duplicates were removed. All titles and abstracts were screened against the inclusion/exclusion criteria. Studies that were not economic evaluations, and/or did not evaluate strategies to prevent VDD were excluded. In total, 2,525 were excluded and the primary reason for exclusion was not being a full economic evaluation. The remaining 27 full-text studies were examined and 16 studies were selected for data extraction, nine from the main search and five from the updated searches. The PRSIMA (125) flowchart illustrating the study selection process is shown in Figure 8.

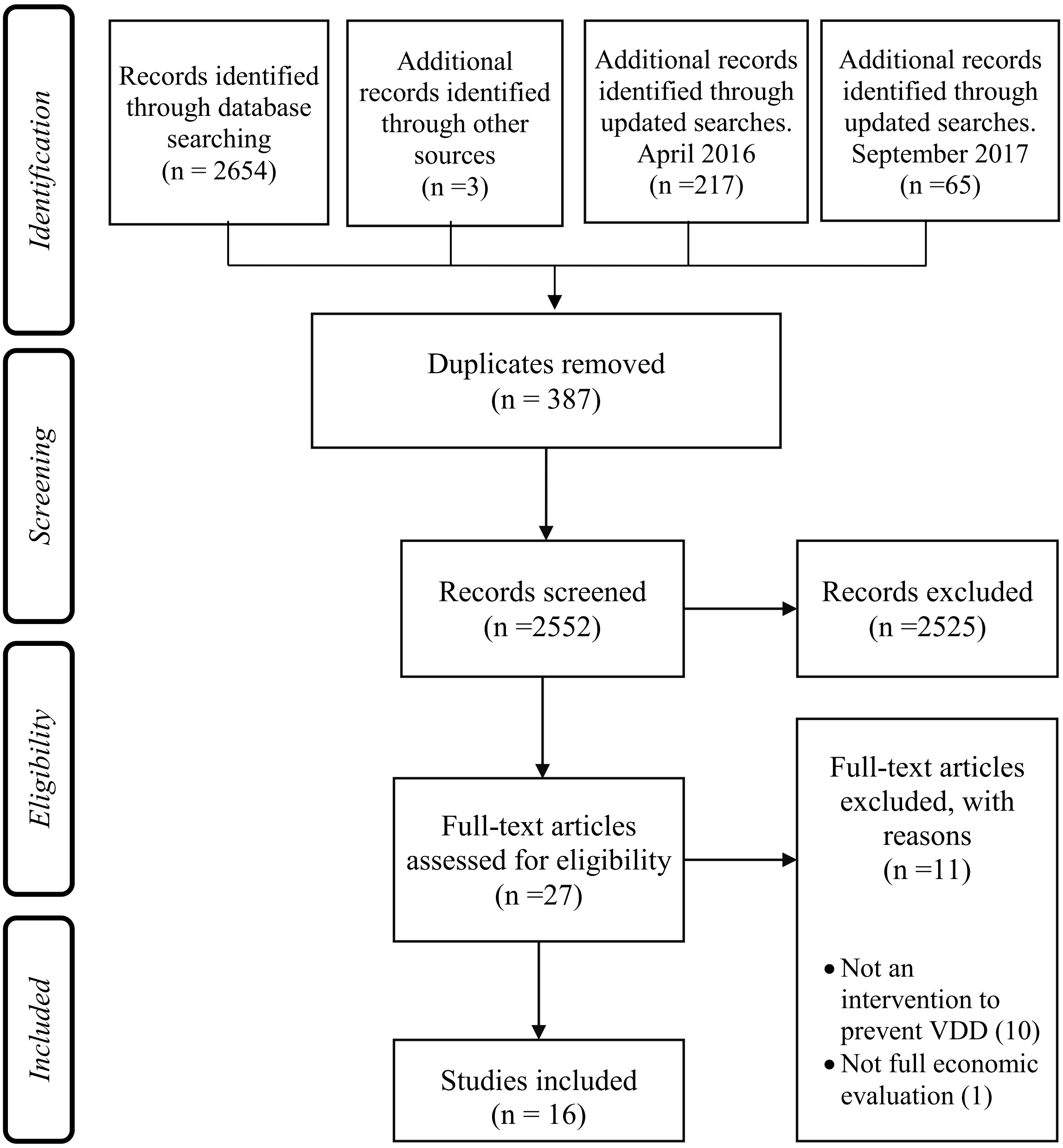


FIGURE 8 - ADAPTATION OF PRISMA 2009 FLOW DIAGRAM

General characteristics of the included studies

The identified studies spanned a period of 20 years, with the earliest being published in 1995 and the majority emerging between 2012 and 2016 (Figure 9). Studies were carried out in the UK (127-131), the USA (132, 133), Australia (134, 135), France (136, 137), Finland (138), Sweden (139), and Germany (140). Additionally, there was one multi-country study that carried out cost-effectiveness analyses in seven European countries (141). The majority of studies (n=7) evaluated supplementation strategies of Vitamin D alone in the adult population (128, 129, 132, 133, 135, 136, 138). Other studies investigated calcium and Vitamin D interventions either through oral supplements (n=4) (127, 134, 139, 141) or food fortification (n=3) (137, 140, 142). One study evaluated interventions of supplementation with multi-vitamins that included Vitamin D (131).

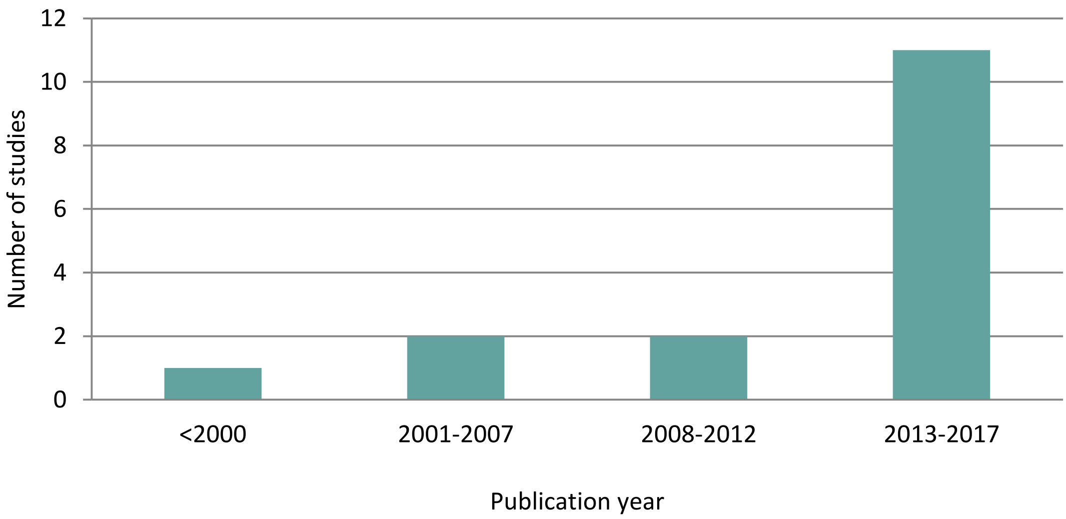


FIGURE 9 – NUMBER OF PUBLISHED ECONOMIC EVALUATIONS WITHIN A 5 YEAR INTERVAL

Supplementation with Vitamin D alone

Eight studies evaluated interventions using supplements with Vitamin D alone (128-130, 132-134, 136, 138) and all except one (130) focused on the elderly population. The characteristics of the studies evaluating supplements with Vitamin D alone are presented in Appendix 2. Five were cost-utility analyses using quality-adjusted life-years (QALYs) to measure benefits (128, 132, 133, 135, 136), two were cost-effectiveness analyses (129, 138) and one was a cost-consequence analysis (130). Three studies compared universal supplementation against screening for VDD followed by supplementation (130, 133, 136), three studies evaluated Vitamin supplements against interventions to prevent falls (132, 135, 138) and two evaluated supplements against current care to prevent fractures (129) and falls (128). Markov models were the preferred analytical method to simulate falls and fractures pathways (n=4) (128, 129, 133, 135). Screening and subsequent treatment was found to be more cost-effective than universal supplementation in the elderly population (133, 136), while universal supplementation was cost-saving when comparing to the screening alternative in the whole population (130). Interventions with Vitamin D supplements in the elderly population were cost-effective when compared to current practice for the prevention of falls (128) and fractures (129), and when compared with multiple interventions for the prevention of falls (132, 135).

Supplementation with Vitamin D and calcium

The complete description of the characteristics of the studies evaluating supplements with Vitamin D alone is presented in Appendix 2. Four economic evaluations focused on the prevention of VDD using supplements with a combination of Vitamin D and calcium (127, 134, 139, 141). Two of them were cost-utility analyses using QALYs as a measure of benefit (134, 139) and two were cost-effectiveness analyses measuring the cost per 'avoided fracture' (127, 141). Three studies (127, 139, 141) sourced the effectiveness data from a large French trial (143, 144) involving women in nursing homes. Two of these performed a trial-based analysis (127, 141) while another modelled the outcomes beyond the trial follow-up period using a Markov model (139). When compared with placebo, Vitamin D and calcium were cost-effective in women aged 50 and 60 years (139) and cost-saving for at-risk women aged over 70-years-old in Sweden (139) and several other European countries (141). When compared with annual supplementation of high-dose Vitamin D only (300 000 IU), the latter was found to be more cost-effective (127).

A different approach was used by Church and colleagues (134), who aimed to identify the most cost-effective intervention to prevent falls by comparing multiple interventions, including Vitamin D and calcium supplementation, as well as Tai-chi, medication reviews and multi-factorial approaches. Two different Markov models were used for the elderly population living in the community and in residential aged care homes. Combined supplementation of Vitamin D and calcium was one of the most cost-effective interventions for those living in residential aged care facilities (ICER AU$7,316), but not for those living in the community (134).

Supplementation with multi-Vitamin preparations

One study evaluated an intervention using multi-Vitamin supplements containing Vitamin D (Appendix 3) (131). Different schemes of universal and targeted supplementation strategies were compared and the effectiveness and outcomes measures were not limited to Vitamin D but included folic acid and Vitamin C for pregnant and breastfeeding women, and Vitamin A and C for infants and young children. (131). The results were largely driven by the effect of folic acid in pregnant women, due to the lack of effectiveness data for the other micronutrients, including Vitamin D.

Food fortification with Vitamin D and calcium

Three studies evaluated the cost-effectiveness of preventing fractures through food fortification Vitamin D and calcium, one in Germany (140), one in France (137) and one in Belgium (142). Two studies used a Markov microsimulation model (137, 142) and one study used a spreadsheet model (140) and all studies used long time horizons. One study considered voluntary bread fortification (140) and two considered fortified yogurts (137, 142). Effectiveness data on the fracture risk reduction was based on a Cochrane review of the effectiveness of Vitamin D and calcium supplements (145). Measures of benefit were number of fractures prevented (137, 140, 142), life-years gained (140) and QALYs gained (137). While bread fortification was cost-saving, diary fortification was cost-effective only for the older age groups, who are at higher risk of fractures. The cost of the food vehicle was an important driver to the results.

Quality Assessment

All papers reported the type of economic evaluation, described the alternatives being analysed and adequately drew conclusions from the results, although none of the studies fulfilled all the checklist’s requirements (full results provided in Appendix 5). There was a general lack of rigour with reporting the methods, and the model inputs and assumptions. Most studies failed to provide justification for key methodological choices such as the time horizon, the analytical approach and the discount rates chosen. There was also limited discussion about the sources of effectiveness data and how these affected the generalizability of the results.

Six out of the 16 studies included the reporting of conflicts of interest, such as being funded by pharmaceutical companies that commercialised Vitamin D supplements (128, 133, 136, 137, 141, 142).

Discussion

This systematic review provides the first synthesis of the economic evidence on the prevention of population VDD. The review demonstrates that economic evaluation of interventions to prevent VDD is an expanding area of research, with five of the 14 included studies being published in 2015. Despite the increasing number of studies, the evidence is still limited and does not address the main questions important to policy makers when considering the introduction of VDD prevention strategies. From the literature, it is not possible to determine the total costs of population strategies, nor the most cost-effective population strategy to prevent VDD and its consequences. Vitamin D is a relatively cheap compound and the literature favours interventions using it, particularly to prevent heavy-burden clinical outcomes, such as fracture in the elderly.

The sections below highlight the main strengths and limitations of the currently available evidence and provide recommendations for future research. A summary of the results is presented in Table 2.

Table 2 - Summary of the results

Study ID	Intervention	Population	Result	Quality
Church et al. 2015 (136)	Supplementation with Vitamin D (800IU)	Elderly (+84 years; nursing homes)	Supplementation (800IU) was cost-saving	Adequate
Church et al. 2011 (135)	Supplementation with Vitamin D (800IU) and calcium (1.2g) vs. No intervention	Elderly (+65 years)	Supplementation with Vitamin D and calcium was cost-effective	Good
Ethgen et al. 2015(142)	Dairy fortification with Vitamin D and calcium	Elderly (+60 years)	Fortification was cost-effective from 70 years in the general population, and from 60 years on in patients with an increased risk of osteoporotic fractures.	Adequate
Filby et al. 2014 (131)	Population screening vs. Universal supplementation with Vitamin D	Pregnant and breastfeeding women, children (< 5 years), elderly (+ 65 years) and dark skinned.	Universal supplementation was cost-saving	Good
Filby et al. 2015 (147)	Universal supplementation with Vitamin D (multi-vitamin preparation) vs. Targeted supplementation based on income status	Pregnant women, women planning pregnancy, infants and young children	Universal supplementation was cost-effective for women pregnant women and women planning pregnancy only	Adequate
Frick et al. 2010 (133)	Supplementation with Vitamin D (800IU) vs. No intervention	Elderly (+65 years)	Supplementation (800IU) was cost-effective	Adequate
Hiligsmann et al. (2017) (137)	Dairy fortification with Vitamin D and calcium	Elderly (+60 years)	Dairy fortification is cost-effective and potentially cost-saving if targeted to high	Adequate

Study ID	Intervention	Population	Result	Quality
			risk groups	
Lee et al. 2013 (134)	Population screening vs. Universal supplementation with Vitamin D	Elderly (+65 years)	Screening was the most cost-effective alternative	Inadequate
Lilliu et al. 2003 (142)	Supplementation with Vitamin D (800IU) and calcium (1.2g) vs. No intervention	Elderly (+65 years; women)	Country-dependent. Costs in placebo group higher than in intervention arm	Adequate
Patil et al. 2016 (139)	Supplementation with Vitamin D (800IU) alone vs. Supplementation with Vitamin D (800IU) and Exercise vs. Exercise alone	Elderly (+65 years)	Supplementation (800IU) alone was dominated. Exercise alone was the most cost-effective	Adequate
Poole et al. 2014 (130)	Supplementation with Vitamin D (800IU) vs. Current practice	Elderly (65-80 years)	Supplementation (800IU) was cost-saving	Adequate
Poole et al. 2015 (129)	Supplementation with Vitamin D (800IU) vs. No intervention	Elderly (+65 years)	Supplementation (800IU) was cost-effective (cost-saving for the older cohorts)	Adequate
Sandmann et al. 2015 (141)	Bread fortification with Vitamin D (800IU) + calcium (200mg)	Elderly (+65 years)	Bread fortification was cost-saving	Adequate
Torgerson et al. 1996 (128)	Supplementation with Vitamin D (800IU) and calcium (1.2g) vs. Annual parenteral with Vitamin D (300,000IU)	Elderly (+65 years; women)	Annual parenteral with Vitamin D (300,000IU) was the most cost-effective	Inadequate
Willis, S 2002 (140)	Supplementation with Vitamin D (800IU) and calcium (1.2g) vs. No intervention	Elderly (50-90 year; women)	Intervention was cost-saving (>70 years) and cost-effective (50-70 years)	Adequate
Zarca et al. 2014 (137)	Population screening vs. Universal supplementation with Vitamin D	Elderly (+65 years)	Screening was the most cost-effective	Adequate

The majority of the economic evaluations focused on the elderly population living in high income countries, highlighting a dearth of studies in all other groups: infants and children, pregnant women, lactating women and ethnic minorities, as well as populations living in other geographical areas.

Severe symptomatic VDD has been reported in dark skinned infants, namely rickets, cardiomyopathy and seizures (3, 4). This review found only one study which attempted a sub-group analysis focusing on dark skinned adult populations but results were limited by the paucity of evidence to support the analysis (130). Despite this, the study showed that, when the incidence of VDD increased, so did the probability of supplementation being cost-effective for that population (130). This suggests that interventions that are not cost-effective for the whole population may be cost-effective for at-risk groups, reinforcing the need for sub-group analysis by risk.

Type of economic evaluation and analytic approaches

The majority of the studies performed cost-effectiveness (n=6) and cost-utility (n=7) analyses, with a focus on health and social care costs and outcomes. The holistic nature of population-based nutrition interventions, which can lead to non-health care costs and benefits, suggests that an alternative method of economic evaluation such as cost-benefit analysis may be more appropriate. This is important as the costs of nutrition interventions are likely to involve public health authorities and other public sectors, food consumers and the food industry. At the same time, the health benefits of population nutrition interventions can be far reaching, for instance, better childhood development will improve productivity in later years.

Regarding the analytical methods used, eight studies presented decision models, most cohort Markov models, simulating the prevention of fractures through cohort simulation (129, 139, 142) and microsimulation simulation (137). The remainder modelled fall prevention (128, 133-135). Markov models are appropriate as they enable long-term programmes to be modelled, and allow recurrence to occur in the disease pathway. VDD and its complications are dynamic HSs, where patients transit from being deficient to being sufficient (i.e. seasonally). This transition is determined by exposure to risk factors, including sunlight exposure, age, and Vitamin D and calcium intake from food and supplements, which vary with time and external factors.

Interventions

Thirteen of the fourteen included studies evaluated supplements with Vitamin D, and different supplementation programmes were considered, all in the elderly. The majority of the studies evaluated oral supplements (n=12) (127-135, 138, 139, 141) while one analysed high-dose parenteral supplementation (136). The comparators varied and included exercise (138), screening followed by treatment (130, 133, 136), multi-interventions to prevent falls (132, 134, 135), parenteral Vitamin D supplementation (127) and no intervention (128, 129, 139, 141). Three studies evaluated food fortification (137, 140, 142).

Most of the interventions considered targeted a specific group of the population and aimed to prevent one clinical outcome related to VDD. The results are not likely to apply to population-based scenarios. For instance, two studies evaluating screening programmes versus supplementation in older adults concluded that screening would be more cost-effective than providing supplements, particularly to elderly people aged over

70 years and those at high-risk of fractures (133, 136). But the one study comparing the same intervention in the whole population found contrasting results, concluding that it is unlikely that universal Vitamin D screening would be superior to universal supplementation at the population level (130).

There is a lack of studies evaluating population-based programmes. The only two studies that undertook broader analyses in several at-risk groups in the UK's population (130, 131) highlight serious limitations due to the evidence gaps to support such analyses.

An evaluation of combined strategies to prevent VDD has not yet been undertaken. Similarly to the literature for other micronutrients (146, 147), the preferred public health approach to improve the nutritional Vitamin D status of the whole population is likely to be a combination of food fortification and supplementation. Although the literature generally refers to food fortification as a highly cost-effective intervention, it is unlikely to reach the whole population, specifically those who do not regularly consume the fortified food (146). Combined strategies are more likely to meet cost-effectiveness and coverage targets (146).

Nonetheless, economic evaluations of combined interventions to prevent VDD have not yet been undertaken. This review reiterates that stand-alone interventions may not be the most efficient strategy and highlights the importance of producing new economic evidence evaluating multiple interventions. .

Clinical outcomes

The most frequent clinical outcomes considered were fractures (n=10) (127, 129, 130, 132, 136, 137, 139-142) and falls (n=5) (128, 133-135, 138), although the evidence supporting such associations is controversial. The latest Cochrane reviews suggest that supplementation with Vitamin D alone has no impact on risk of fractures (145) but may reduce the risk of falls in individuals with low Vitamin D status at baseline, if a minimum of 800 (IU) per day is provided (148). The association of Vitamin D and calcium is likely to prevent a small number of hip and non-vertebral fractures in the elderly population (145).

The choice of clinical outcome and the source of effectiveness data must be carefully considered and estimates tested using sensitivity analysis. For example, hip fractures have a great impact on morbidity, quality of life and mortality. They are also one of the most expensive health implications in the elderly population. Therefore, risk reduction of hip fractures is likely to drive cost-effectiveness results (140).

VDD has severe clinical consequences in children, namely rickets, which is associated with pain, deformities, muscle weakness, poor growth, hypocalcemic seizures, tetany and heart disease and their sequelae, including death (8). Despite their high prevalence in risk groups (123), these outcomes have not yet been captured in health economics research.

Effectiveness

The effectiveness of supplementation programmes was largely sourced from clinical trials and meta-analyses of clinical trials. Because clinical trials are conducted in controlled environments and generally have a short time frame, the recorded uptake rates are expected to be higher than those observed in real-life conditions. The World Health Organization (WHO) states that the uptake rate for supplementation is approximately 50% (149). Much lower rates, as low as 6%, were reported for the

Vitamin D supplements provided under the free supplementation scheme for infants in the UK (150). Therefore, economic evaluations assuming 100% uptake rate will overestimate the benefits of supplementation programmes. Furthermore, the review found that pooled estimates of the effect of Vitamin D supplementation frequently included data from trials using Vitamin D alone and Vitamin D in combination with calcium (128, 129), making it impossible to determine how much of the effect is attributable to Vitamin D alone.

The effectiveness of food fortification with Vitamin D is an under-researched area and this may explain the paucity of economic evaluations of these strategies. The studies evaluating fortification programmes sourced effectiveness data of Vitamin D and calcium from a Cochrane review using supplements (137, 140, 142, 145). Several important parameters must be taken into account when considering the effectiveness and coverage of food fortification, such as the characteristics of the food vehicle and its bio-availability. The results showed the importance of choosing an adequate vehicle. Bread fortification seems to be more cost-effective than that of dairy products. The latter are more expensive. The food vehicle needs to be accessible, ideally a staple food with a well-established consumption pattern within the targeted population (146). Moreover, chemical characteristics of both the nutrient and the food need to be considered to guarantee that the nutrient will be delivered in the desired amounts after food processing, package and storage.

Utilities

The QALYs gained from the prevention of VDD were estimated in eight of the fourteen included studies (128, 131-136, 139). Utility scores were sourced from osteoporosis studies and used in economic evaluations of preventing falls (128, 133-135) and fractures (132, 136, 139). In studies focusing on falls prevention, fear of falling after a fall was an important cause of QALY decrement, in some cases having more impact on the quality of life of those who suffered a fall than actual fractures (151).

Although attempts have been made to include QALY estimates for pregnant women and children (6), the authors were limited by the complete lack of evidence on the disutility of being Vitamin D deficient beyond the falls and fractures related outcomes.

Costs and resources used

The current literature is relatively homogenous in the methods used to cost programmes, and how these are reported. The studies focused on the healthcare sector, with emphasis being given to the cost of purchasing Vitamin D, either as a supplement or as a fortificant, and to treating clinical events related to VDD. However, micronutrient interventions are complex and their costs span across the public and private sectors. The current literature still treats these interventions as exclusively health programmes, providing limited information for policy makers.

Previous research on Vitamin A programmes showed that the main driver of the overall cost of the programme was staff costs associated with supplementation and the nutrient's cost in food fortification programmes (146). Moreover, it highlighted the importance of accounting for information campaigns and staff training, without which the effectiveness of the programmes is compromised.

Quality of the studies

In general, most studies were considered to be of, at least, adequate quality. Most studies describe the interventions compared, the outcome measures and drew conclusions from the results reported. Nonetheless, the quality assessment highlighted poor reporting practices, namely the lack of justification for important methodological choices such as the type of economic evaluation used, the choice of perspective, and set of alternatives compared. Most studies were published in clinical journals and it is therefore possible that the authors have chosen to emphasise clinical aspects rather than focus on analytical methods. The full results of Drummond's checklist are presented Appendix 5.

Conclusion

Interventions to prevent VDD have been referred to in the literature as highly cost-effective and even cost-saving for some groups of the population. Nonetheless, the evidence shows several limitations that need to be addressed for a better understanding of what would be the most cost-effective approach to prevent VDD at a population level. This review found a lack of economic evaluations supporting population VDD prevention, and corroborates previous concerns about the underuse of economic evaluation to inform public health nutrition strategies (152, 153).

MNDs are effectively prevented through supplementation and food fortification programmes and most countries have adopted a combination of both (146). None of the studies included in this review presented a direct comparison of the two strategies, or considered a combined intervention of food fortification and supplementation. Therefore, it is not possible to conclude which intervention is the most cost-effective. The literature suggests that supplementation with 800 IU of Vitamin D is likely to be cost-effective to prevent fractures and falls in older adults, especially for the elderly, high-risk population. Economic evaluations focusing on population-based interventions are needed, as well as sub-group analysis of other at-risk group such as infants, children, breastfeeding and pregnant women and individuals with darker skin.

The literature on micronutrient programmes refers to food fortification as a highly cost-effective alternative to tackle deficiencies due to its wide population coverage and low maintenance costs (146). Further research is needed to evaluate if the same applies to Vitamin D interventions.

IMPORTANT MESSAGES FROM THIS CHAPTER

- There is limited evidence on the cost-effectiveness of preventing population VDD;
- Available economic evaluations have focused mainly on the elderly population, with the aim of preventing falls or fractures;
- Studies report that, in general, supplementing older adults is a cost-effective way to prevent falls and fractures;
- There is a dearth of economic evaluations assessing prevention of VDD in children and in ethnic minority groups;
- Current economic evaluations have given little attention to food fortification interventions.

CHAPTER 4

COST-EFFECTIVENESS OF PREVENTING MICRONUTRIENT DEFICIENCIES: A LITERATURE REVIEW

Introduction

The previous chapter presented a systematic review of economic evaluations of interventions to prevent VDD. The results showed that few model based analyses had evaluated population interventions, highlighting the paucity of evidence to support modelling methods, particularly to inform the economic evaluation of food fortification strategies.

In this chapter, a review of economic evaluations is presented, with a focus on decision analytic models evaluating the prevention of MNDs, other than VDD. The aim was to inform the methods to build a new decision-analytic model for the case of preventing VDD in the UK and therefore the review focused on the methodological features that are likely to be applicable to the Vitamin D context.

Since the early 1990s, the eradication and prevention of MNDs has been a priority in the global public health agenda (146). The main strategies available to tackle MNDs are supplementation and food fortification (154).

Methods

A comprehensive literature review was undertaken to identify economic evaluations of strategies to prevent MNDs. The search was done using the main health economics databases - CEA registry, HEED: Health Economic Evaluations Database and NHS EED – as well as using the Google© scholar search engine and the reference lists of the relevant studies. Search terms included food fortification, supplementation, health economics, economic evaluation, cost-effectiveness, cost-utility, cost-benefit, and micronutrients such as Vitamin A, folic acid, iodine and iron. Preference was given to studies estimating the long-term costs and benefits of interventions through decision analytic models.

The results of this review are presented narratively in the following sections and the characteristics of the studies are detailed in Appendix 6 and 7. Emphasis was given to describing the model-based methods, in terms of the analytic framework, time horizon, population, data sources, discount rates, and equity considerations, as well as the challenges encountered. The description focuses on the most relevant findings, namely the methodological and practical features found in the reviewed studies that could be applicable to the VD context.

Results

This review included eleven studies, of which three were decision model-based analyses estimating the long-term costs and benefits of preventing MNDs. Of the three, one (155) used a Markov model and two used decision trees (156, 157). Several other economic evaluations extrapolated long-term costs and benefits through cost-effectiveness estimation methods (158-166). The majority of the economic evaluations identified were developed prior to the implementation of the intervention. The micronutrients studied were folic acid (N=6) (155, 156, 158, 163-165), iodine (N=3) (157, 162, 166), iron (N=1) (161) and fluoride (N=1) (160).

The summary of the characteristics of the studies described in this chapter are presented in Appendix 6 for the model-based analyses and Appendix 7 for the non-model based studies.

Type of economic evaluation

Noticeably, the most common types of economic evaluation were cost-utility analyses (CUA) (155, 156, 160, 161, 163, 164), and cost-effectiveness analyses (CEA) (156-158, 162). In CEA, the benefits were expressed in terms of life-years gained (156, 158) or events averted (156, 157, 162). CUAs used QALYs gained (155, 156, 160, 164), and disability-adjusted life years (DALYs) averted (161, 163) as the measure of benefit. There were two cost-benefit analyses (165, 166) one used a WTP method (165) while another used the human capital approach (166) to estimate Net Monetary Benefits (NMBs).

Interventions

Studies evaluated food fortification and supplementation programmes using a variety of comparators: food fortification at different fortification rates (155), food fortification compared to no fortification (160, 162, 164), supplementation compared to no supplementation (157, 158), and multiple interventions including voluntary fortification, mandatory fortification, and supplementation (156, 161, 163). Most studies adopted a societal perspective (156-159, 161, 162, 164-166).

Population and setting

The populations targeted varied according to the MND being studied. Folic acid, iodine and iron are typically targeted to pregnant women since these micronutrients guarantee the optimal development of the foetus.

Researchers have sensibly highlighted that the results of their economic evaluations are country-specific and sometimes even region-specific, discouraging policy-makers to use their results to inform interventions in different settings (161, 164). The population varies in terms of the prevalence of the MND, the rural/urban distribution of the population and the degree of geographic clustering of the deficiency (167) and the prices and resources used vary by setting (161). These differences limit the external validity of the results.

Time horizon and discounting

The minimum time horizon was 10 years (158, 161-163) and the maximum was lifetime (156, 157, 164). All studies applied a discount rate to both costs and benefits, and the rates ranged from 2.3% to 10%. The majority applied the same rate to costs and benefits and tested the impact of discounting using a sensitivity analysis. Moreover, Goodall et al. justified the choice of a long time horizon in term of allowing enough time to offset the initial costs of the programmes (162).

Model type

The analytic techniques applied varied and the majority of the studies did not describe in detail what framework they used. The decision model analyses are described below.

Rabovskaja et al. (156) developed a decision tree to model wheat flour fortification with folic acid in Australia. The whole population was considered since all were exposed to the intervention and a life-time horizon was used. The different arms separated the population by age groups. The benefits were limited to pregnant women (neural tube defects averted in new-borns) while the adverse events due to high doses of folic acid were modelled for the elderly population, who are at-risk of toxicity (156).

Monahan et al. (157) also used a decision tree to model iodine supplementation of pregnant women in the UK. The model estimated the percentage of women with a viable pregnancy and further estimated the cost-effectiveness rates by increased IQ point of the child. The decision tree used a separate arm to account for adverse events due to supplementation.

Bentley et al. (155) developed a Markov model to compare the costs and benefits of four interventions: no fortification, and fortification with 140, 350 or 700mg folic acid per 100 g enriched grain. The authors reported the annual costs and QALYs gained.

Epidemiological data

Population data is particularly important to inform the model on the characteristics of the population that is deficient, the populations' food consumption data (for fortification models), the prevalence of illness related to the MND, and the prevalence of adverse events related to high intake of a micronutrient (potential adverse events caused by the intervention). A general message from the included studies was the dearth of population data, particularly when attempts were made to model subgroups in terms of risk and nutrient consumption. Moreover, the scarcity of data on the proportion of illness attributable to a MND was cited as a common obstacle across most of the economic models. Commonly, studies used international data (156, 166) derived from effectiveness and observational studies and/or assumptions.

Effectiveness data

The source of effectiveness data varied and the majority of the studies refer to a paucity of evidence concerning micronutrient interventions. Most studies used secondary data from multiple sources and assumptions were made and tested in sensitivity analyses.

Some studies using trial data (161, 168) suggesting the results should be interpreted with caution since efficacy data from trials are likely to differ from those observed in the general population. Issues about using effectiveness data from other countries have also been raised due to the previously mentioned high variability across countries and populations (163).

Food fortification

The effectiveness of food fortification generally was considered through the following parameters:

- Intake of micronutrient before intervention based on all sources: natural sources, existing voluntary and/or mandatory fortified foods and supplement intake;
- Consumption data of the food to be fortified;
- Dose-response data to inform the amount of micronutrient that should be added.

Figure 10 outlines a framework for the estimation of the impact of a fortification programme.

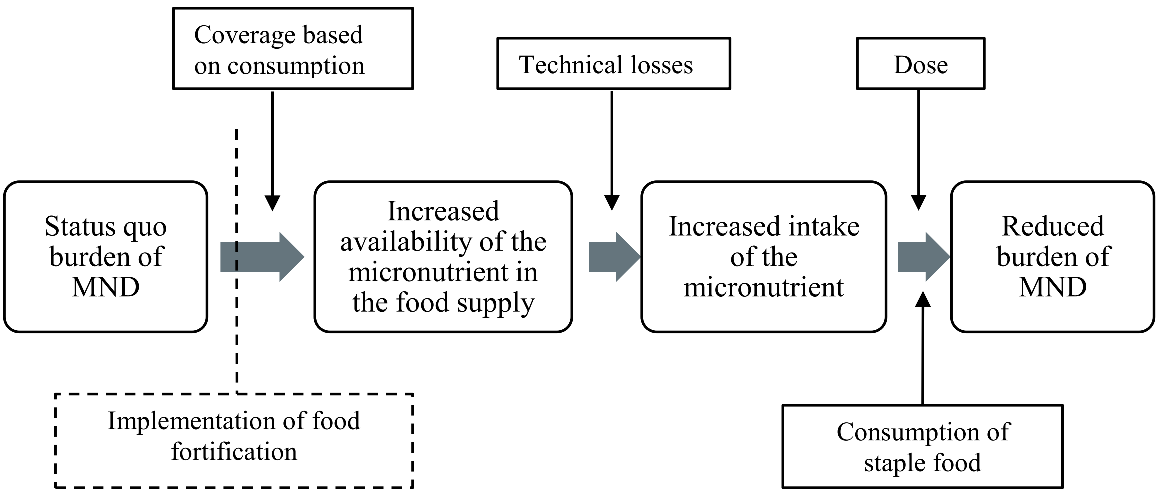


FIGURE 10 - STEPS CONSIDERED WHEN MEASURING THE IMPACT OF FOOD FORTIFICATION. ADAPTED FROM MEENAKSHI ET AL. (169)

In some cases, the impact assessment models were already available from food and nutrition authorities, which is the case for folic acid and iodine fortification studies in Australia (165, 166, 170).

Cost data

Food fortification

The majority of the cost related to food fortification programmes fall on the industry and include set-up costs, as well as the ongoing costs of maintaining the programme. (146). Public sector costs are related to enforcement.

There has been a remarkable effort in elucidating the methods for costing fortification programmes, with a special focus in low- and middle-income countries (LMICs) through a review of the literature (146), cost-analyses (171, 172), and economic evaluations (167, 172).

In high-income countries, the Australian and New Zealand food standards authority (FSANZ) commissioned economic evaluations to inform decisions to improve the micronutrient content in the food supply of these countries. The reports include a detailed description of the model inputs including the cost parameters. Segal (170) and Dalziel (163) considered multiple public health interventions to improve folic acid uptake in pregnant women, including extended voluntary fortification and extended mandatory fortification. Additionally, two cost-benefit analyses were produced regarding the fortification of salt with iodine (166) and the fortification of wheat flour with folic acid (165).

From the evidence reviewed, it is clear that the cost structure of the programme is highly dependent on the industry, which in turn is a country specific item. Things to consider include: the industry dimensions in terms of the number of production sites in the country, quantities produced by year, import/export data, purchase/consumption data, as well as the structure of the companies in terms of personnel, machinery and administration (146). In order to ensure the robustness of the data, researchers surveyed industry representatives, suppliers and national authorities. Estimates of prices, costs, training needs and the impact on trade were generally based on the statistical weighting of estimates reported from more than one source.

INDUSTRY COSTS

These include the price of the fortificant, quality control tests and lab personnel. Examples of the more commonly mentioned items are detailed below:

SET-UP COSTS

Initial costs reported in the studies included:

- Tank for mixing the micronutrient, machinery to mix the micronutrient, and accessories. These costs are only taken into account in countries where the vehicle is not yet fortified. If fortification for other micronutrients is already in place, the industry would have already incurred these set up costs (165).
- Training staff and lab personnel for assuring quality and performing control tests.
- Redesign label and printing plates. This applies not only to the package of the food vehicle, but also to final products that use the vehicle as an ingredient. For example, in the case of flour, it is likely that bread, cakes and other products need to update their labels. This is dependent on country-

specific legislation and generally is defined by minimum thresholds for content.

RECURRENT COSTS

The recurrent costs of maintaining a food fortification programme were:

- Micronutrient purchasing;
- Quality assurance and quality control tests.
- External lab costs. In some setting, suppliers were required to send a sample of their product to an external lab for quality control;
- Various incremental production costs such as electricity costs for the new mixing machinery, additional staff, reporting activities, flushing mils and storage (165).

Consumer costs

CONSUMER CHOICE

It has been argued that mandatory fortification of a staple food means the loss of consumer choice for those outside the targeted group. In the case of folic acid, for example, this means everyone except pregnant women. Some authors recommend a WTP method to estimate this cost, although none of the studies found in this review used it. Dalziel et at. (163) assumed this cost to be $1 per person per year.

INCREASED PRICE OF THE FOOD

Although the costs of fortification fall largely on industry, these are expected to rapidly pass on to the consumer (146, 165, 167). Nonetheless, some studies pointed out that the surveyed industries guaranteed that they would bear all the costs related to fortification (165, 166), without increasing the price of the food. In contrast, an economic evaluation of oil fortification in Uganda found that the retail price per litre would increase by 0.26%, meaning that the average consumer would pay an additional US$0.030 per year for fortified oil (167).

Public costs

AWARENESS CAMPAIGNS

Different actions from the national authorities can be expected to inform the general population and the suppliers about food fortification. The FSANZ reports (165, 166) surveyed local authorities in order to understand the costs and resource use related to this activity. Some local authorities reported that a letter to the companies would be sufficient while others proposed industries should be provided with information sessions, workshops, and a handbook, as well as a new online platform.

MONITORING

The costs of monitoring the impact of a fortification programme relate to the creation of a database of the nutritional and health status before and after the intervention (170). In countries where nutritional and health surveillance is already in place, the incremental cost of monitoring is expected to be zero.

ENFORCEMENT

Enforcement requires visits to the production sites to test that the amount of fortificant added is in accordance with the legislation. The cost depends on the number of industries in the country. Often authorities randomly visit a proportion of the companies per year.

ADMINISTRATIVE COSTS

These include costs of changing the current law, training staff, and dealing with complaints from the public and industries (165, 166).

Other costs

Adverse health events linked to excessive micronutrient intake (163, 165).

Supplementation

Cost data was collected from a variety of sources (157-159, 161, 163). In some studies, the costs of supplementation were limited to the cost of the supplement itself (157, 158). Dalziel et al. included also the costs of the physician's advice, and of a national promotion campaign (163). Baltussen et al. calculated the cost of supplementation through a multi component cost equation that included the unit price of the supplements, and the additional time spent by a health care professional to provide the service (161). Moreover, programme-level resource inputs, such as the salaries of central administrators, capital costs of vehicles, storage costs, offices, and furniture (161) were considered. Phillips et al. took a provider perspective to compare Vitamin A fortification with supplementation (159). The study found that the majority of the costs of the fortification programme were linked with the fortificant (Vitamin A), while personnel and transportation accounted for the majority of the expenditure within the supplementation programme.

Equity considerations

Studies did not formally introduce equity weight measures into the analysis, although most acknowledge that MNDs are more likely to affect lower socio-economic groups. Equity concerns were described predominantly when the choice of alternatives was considered. It has been suggested that mandatory fortification of staple foods is more likely to have a wider coverage and reach all socioeconomic strata, as it has been suggested for fortification of sugar in Guatemala (159), and wheat flour fortification in Australia (163). Dalziel et al. (2010) reported challenges in measuring the impact on subgroups due to the lack of stratified data on food consumption and uptake of supplements. Bentley (2009) presented subgroup analyses by different age and ethnic groups and found substantial ethnic differences in disease outcomes (155). The authors concluded that targeted supplement interventions might reduce inequalities and recommend future research to look into ethnic differences related with the intake of fortified and non-fortified foods.

Discussion

This review found a number of studies presenting relevant methodological approaches to evaluating the costs and benefits of programmes to prevent MNDs. In-line with the findings of previous reviews, the methods applied vary widely (173). Seemingly, the micronutrient studied was an important determinant of the overall study design, as each micronutrient has its own population of interest, cost profile and health burden. Several lessons can be drawn from the existent literature, which are valuable to inform future decision analytic models:

Interventions

Food fortification and supplementation are the main interventions to prevent MNDs. The literature refers to mandatory fortification as a valid option when the MND affects a significant proportion of the population and/or when the uptake of supplements is low. Fortification does not require behavioural change and has a broad impact (163). On the other hand, supplements are more likely to provide a higher concentration of micronutrients. Nonetheless, authors seem to find it unlikely that a single intervention will effectively tackle MND in a given population. The existing evidence guides us towards a combined approach in order to balance cost-effectiveness and coverage. An impact model by the Food Standards Australia New Zealand (FSANZ) on iodine fortification found that the programme would not reach all at-risk groups and therefore, it would be likely that pregnant women and lactating mothers would still require supplements even after fortification implementation (166). Despite this, this review did not identify any economic evaluations of combined interventions to prevent MNDs. Dalziel et al. (163) highlight the lack of evidence for the synergistic impact of several interventions in place at the same time (163). It is not clear in what direction effectiveness may shift. For example, if foods are fortified, individuals may be more relaxed about taking supplements. On the other hand, it may be that food fortification increases awareness about the importance of the micronutrient and this consequently increases the uptake of supplements (163). The choice of which interventions should be compared depends on the setting, and should ideally be informed by expert opinion, such as policy-makers.

The review showed that the design of interventions compared is shaped according to the MND prevalence, the at-risk population, the setting in which the intervention is to be implemented and the prevalence of the MND. For example, in some settings it is impractical to implement public health campaigns or supplementation programs as the targeted population live in remote areas, and would therefore result in high delivery costs. In such a setting, a fortification programme is more likely to reach the targeted population. On the other hand, a supplementation program may be more cost-effective to implement in the more accessible areas with a high population density.

Importantly, feasibility and therefore cost-effectiveness of a fortification strategy is highly determined by the choice of the vehicle. When considering a fortification programme, it is important to choose a food that is consumed in known, predictable and adequate amounts by the targeted population (159, 161). Frequently, staple foods such as flour, sugar, and oil are chosen to be fortified. Moreover, the stability and bioavailability of the micronutrient must not change when added to food (161). Additionally, fortification must not change the characteristics of the food such as smell, colour and texture (159, 161).

As Fielder et al. (171) point out, the choice of the vehicle also needs to consider various factors concerning the food industry such as its structure, the nature of the food, marketing considerations, and willingness of the suppliers to fortify (171).

The literature also highlights the lack of population data on the effectiveness of the interventions. Baltussen et al. (2004) mention how effectiveness data from RCTs are likely to overestimate the benefits of supplements, since uptake is monitored and generally higher than in the population (161).

Populations and setting

A thorough definition of the target population is important, not only for an accurate population for the model but also to ensure robust estimates of the coverage of each intervention compared. The definition must include age, ethnicity, socio-economic status, geographic location (i.e. urban/rural) and food consumption data. Individual food consumption data, by age and ethnicity, is essential to estimate the impact of the food fortification programme. Additionally, an in-depth description of the setting where the intervention will be implemented is also fundamental. The health system structure, personnel pay rates and existing infrastructures affect the programmes. In food fortification interventions, it is important to know the food industry structure, for example, in wheat flour fortification models, the number of mills available and the size of the mills may have an impact on the costs.

Costs

SUPPLEMENTATION PROGRAMMES

Fiedler et al. found that in LMICs, personnel costs account for the greatest share of the total costs of a supplementation programme and therefore need to be carefully considered (146). This includes salaries, time, requirements for additional health/administrative staff, and training. In the current review, the majority of the costs were from the supplement itself. It is important to note that Fiedler's review included mostly studies from LMICs and this review has gathered evidence mostly from high-income settings. A different structure of the health care system and infrastructure may explain the differences.

FOOD FORTIFICATION PROGRAMMES

Costs relating to fortification programs are likely to be four-fold: industry costs, government costs, consumer costs and healthcare service costs. The main contributor to the total cost is the fortificant itself and it is therefore important to ensure certainty about the estimated price and guarantee that the cheapest formula is being considered.

Conclusion

Although only a small number studies used decision analytic models to evaluate the cost-effectiveness of strategies to prevent micronutrient deficiencies, the review presented in this chapter carries valuable evidence regarding the methods to model the cost-effectiveness of such strategies such as the relevant comparators, the handling of population and effectiveness data, and the costing methods.

With this chapter, the literature review section of this thesis is completed. Following the results and recommendations from chapters one, three and four, the thesis moves on to its the empirical section, presented next in chapter five, before describing the methods to build a decision analytic model to compare strategies to prevent VDD, in chapter six.

IMPORTANT MESSAGES FROM THIS CHAPTER

- Few economic evaluation of the prevention of MNDs used decision analytic models;
- Cost analyses and budget impact analyses have been the preferred method to inform policies in LMICs;
- The following key messages emerged from this literature review that subsequently informed the development of the decision-analytic model presented in chapter 6:
  - Strategies to prevent MNDs are generally cost-effective, and food fortification is potentially cost saving;
  - A combination of supplementation of at-risk groups and food fortification is likely to be the most effective way of preventing poor health due to MNDs. Nonetheless, the cost-effectiveness of combined strategies has not yet been studied.
  - The choice of which food is fortified is crucial for the success of a mandatory food fortification policy. Access of the targeted population to the food and costs are particular important items. In addition, technical aspect such as the chemical proprieties and stability of the fortificant need to be considered.

IMPORTANT MESSAGES FROM THIS CHAPTER (CONT.)

- The cost structure of national programmes is country specific. For example:
    a) Fortification programme: in the UK, adding a micronutrient to wheat flour will not incur initial costs for the millers as the technology and training is already in place with current flour fortification.
    b) While the main costs of delivering a supplementation programme are linked to personnel in LMIC's, in HIC's they are linked to the monitoring of the programme, and the provision of the supplements.
- There are many data constraints limit subgroup analysis of vulnerable groups in the population, such as ethnic minorities or deprived populations.

CHAPTER 5

PROXY ELICITATION OF PREFERENCE VALUES FOR HEALTH STATES IN THE VITAMIN D DEFICIENT POPULATION USING EXPERTS

Introduction

The empirical study presented in this chapter was motivated by the findings from the literature review section of this thesis. The systematic review presented in chapter three found a dearth of utility data for VDD–related outcomes, which has been highlighted as one of the reasons for the lack of cost-utility analyses evaluating the prevention of population VDD. In chapter one, evidence that VDD leads to poor health in children and adults was presented. It is therefore reasonable to assume that VDD-related HSs result in a decrement in health-related quality of life (HRQoL). Moreover, utility data can be used to estimate QALYs in a CUA, which, as mentioned in chapter two, are the preferred measure of benefit in economic evaluations of health and public health interventions. Hence, it seemed appropriate to design a study to collect data on the HS utility values for VDD-related outcomes. The results from the valuation exercise presented in this chapter will fill a literature gap and will be used to inform the model parameters, described in the following chapter.

The use of QALYs as a measure of benefit of interventions to prevent VDD has numerous advantages. The QALY combines length of life with quality of life data, being able to capture the wider effects of preventing VDD, that go beyond the clinical sphere (92). At the same time, it is a generic outcome that is extensively used by decision makers, which allows comparison with other economic evaluations in the Public Health domain. In the UK for example, NICE recommends the use of CUAs as the base case for the evaluation of health technologies, as well as public health programmes (89, 174).

Utility values can be derived through direct valuation methods, such as standard gamble (SG) and time-trade off (TTO), or indirect methods, based on preference-based multi-attribute systems (175). SG is based directly on the fundamental axioms of utility theory by von Neumann and Morgenstern (176), more specifically the principle of continuity of preferences. Respondents are given a choice between two alternatives: alternative one is a certain chronic HS and alternative two is a treatment with two possible outcomes: full health (probability P) or being dead (probability 1-P). Probability P is varied until respondents are indifferent between the chronic HS and a specific probability P of success, at which point the utility score of the certain HS is equal to P at the point of indifference (92).

In turn, TTO uses time instead of probabilities to estimate utility values for a given outcome. In TTO, respondents are presented with two certain outcomes, and are asked how many years in a given HS are equivalent to a pre-determined time in a poorer HS.

Utility values are estimated from the comparison between the two time periods (175). TTO was developed to overcome SG limitations, mainly the difficulty respondents may have in understanding the concept of probabilities. Nonetheless, both TTO and SG are seen as demanding in terms of time and the cognitive commitment needed (91).

Hence, the use of indirect methods has become increasingly popular as they generally constitute simpler and less time consuming tasks, compared to the direct methods (92). With indirect methods, the HSs are described based on an individual's response to physical, social and mental dimensions contained within a questionnaire. Preference weighted utility scores are then applied to the HS descriptions using an external dataset developed using general population values.

For the present work, two multi attribute preference-based questionnaires were used – the Child Health Utility 9 Dimension (CHU9D) for children and the EuroQol 5 dimensions (EQ-5D) for the adults.

Evaluation of HRQoL by a proxy

HRQoL is a subjective measure that reflects how individuals feel and perform when in a given HS (177). Whose values should be used to inform outcomes within economic evaluation is a controversial matter (178). Proxy questionnaires are available and used as the best alternative when patients cannot be reached or are unable to evaluate their HS. This is particularly the case in the paediatric population, namely for young cohorts (179), and for people with cognitive impairments or in a frail condition (180, 181). Additionally, proxy HRQoL data has been used to overcome recruitment issues. In such cases, studies use proxies, more commonly health professionals, to improve response rates in clinical settings and trial studies, where patients may not be as reachable as the formal carers involved in the study (182). Notwithstanding this, self-reporting is the preferred method to estimate HRQoL in a clinical setting (181). Where impractical, parents, carers, and clinical experts are suitable candidates to provide information about the patient's quality of life (182-185). Proxies provide substitute estimates of HRQoL by being asked to complete a HRQoL questionnaire from the patient's perspective, i.e. responding as they think the patient would.

Several studies have compared utility values from different groups and the vast majority concluded that there is disagreement between results (175, 186). This means that it is likely that the ranking and valuation of HSs differs according to whose values are elicited, which will have an impact on the results of the economic evaluation, and consequently on the policy recommendation. As an example of such variations, it has been noted that the general population tends to give lower values as compared to the patients, which has been attributed to the patient's ability to adapt to their condition (187).

The source of utility data may depend on the aim of the study, namely on who it aims to inform. NICE recommends health benefits to be valuated using a representative sample of the UK's general population (89), as economic evaluations submitted to NICE aim to inform decision that are publicly funded. Other sources of values are used in clinical settings to gather insights from patients' experience.

HRQoL and VDD in the general population

Few studies have attempted to analyse the association between Vitamin D status and HRQoL. Chao et al. (188) used a non-representative sample of the Canadian elderly population to estimate the association between Vitamin D status and HRQoL (188).

Participants were volunteers aged over 50 years who had their blood samples analysed and were asked to answer the EQ-5D-5L questionnaire. The authors found that Vitamin D sufficient participants were less likely to report issues with mobility, usual activities, anxiety and depression. Overall, a mean utility score of 0.766 was reported for those with 25(OH)D below 25 nmol/L, opposed to a mean score of 0.814 for those with 25(O)D > 100 nmol/L (188). From the report, it is not clear if the participants were otherwise healthy or suffered from any acute or chronic condition that may have also affected their HRQoL. Rafiq et al. (189) reported on the HRQoL of a large elderly cohort in the Netherlands, using the Self-rated Health (SRH) and the physical component of the SF-12, with the aim of investigating the impact of low Vitamin D on these measures. The study also examined the association between VDD and depression, low physical activity performance, and chronic diseases. All participants were aged over 65 years. Results were adjusted for possible confounders: gender, age, body mass index, alcohol consumption, smoking status, season of blood collection, and serum creatinine. The authors found that Vitamin D deficient individuals reported lower SRH and lower scores of the SF-12 physical component, when compared with Vitamin D sufficient participants. Additionally, those with low serum 25(OH)D scored lower on physical performance, had more chronic diseases, and more depressive symptoms (189). Finally, Tolentino-Wilson et al. (190) estimated the impact of Vitamin D supplements on the HRQoL of VDD subjects. The intervention used high dose Vitamin D supplements (2000 IU to 6000 IU) in 76 adults with age ranging from 18 to 59 years. The HRQoL was measured using the Functional Assessment of Non-life Threatening Conditions (FANLTC) instrument and scores were compared for before and after the intervention. The authors reported an increased score in all dimensions of the FANLTC questionnaire, and an overall improvement in HRQoL. None of the studies available explored the impact of VDD upon the HRQoL of children.

Fall-related HRQoL and its use in economic evaluation of VDD

Falls, and consequent fractures, are an important cause of morbidity and mortality in the elderly population (148). As shown in the review presented in Chapter 3, there have been a number of economic evaluations assessing interventions to prevent and treat falls and fractures related to VDD. Three of them considered QALY loss due to falls (132-134) based on the disutility of feeling fear of falling (133, 134), fall-related hip fractures (132) and other fall-related fractures (133, 134). Among these studies, the source of disutility data is consistent. Studies considering fear of falling derived their estimates from Iglesias et al. (191). Iglesias and colleagues analysed three large datasets: two clinical trial-based datasets and one from a cohort study. HRQoL was estimated using the EQ-5D instrument and participants were all women over 70 years. Fear of falling was measured using a Likert scale that went from feeling fear of falling "little of the time" to" all of the time". The authors found fear of falling to be an important source of morbidity – it was found to be associated with a 6% decrement in QALY per woman per year (191). Further literature support the findings that fear of falling has a depreciative impact upon the HRQoL (192, 193), as it causes anxiety, distress and limited mobility.

Studies focusing on the disutility of fractures sourced their estimates from the systematic review of HS utility values for osteoporosis outcomes by Brazier et al. (194) and its update by Peasgood et al. (195). These reviews summarise the evidence on the utility values for the main osteoporosis HSs, including hip fractures, vertebral fractures, wrist fractures and several others. Although used in VDD economic evaluations, the applicability of such estimates to the VDD context is questionable as experts are sceptic of linking low Vitamin D with osteoporosis-related outcomes.

More recently Stenhagen et al. studied the long term effects of falls on the HRQoL and life satisfaction of Swedish adults (196). The study followed a cohort of subjects aged between 60 and 93 years old. It used the SF-12 instrument and found those who had experienced a fall reported a lower HRQoL and life satisfaction. The impact was more evident within the physical component of the SF-12 instrument.

The utility values for fear of falling and VDD-related fractures elicited within the survey presented in this chapter will be estimated and compared with the values reported in the literature.

Methods

The relevant HSs for each population group were described based on the literature and expert consultation. The questionnaires for utility elicitation were then selected and structured into an online survey.

Health state definition

The HSs were defined to represent the clinically relevant consequences of VDD that could potentially affect HRQoL. The initial descriptions were based on the evidence presented in Chapter 1 regarding the relevant VDD-related metabolic bone outcomes.

For children, five HSs were initially defined: hypocalcemic cardiomyopathy (64), hypocalcemic seizures (70, 71), skeletal abnormalities (3, 71), delay in motor milestones and poor growth (3, 71), and asymptomatic VDD.

For adults the HSs identified were: osteomalacia (10, 17, 57), fall and consequent fear of falling (128, 197), fall and minor fracture (197), fall resulting in hip fracture (128, 197), fall resulting in hip fracture and requiring admission to care home (128, 197), and asymptomatic VDD. The description of the fracture and fear of falling HSs was based on the description by Salked et al. for a TTO study with women at risk of fracture (197).

An asymptomatic VDD HS has been defined for both children and adults as a subclinical HS, in which individuals have low serum 25(OH)D that would result in diagnosis of VDD, but no evident symptoms manifest.

EXPERT CONSULTATION

The preliminary set of HSs was reviewed by two clinical experts with experience in treating symptomatic VDD in children, and one expert with experience in treating symptomatic VDD in adults. This stage aimed to gather informed opinion on the relevance of the HSs to increase the overall acceptability of the survey. Feedback was sought on a range of different aspects: the content, the wording and clarity of the descriptions, and the possibility of adding HSs that could have been missed through the literature review or removing any HSs that were considered irrelevant. Additionally, informal feedback was sought on the acceptability of the task and how clinical experts thought it would be received within their community. As a result of this initial consultation, some revisions were suggested for the description for the HSs and two new HS were added, as shown in Box 2 and 3. In addition, the HSs were further divided by age group. For example, hypocalcemic cardiomyopathy has only been reported in infants and falls linked to VDD are not reported in the younger adult population (aged between 19 and 59 years old). The final age groups were young children (0-4 years), older children (5-18 years), younger adults (19-64 years) and older adults (above 64 years).

Health State A

The patient is Vitamin D deficient, ~~confirmed by serum concentration of 25-hydroxyVitamin [25(OH)D~~] [25(OH)D <30nmol/L]. The child presents with hypocalcemic cardiomyopathy. The condition requires hospital care, including ventilation and inotropic support.

Health State B

The patient is Vitamin D deficient ~~confirmed by serum concentration of 25-hydroxyVitamin [25(OH)D~~] [25(OH)D <30nmol/L]. The child presents with hypocalcemic seizures and requires hospitalisation**.**

Health State C

The patient is Vitamin D deficient, ~~confirmed by serum concentration of 25-hydroxyVitamin [25(OH)D~~] [25(OH)D <30nmol/L]. The child presents with overt rickets, with skeletal abnormalities such as bowed legs, swollen ankles and deformed chest.

Health State D

The child presents with leg deformities following active rickets (rickets healed in deformity). If not continuously supplemented with Vitamin D for life, the child may require surgery to correct deformities, and may develop active rickets again.

Health State E

The patient is Vitamin D deficient, ~~confirmed by serum concentration of 25-hydroxyVitamin [25(OH)D~~] [25(OH)D <30nmol/L]. The child presents with pain and muscle weakness and may show signs of delay in motor milestones and poor growth.

Health State F

The patient is Vitamin D deficient, ~~confirmed by serum concentration of 25-hydroxyVitamin [25(OH)D~~] [25(OH)D <30nmol/L]. The child may be in a pre-rickets state but nonetheless, the child is asymptomatic**.**

BOX 1 - FEEDBACK FROM PAEDIATRICIANS ON THE INITIAL SET OF HSS (SUGGESTED CHANGES IN BLUE).

Heath state A

The patient is Vitamin D deficient [25(OH)D] <50nmol/L] ~~and presents with **osteomalacia**, characterized by elevated ALP and secondary hyperparathyroidism~~. The patient presents with <u>diffuse bone pain and muscle weakness</u>, elevated ALP and secondary hyperparathyroidism. The muscles affected are mostly thighs, shoulders and main trunk of the body. Physical activities, such as climbing stairs or getting up from a chair without using the arms for support, may be limited. The patient has consequently been diagnosed with <u>**osteomalacia**</u>.

Health State B

The patient has osteomalacia. He/she presents with diffuse bone pain, diagnosed as <u>**pseudo-fracture (Looser zone**</u>). The patients reports that the pain is persistent during day and night and show signs of distress.

Health State C

The patient has osteomalacia and marked muscle weakness. As a consequence, the patient <u>**fell**</u> and was badly cut and bruised, although no fractures occurred. After the fall, the patient is experiencing <u>**fear of falling**</u>. The patient continues to walk independently but is uncomfortable when outside, as he/she is scared of falling again.

Health State D

The patient has osteomalacia and marked muscle weakness. As a consequence, the patient <u>**fell**</u> ~~and suffered.~~ The fall resulted in a <u>**minor fracture**</u> (e.g. wrist fracture). The patient was assisted in A&E and was released on the same day.

Health State E

The patient has osteomalacia and marked muscle weakness. As a consequence, the patient <u>**fell**</u> ~~and suffered~~. The fall resulted in a <u>**hip fracture**</u>. The patient was admitted to hospital and released back home again. After recovery, the patient still requires a walking aid and can no longer drive or go shopping alone.

Health State F

The patient has osteomalacia and marked muscle weakness. As a consequence, the patient <u>**fell**</u> ~~and suffered~~. The fall resulted in a <u>**hip fracture**</u>. The patient was admitted to hospital and released to a nursing home. The patient walks very short distances now and needs a frame for support.

Health State G

The patient is Vitamin D deficient [25(OH)D] <50nmol/L]. The patient is considered to be <u>**asymptomatic**</u>.

BOX 2 - FEEDBACK FROM ADULT BONE SPECIALISTS ON THE INITIAL SET OF HSS (SUGGESTED CHANGES IN BLUE)

Respondents

Clinical experts were chosen to complete the survey for three main reasons. First, the population of interest is partly formed by infants and young children who would be unable to provide self-reported HRQoL estimates. Second, while associated with high morbidity, some clinical outcomes of VDD are rare in the UK. For instance, this is the case with rickets, seizures, and cardiomyopathy. To identify and recruit patients suffering from rare events would be time and resource consuming. Lastly, frequent symptoms of VDD such as pain and muscle weakness due to VDD are largely underdiagnosed and commonly linked to other health conditions. Recruitment of patients with diagnosed pain and muscle weakness due to VDD would be a highly demanding task.

Hence, it was considered more practical to estimate utility-based HRQoL using VDD expert as proxy respondents of multi-attribute HRQoL questionnaires.

Sampling

The expert sample for children, recruitment was done via email to three groups of experts: the Global Rickets Consensus Group; the British Pediatric and Adolescent Bone Group; and the Bone and Growth Plate Working Group belonging to the European Society for Pediatric Endocrinology. For the adult expert sample, contact was made through the National Osteoporosis Society (NOS). The recruitment of participants was based on a snowball sampling method, also known as network sampling. In snowball sampling, a group of participants, made up of individuals that are within the reach of the researcher, are initially contacted. These are then asked to invite other eligible participants, in order to increase the sample size (198).

For the child survey, a total of 136 experts were recruited through email. The template of the invitation email is shown in Appendix 8. Individuals were asked to fill in the questionnaire and forward the email to other experts in the field whom they thought had the expertise to answer the questionnaire. A reminder was sent out a week after the first invitation.

For the adult survey, the NOS sent the invitation through its monthly electronic newsletter. This method did not allow for the estimation of how many individuals were reached. Moreover, it was not possible to send a reminder.

Choosing the questionnaire

Selecting which multi-attribute system to use to elicit preferences is an important decision (92) since the existent systems differ in their structure, the theory that underpins them, and the methods and populations used for their valuation. The literature shows that utility values derived indirectly from multi-attribute systems vary in the same group of patients, according to the system used. In this thesis, the choice of the questionnaire took into consideration the targeted population, the characteristics of the respondents and the accessibility of the questionnaire itself. A questionnaire with a proxy version suitable for clinical experts' completion was considered ideal. Additionally, preference was given to an open access instrument, involving a simple and relatively short task, so as to not discourage participation.

Several questionnaires are available for the paediatric population and as Solans et al. (2008) noted, there has been increasing interest in evaluating the HRQoL of children, resulting in the development of a number of instruments in the last couple of decades (199). Amongst those available for proxy completion, the most widely used include the

Health Utilities Instrument (HUI2), the EQ5D-Y, the PedsQL and the CHU9D. The HUI2 was developed for the use in children and has been valued using a sample parents from Hamilton, Canada. The questionnaire has seven dimensions (sensation, mobility, emotion, cognition, self-care, pain and fertility), each of which has between three and five levels. The HUI2 developers recommend its use in children of 5 years and older. The EQ5D-Y is an adaption of the adult version of the EQ5D-3L, and uses child and teenager friendly language to describe each of the dimensions - mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The instrument developers recommend that this instrument is used only to describe health states within children, and not as a utility-valuation instrument (ref). The CHU9D was developed based on interviews and ranking exercises with children from 7-11 years (200). The tool has successfully been applied to wider populations, from five years old up to 17 years old (201, 202). The questionnaire comprises nine dimensions (worried, sad, pain, tired, annoyed, school work/homework, sleep, daily routine, ability to join activities) each with five levels. The five levels provide a scale from total 'inability to perform/feel' to 'perfect ability to perform/feel'.

For adults, widely used instruments that allow indirect utility estimation include the HUI, the EQ5D, and the SF6D. The HUI3 is recommended for primary analysis in adults. Dimensions include vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain. The system exists in two complementary forms HUI2 and HUI3, and while HUI3 is recommended for primary analysis, the use of both can result in insightful results. Table 3 lists the advantages and disadvantages of each instrument in the context of the present study.

TABLE 3 – ADVANTAGES AND DISADVANTAGES OF THE GENERIC INSTRUMENTS FOR HEALTH-RELATED QUALITY OF LIFE CONSIDERED FOR THIS THESIS

Instrument	Advantages	Disadvantages
Children		
EQ-5D-Y	Open resource Instrument is familiar to clinical experts Proxy questionnaire available	Not applicable for infants and young children younger than 4 years No value set to generate utility values from the descriptive system Adaptation of the adult questionnaire
CHU9D	Open resource Developed for children Allows direct utility estimation Validated for children 6-17 years old Pilot proxy questionnaire available for children younger than5 years old	Young children version is a pilot, and not yet validated.
HUI2	Developed for children Allows direct utility estimation Proxy questionnaire available	Not open access Value set to generate utility from based on preferences of Canadian population
PedsQL	Developed for children Proxy questionnaire available	Not open access Validated for use in children over 5 years old. Does not allow direct utility estimation
Adults		
EQ-5D	Open resource Proxy questionnaire available Widely used in clinical settings Allows direct utility estimation Recommended by NICE Scored based on preferences of UK population	No major disadvantages were noted in the context of this study
HUI3	Version available for population Allows direct utility estimation Proxy questionnaire available	Not open access Not recommended by NICE Value set to generate utility from based on preferences of Canadian population
SF-6D	Allows direct utility estimation Proxy questionnaire available Some use in clinical settings Scored based on preferences of UK population	Not recommended by NICE Less common in clinical setting than the EQ-5D

After careful consideration of the advantages and disadvantages of each instrument, the proxy version of the CHU9D questionnaire was selected (203) for having the advantage of being a flexible tool that can be adapted for use in young children. And, the results can be used to estimate utility values directly, without the need for further mapping techniques (204). Although clinicians might be more familiar with the EQ5D-Y instrument, this instrument is not recommended for utility estimation in a childhood population(205).

Some parts of the original instruments are not suitable for infants and pre-school children. Namely, questions about school activities, self-care and states of anxiety are not applicable to the younger population. For this reason, the questionnaire development group were contacted and they provided a pilot version of a CHU9D questionnaire for younger children. This version has the same questions as the original, but provides a short explanation of how questions should be interpreted for pre-school children. This was the version used for the HSs relating to young children and is presented in Appendix 9.The utility values were valued using a UK value set from children.

For the adult survey, the EQ-5D-5L was chosen as it is one of the most commonly used instruments to estimate HRQoL (109), and is well known by clinical professionals, and is the NICE recommended tool for indirect utility measurement(89). It has five dimensions - mobility, self-care, usual activities, pain/discomfort and anxiety/depression. In each dimension, respondents can choose one of the five levels that best describe the HSs. For example, in relation to mobility, one could choose between ‘no problems in walking around’, “slight problems walking around”, “moderate problems walking around”, “severe problems walking around” and “unable to walk around". Results are converted into a preference-based utility score, using an appropriate valuation set. The results of the proxy EQ5D questionnaire were valued using the value set from the general population, through the Hout et al. mapping function(206), as recommended by NICE.

Structure of the Questionnaire

RANKING TASK

For each age group, the first task presented was a ranking exercise where experts were asked to rank the HSs according to their severity. In this scale, one represented the least severe HS and the highest number corresponded to the most severe.

This task was included to familiarise the respondent with the HSs before they started the main questionnaire (207). The online version of the ranking task was designed so that respondents were not allowed to repeat scores and forced them to attribute a ranking value to each HS before being allowed to continue.

UTILITY EXERCISE

HSs were described for a hypothetical patient and the respondent was asked to provide a 'best guess' on how the patient would feel/perform in that given state. The online questionnaire was designed so that an answer to each dimension was mandatory and only one level in each dimension could be selected.

PROFESSIONAL BACKGROUND

In the last section, respondents were asked about their professional practice. Multiple choice answer options were general practitioner, nutritionist, rheumatologist, and other, where experts could describe their speciality. Furthermore, as a measure of clinical expertise, respondents were asked to specify which country they were practicing in, and how many cases of rickets or osteomalacia they had seen in the last two years.

Results

The Child Survey

The child survey reached a total of 143 specialists, and 38 completed the questionnaire, resulting in a response rate of 26.6%.

Characteristics of the respondents

Respondents were from 18 different countries, the majority being from the UK (23.7%) and France (13.2%). Most experts were paediatric endocrinologists (39.5%) and paediatricians whose speciality was not specified (31.6%). Table 4 presents the participants speciality and country of practice.

TABLE 4 – COUNTRY OF PRACTICE AND SPECIALITY OF RESPONDENTS FOR THE CHILD SURVEY

Speciality	**N (38)**	**%**
Biologist	2	5.3
Endocrinologist	15	39.5
General Practitioner	1	2.6
Metabolic Bone specialist	3	7.9
Paediatrician (non-specified speciality)	12	31.6
Paediatric Nephrologist	1	2.6
Rheumatologist	3	7.9
Special interest in paediatric bone disease	1	2.6
Country of practice		
Argentina	1	2.6
Czech Republic	1	2.6
Denmark	1	2.6
Estonia	1	2.6
France	5	13.2
Germany	1	2.6
Greece	2	5.3
India	1	2.6
Ireland	1	2.6
Italy	1	2.6
Poland	2	5.3
Russia	1	2.6
South Africa	2	5.3
Spain	1	2.6
Sweden	3	7.9
The Netherlands	2	5.3
UK	9	23.7
USA	1	2.6

Most of the respondents had experience in treating rickets - 92% had seen at least one case of rickets in the last two years, and the total number of cases seen ranged from 0 to 30 cases Figure 11.

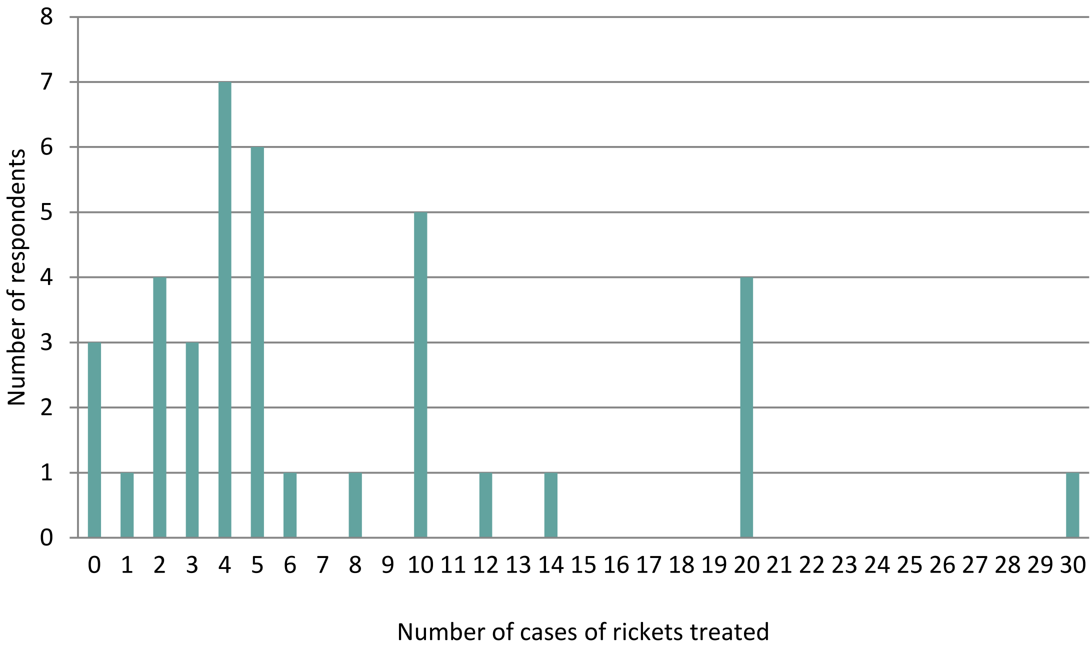


FIGURE 11 - TOTAL NUMBER OF CASES OF RICKETS SEEN BY RESPONDENT IN THE PAST 2 YEARS

Ranking scores

In infants, hypocalcemic cardiomyopathy was ranked as the most severe HS followed by hypocalcemic seizures, active rickets, leg deformities, pain and muscle weakness and the asymptomatic HS (Figure 12).

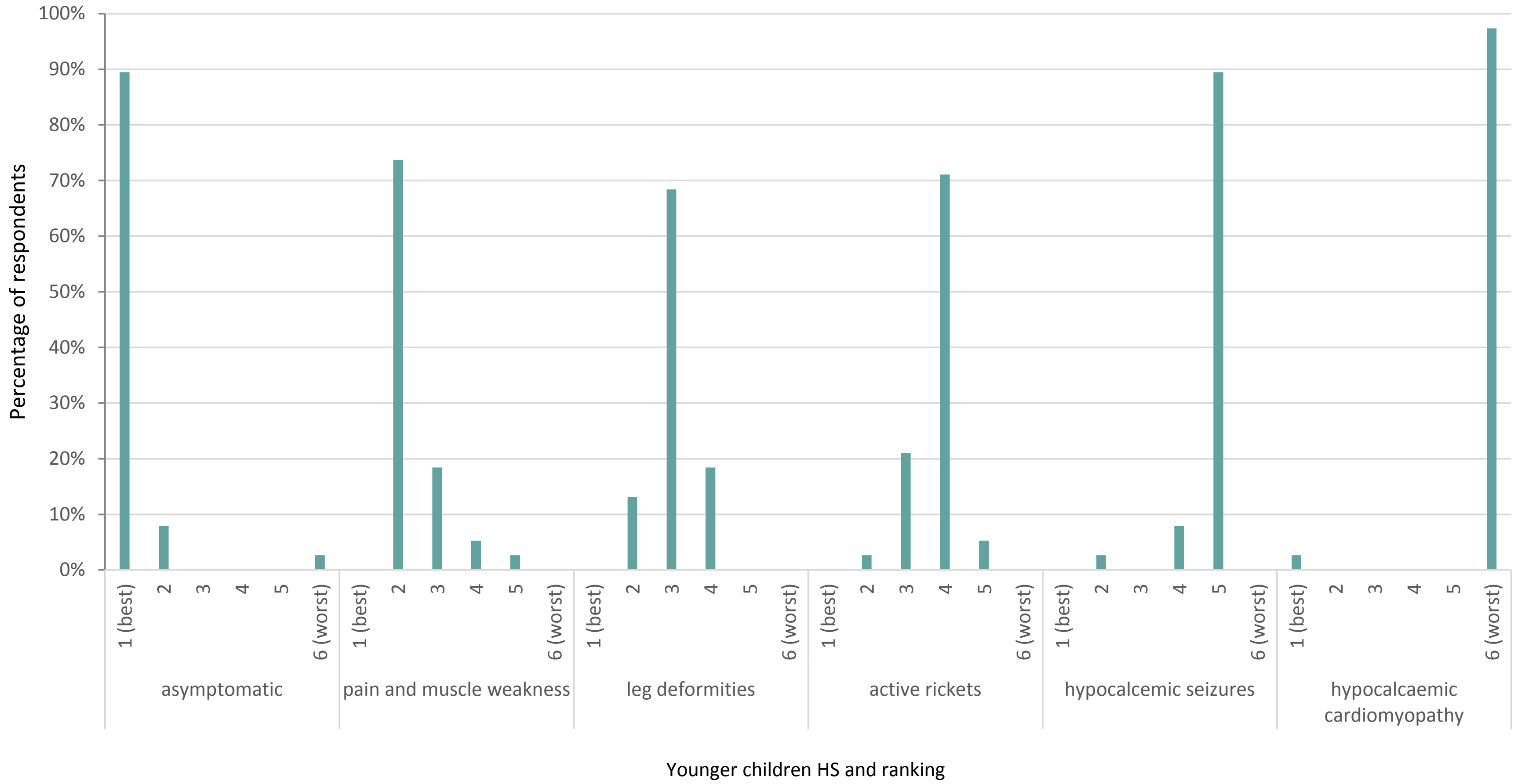


FIGURE 12 - RANKING SCORES FOR THE YOUNG CHILDREN HSS

For thesub-group relating to older children, active rickets was considered to be the most severe HS, followed by leg deformities, pain and muscle weakness and asymptomatic VDD (Figure 13). As expected, asymptomatic VDD was consistently the least severe HS in both sub-groups. There was less agreement on the ranking result for the mid-ranked HSs. There was one inconsistent response where it is possible that the responding clinician inverted the scale when responding.

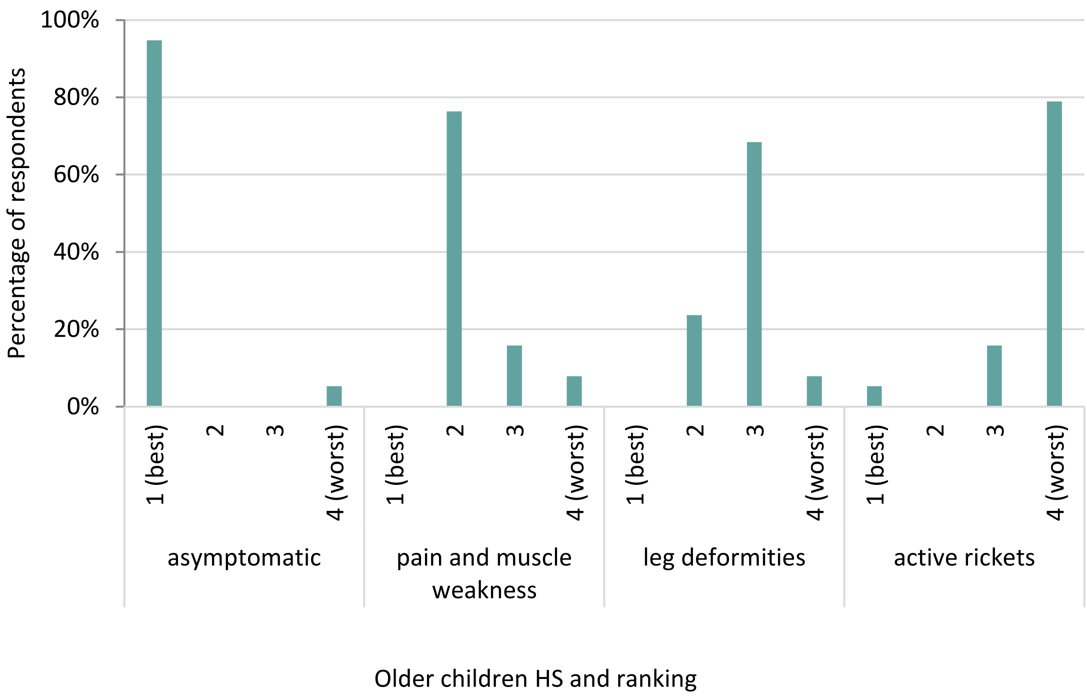


FIGURE 13 – RANKING SCORES FOR THE OLDER CHILDREN HEALTH STATES

Utility scores

All HSs resulted in some disutility, with cardiomyopathy (0.465; 95%CI [0.425; 0.5046]), and hypocalcemic seizures (0.49; 95%CI [0.458; 0.531]) having the lowest utility scores. The HSs repeated in both age groups, namely active rickets, leg deformities, pain and muscle weakness and asymptomatic VDD, had similar utility scores (Table 5). The full results are presented in Appendix 11.

TABLE 5 –MEAN UTILITY SCORES FOR CHILDREN WITH VDD

Health State	Mean	Std. Err.	[95% Conf. Interval]
Infants and young children			
Active Rickets	0.621	0.0175	[0.586; 0.657]
Cardiomyopathy	0.465	0.0195	[0.425; 0.505]
Seizures	0.495	0.0181	[0.458; 0.532]
Leg deformities	0.758	0.0189	[0.720; 0.796]
Pain and muscle weakness	0.612	0.0224	[0.566;0.657]
Asymptomatic	0.955	0.0138	[0.927; 0.983]
Older children			
Active Rickets	0.567	0.0210	[0.524; 0.61]
Leg deformities	0.708	0.0197	[0.668; 0.748]
Pain and muscle weakness	0.608	0.0198	[0.567; 0.648]
Asymptomatic	0.946	0.0121	[0.921; 0.970]

The adult survey

The adult survey was completed by a total of 10 clinical experts. The survey was distributed online through the NOS's monthly newsletter (July 2016). Although it was possible to know the total number of experts in the mailing list, it was thought that this was not an appropriate denominator to estimate the participation rate, since many might not have opened the newsletter, or might have missed the invitation. It was therefore not possible to work out the response rate. Nonetheless, it was clear that the participation rate was much lower than that of the survey focusing on children.

Characteristics of the respondents

Experts practicing in the UK (n=5), USA (n=2), India (n=2) and Austria (n=1) completed the survey focusing on adults and the majority were endocrinologists (n=6) (Table 6). All experts had treated at least one case of osteomalacia in the past two years, and seven had treated more than 10.

TABLE 6 - COUNTRY OF PRACTICE AND SPECIALITY OF RESPONDENTS FOR THE ADULT SURVEY

Country	**N (10)**	**%**
UK	5	50%
USA	2	20%
Austria	1	10%
India	2	10%
Speciality		
Endocrinologist	6	60%
Rheumatologist	2	20%
Orthogeriatrician	1	10%
Geriatrician with a special interest in metabolic bone disease and falls prevention	1	10%

Ranking scores

All participants ranked asymptomatic VDD as the least severe HS (Figure 14). For young adults, “bone pain and muscle weakness” was ranked the most severe HS for 70% of the respondents.

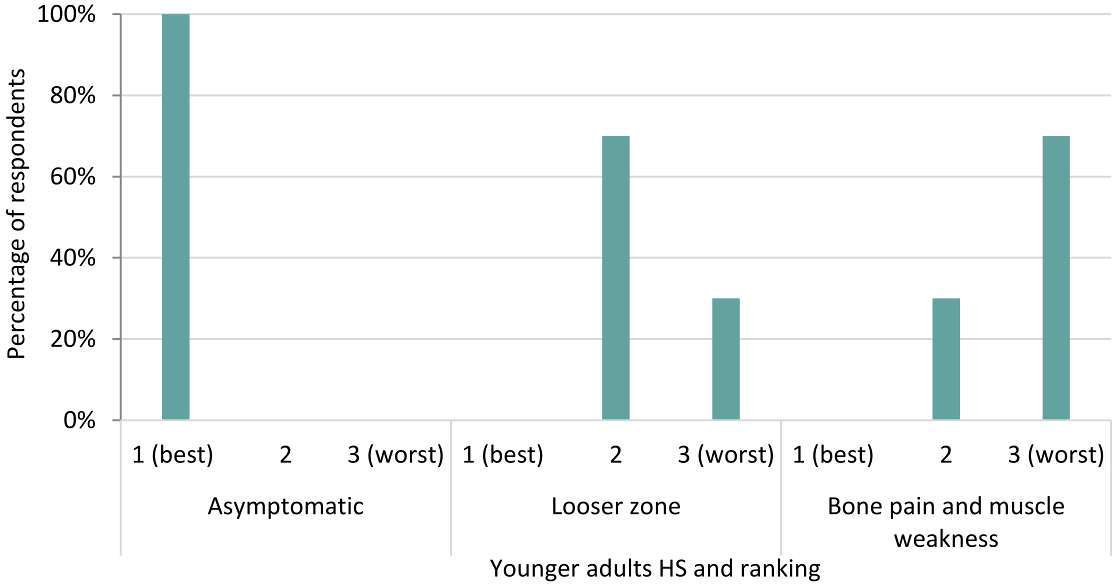


FIGURE 14 – RANKING SCORES FOR THE YOUNG ADULTS HSS

The ranking scores for the HSs relating to older adults were slightly scattered (Figure 15). Hip fracture followed by admission to a nursing home was the most severe HS for the older adult population. As expected, there seemed to be more agreement with the extreme HS, as opposed to the mid-ranked HS.

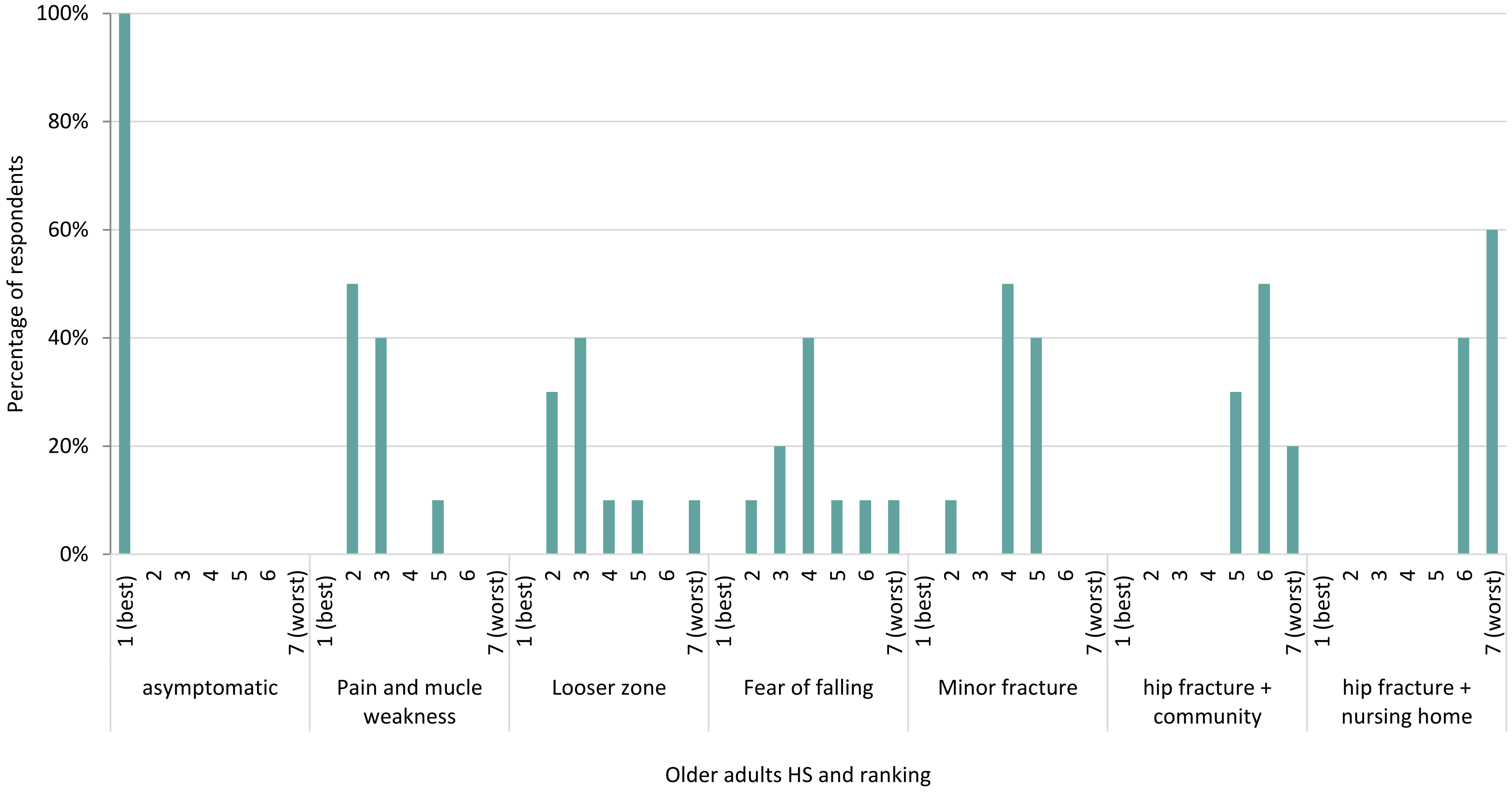


FIGURE 15 - RANKING SCORES FOR THE OLDER ADULT HSS

Utility scores

In general, utility scores for the adult HSs were lower than those found in children, including for the asymptomatic HSs (Table 7). For the young adults sub-group, bone pain and muscle weakness had similar scores to Looser zone fractures. For older adults, hip fracture and consequent release to a nursing home was the least preferred HS, resulting in a negative score of -0.051 (95% CI [-0.210; 0.108]). Fear of falling had a high impact on the HRQOL of patients (0.243 95% CI [0.08; 0.405]), resulting in more disutility than minor fractures (0.406 95% CI [0.269; 0.543]) and pain and muscle weakness 0.310 ([0.153; 0.467]). The full results are presented in Appendix 12.

TABLE 7 - MEAN UTILITY SCORES FOR ADULTS WITH ACUTE SYMPTOMATIC VDD

Health State	Mean	Std. Err.	[95% Conf. Interval]
Younger adults (19-64 years)			
Looser zone fractures	0.306	0.2220	[0.071; 0.540]
Pain and muscle weakness	0.303	0.0724	[0.161; 0.445]
Asymptomatic	0.869	0.0723	[0.786; 0.952]
Adults (over 65)			
Health State	**Mean**	**Std. Err.**	**[95% Conf. Interval]**
Hip fracture + nursing home	-0.051	0.081	[-0.210; 0.108]
Hip fracture + community	0.201	0.061	[0.080; 0.321]
Fear of falling	0.243	0.083	[0.080; 0.405]
Minor fracture	0.406	0.070	[0.269; 0.543]
Looser zone fractures	0.228	0.095	[0.043; 0.414]
Pain and muscle weakness	0.310	0.080	[0.153; 0.467]
Asymptomatic	0.766	0.048	[0.672; 0.861]

Discussion

Two surveys were developed with the aim of eliciting the HRQoL of patients with VDD across all age ranges. The results showed that clinical experts consider VDD to have a significant impact on the HRQoL of the population, and even the mildest HS - asymptomatic VDD – was judge to result in some disutility.

For infants and young children, cardiomyopathy resulted in the lowest utility scores, followed by hypocalcemic seizures. For children aged between five and 18 years, active rickets was the least preferred HS. Asymptomatic VDD had similar utility scores in both the younger and older children.

In the adult population, hip fracture and admission to a nursing home was the least preferred HS, followed by hip fracture and release to the community. The bone pain and muscle weakness HS was the least preferred in younger adults.

The direct ranking scores and the utility values estimated through the proxy preference-based exercises had comparable results for those HSs ranked in the extremes, however, lower agreement rates for the HSs in the middle of the ranking scales. This was somewhat expected since the perception of the patients' wellbeing can be more nuanced in mid severity states.

It needs to be acknowledged that the use of different instruments will result in different utility values, as demonstrated within studies that have compared SF-6D and EQ5D (208, 209), CHU9D and EQ5D-Y (205), Standard Gamble and Time Trade Off(210). The choice of questionnaire was based on the characteristics of the questionnaire in terms of the population it applied to, the availability of a proxy version, and open access. The use of the same questionnaire for the whole population of interest was not deemed appropriate, mainly due to the reported issues of using EQ5D-Y for utility values, and lack of availability of an instrument that covers the entire life course including infants, children and adults.

The sampling method used for the survey focusing on children was based on a robust network of clinical experts with a high level of interest in research and VDD. It was felt that having one of their colleagues involved in the study motivated them to participate. The same has been mentioned in a literature review, which found that studies using a "physician-recruit-physician" approach had higher response rates (211). For the success of the survey, it was found that it is important to involve clinical specialists in the development stages, in order to test the acceptability and feasibility of the task. Moreover, it is important to evaluate the robustness of the professional network and how it will be reached.

A lower number of respondents answered the adult survey. Several reasons are thought to explain the differences between the final sample of the child and adult surveys:

1. Contact person: it was not possible to implement a "physician-recruit-physician" approach for the adult survey and therefore specialists had to be contacted through the NOS newsletter.
2. Format: the adult survey was sent within the NOS newsletter, which is more easily missed than a personal email.
3. Timing: the adult survey was circulated in the July newsletter. Respondents were more likely to be on leave at this time and therefore miss the newsletter.
4. Reminder: after two weeks of sending the email to children's experts, a reminder was sent to boost the sample size. The same could not be done for the adult experts as the NOS research office stated that this was not in line with the charity's policy.

Ultimately, the small sample sizes, particularly in the adult survey suggest that the utility values estimated here, may not be representative of clinical experts' preferences regarding VDD HS.

Furthermore, it is important to consider the type of respondents when interpreting the results of the surveys. It is not known how the expert preferences for VDD HSs would compare to those from patients or a representative sample of the general population as it is recommended by NICE (89). Overall, it has been suggested that using health care professionals is likely to result in lower utility scores than if patients are asked, (182). Moreover, proxy and patient preferences tend to correlate better in the physical health components of the HRQoL questionnaires, when compared to the mental health and social wellbeing components (182, 185).

Conclusion

The work developed in this chapter fills a literature gap by providing utility values for VDD-related HSs. Clinical experts with experience in treating VDD provided preferences for a hypothetical patient. The utility scores resulting from the surveys presented will be used to inform the model parameters for a CUA, as it is described in the next chapter, where the model development steps are described.

CHAPTER 6

BUILDING A DECISION-ANALYTIC MODEL FOR THE PREVENTION OF VITAMIN D DEFICIENCY

This chapter describes the methods followed to build a decision-analytic model to simulate the prevention of VDD in England and Wales. Two main alternatives were compared: food fortification and supplementation. In order to inform several of the modelling steps, including the design of the alternatives, the methods to simulate each alternative, and the relevant parameters, the model benefited from thorough expert consultation throughout its development.

A health-state transition individual level simulation model was chosen to simulate the prevention of population VDD in England and Wales focusing on four different scenarios. The model was built using the TreeAge Pro software 2017.

As explained in Chapter 2, there are different types of decision analytic models that can be used to simulate costs and benefits of public health interventions over time. The choice of model was determined by the flexibility provided by individual level models to evaluate interventions within heterogeneous populations, as is the case of the population in England and Wales. This is particularly relevant for the prevention of VDD, where factors such as age, ethnicity, and sex are associated with different risks of VDD. Individual simulation allows for the model to take into account patient characteristics at baseline, as well as the patient pathway along the model, without needing an excessive number of HSs (212, 213). The model development followed guidance from NICE's Decision Support Unit technical guide on individual-level simulation models (213)

Interventions/Comparison of interest

The model compares four alternative scenarios:

1) No additional intervention;
2) Wheat flour fortification;
3) Universal Supplementation;
4) Combined Strategy.

The no additional intervention scenario was modelled to simulate the current scenario in the UK. In this alternative, no additional intervention was planned and no additional costs were computed.

For the food fortification scenario, the food vehicle chosen to deliver Vitamin D to the population was wheat flour. A staple food was the preferred alternative and, following the examples from the Scandinavian countries, Canada and the US, milk was a strong candidate. Nonetheless, a recent work developed by Allen et al. (214) found that flour was likely to be a suitable food vehicle to tackle VDD in the UK – the authors found that it had a lower risk of toxicity and a higher potential to reach ethnic minority groups, when compared to milk. In this scenario, wheat flour would be fortified at 400IU of Vitamin D per 100 g of wheat flour. The amount of Vitamin D added was informed by a nutrition model (214, 215) that found this level of Vitamin D to be the maximum that can be added without exceeding the recommended upper limit. The same study concluded that wheat flour is a more suitable vehicle compared to milk, because it is consumed more evenly among the UK population, providing a better coverage across the different population groups (215).

In the universal supplementation scenario, it was assumed that Vitamin D supplements are provided to all populations at risk of symptomatic VDD: 1) All infants and young children up to 18 years old; 2) the whole Black and Minority Ethnic (BAME) population; and 3) all individuals aged over 65 years. Supplement dosage is 400IU per day for all groups except the elderly, who receive 800IU per day (148). Older adults receive an additional 400IU per day as the literature suggests that this is the minimum dose required to prevent falls (148). The supplementation programme was modelled as a pharmacy-led intervention, with a payment scheme similar to other advanced services, such as the flu vaccination service. The universal Vitamin D supplementation scenario was based on the universal Healthy Start supplementation programme developed by Public Health Lewisham in London, which is currently expanding to other boroughs. The public health team from Lewisham's health authority was contacted to provide expert advice during the model development. In this scenario, supplements would be made available nation-wide through community pharmacies, which would receive an initial finance incentive for participating in the programme and would be reimbursed for the cost of the supplements dispensed to eligible subjects. An additional incentive would be provided for each supplement dispensed, in order to encourage adherence to the programme in the long term. Pharmacists would play the central role in distributing the vitamins and managing the storage and stocks.

Finally, a combination of universal supplementation and wheat flour fortification was modelled. As it was found in Chapter 4, combined strategies of supplementation and food fortification are likely to be a more cost-effective way of preventing MNDs and this alternative strategy will explore this claim. The payoffs of this alternative were estimated by adding the costs and benefits of each separate intervention.

Expert consultation for the model development stage

Several contacts were made with experts during the model development (Table 8). The first stage consisted in the participation in the Rickets consensus meeting, where clinical, public health, nutrition, and health economics experts discussed nutritional rickets around the world and produced guidelines on its prevention and treatment (17).

TABLE 8 – THE STAGES OF MODEL DEVELOPMENT

Type of consultation		Topics
Expert consultation	Rickets Consensus meeting	Clinical outcomes
Expert consultation	Dr. Helena Pachón, Food Fortification Initiative; Toby Cuswroth, LFI (Vitamin D fortificant supplier), UK	Feasibility of wheat flour fortification Costs of fortification programmes
Expert consultation	Dr. Sue Horton, University of Waterloo, Canada	The economics of MNDs
Research visit Expert consultation	Dr. Kim Dalziel, University of Melbourne, Australia Dr. Stephen Goodall CHERE, Sydney, Australia Dr. Philip Haywood, CHERE, Sydney, Australia	Modelling supplementation Modelling wheat flour fortification Challenges to policy makers
Expert consultation Data access	Eleanor McGee, Birmingham Public Health, UK Smita Hanciles, Lewisham Public Health, UK Gwenda Scott, Lewisham Public Health, UK	Feasibility of universal supplementation strategy Vitamin uptake rates Costs of supplementation programmes
Expert consultation	Bone Research Group based in the Birmingham's Children's Hospital	Face validity
Expert consultation	York's Health Economics Consortium	Modelling supplementation strategies to prevent VDD

Regarding fortification in the UK, experts were consulted about the potential benefits and the costs of a flour fortification programme. This included a meeting with an international expert on wheat flour fortification, Dr. Helena Pachón, who advised on the feasibility of wheat flour fortification in the UK and provided contacts of experts in food technology, as well as data from other countries. Concerning the costs of the programme in the UK, the company that supplies micronutrients to the food industry (LFI) provided a quote for national supply of Vitamin D, in the required amounts. The methods to estimate the cost-effectiveness of preventing micronutrient deficiencies were discussed with an expert on global health, Dr. Sue Horton, and two research teams in Australia that have evaluated folic acid interventions. Lastly, two local public health authorities in the UK were contacted to discuss the current Healthy Start scheme. Insights from evaluating the Healthy Start scheme were sought from the York Consortium on Health Economics (130, 131).

Model structure

The model simulated a cohort of individuals from the population of England and Wales, in terms of age, sex and ethnicity distributions. At the beginning of each simulation, the characteristics of each individual were defined based on population data from UK Census (216). These individuals' demographic characteristics determined the risk of VDD at each cycle. The age of the simulated individual was updated at each cycle, and with it, so were the Transition Probabilities (TPs). The core model structure was the same for each of the alternative scenarios. Under different alternatives, individuals had different risks of being VDD and different initial and recurrent costs, depending on the programme in place.

The model comprised three main HSs (Figure 16). These HSs were mutually exclusive, and represented clinically relevant stages of VDD:

1) <u>Vitamin D deficient (VDD)</u>, which includes all individuals at a higher risk of poor muscle and bone health due to low serum 25(OH)D; VDD has been defined as serum 25(OH)D

below 30nmol/L for children and below 50 nmol/L for adults. The justification for using these cut-offs has been given in Chapter 1.

2) Vitamin D sufficient (VDS), which includes all those with a serum 25(OH)D above the VDD threshold;

3) Dead is the absorbing HS. This means there are no possible transitions from this HS and the simulation ends once an individual reaches the Dead HS.

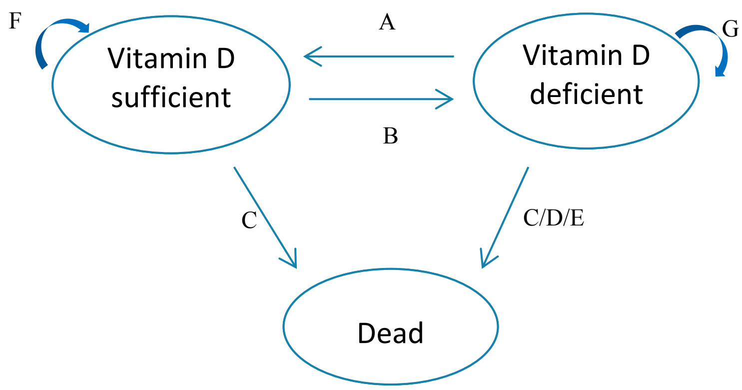


FIGURE 16 – STATE TRANSITION MODEL STRUCTURE

The arrows in Figure 16 represent any possible transition between the HSs within one cycle. The probability of an individual going from one HS to another is determined by TPs, represented in Figure 16 with the letters A to G. Individuals can only be in one state at any one time throughout each cycle, and are allowed to move to a different state or stay in the same state for the next cycle. The sum of the TPs moving to and from a HS equates to one. For example, for an individual at the VDS HS, the TP of moving to the VDD HS is given by B= 1- (C+F).

The model's internal validity was tested through a series of logic tests, which included dummy runs, where extreme values were inputted, as well as the simulation of one patient at a time and subsequent analysis of the written report of the patients' pathway and resulting cost-effectiveness. Moreover, clinical expert advice was sought to validate the individuals' pathways and relevant outcomes included (213).

Simulation of VDD in the population

A total of 50,000 Monte Carlo simulations were performed to derive estimates of the costs and consequences of each alternative strategy in the model, over a maximum of 90 cycles. The cycle length was one year. In each simulation, a hypothetical person ran through the model under the four alternative strategies, until they reach the dead HS or until 90 cycles were complete.

Several simulations were tried before settling for 50,000 – namely 1,000, 5,000, 10,000, 50,000 and 100,000. Stability was reached at 50,000 iterations at a reasonable running time of around 2 minutes per deterministic analysis. The time horizon was chosen to allow for a long term analysis, which was able to include the lifetime of the majority of the population, as well as making the best use of available nutrition data without extrapolation.

In order to incorporate the relevant outcomes of VDD in the model, decision trees were embedded within the VDD HS, as depicted in Figure 17. If deficient, the individual can be either in an asymptomatic HS, in which no medical assistance is sought, or a symptomatic HS - rickets if aged 0-18 years, or osteomalacia if older than 18 years.

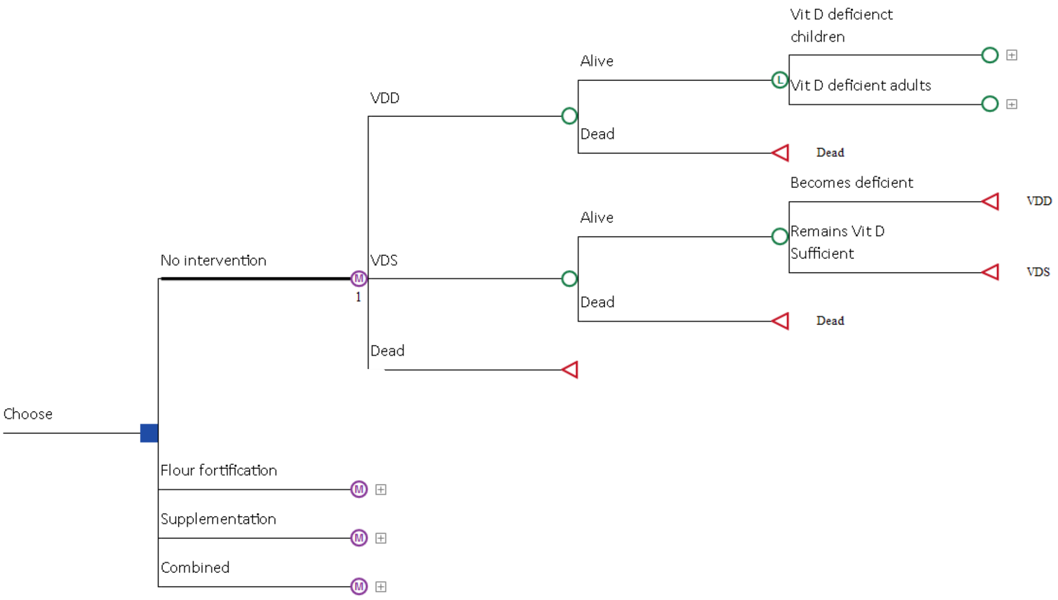


FIGURE 17 – MODEL STRUCTURE SHOWING MARKOV HS (VDD, VDS, AND DEAD) AND THE EMBEDDED TREES

Rickets can manifest as bone deformities, hypocalcemic seizures, or dilated cardiomyopathy (Figure 18). After clinical consultation, it was assumed that, in the UK, all cases of symptomatic VDD were identified and treated within a year, using high dose Vitamin D (17). Therefore, all children diagnosed with rickets move to the Vitamin D sufficient HS in the next cycle.

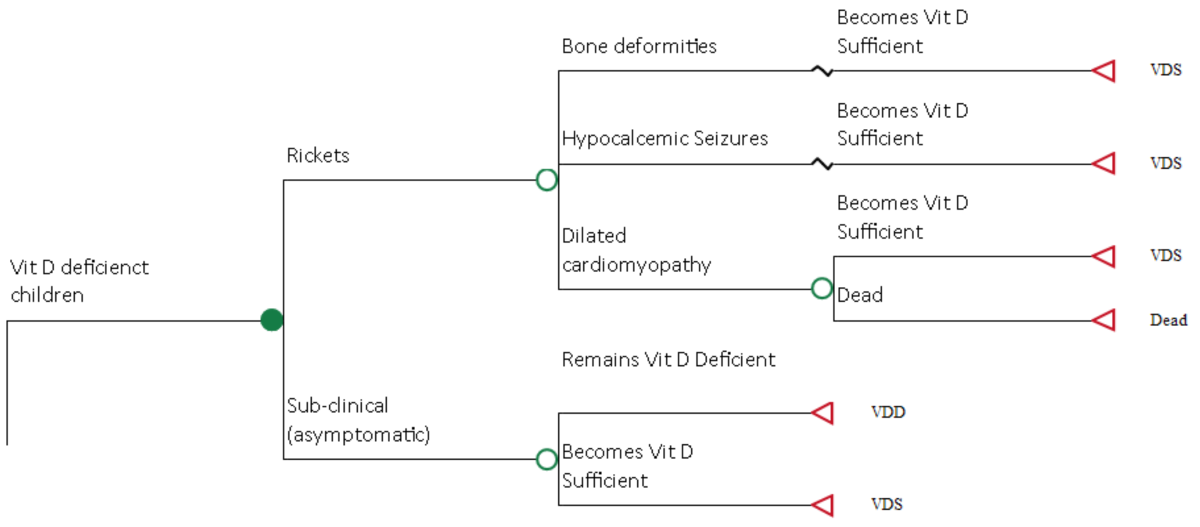


Figure 18 – MODEL'S TREE BRANCH WITHIN THE VDD HS FOR CHILDREN

In adults, symptomatic VDD manifests as osteomalacia. Adults with osteomalacia suffer from poor bone and muscle health, and present clinically with diffuse bone pain and muscle weakness (217). Older adults (≥ 65 years) have an increased risk of falls due to VDD-related muscle weakness that causes imbalance (218). In the model (Figure 19), young adults with osteomalacia incur a disutility due to diffuse pain and muscle weakness. At the end of each cycle, young adults with osteomalacia can become sufficient or remain deficient. Older adults with osteomalacia, also incur a disutility due to diffuse pain and muscle weakness. Moreover, older adults with osteomalacia will have a risk of falling (Figure 19). At the end of any of the outcomes, older adults with osteomalacia can become sufficient or remain deficient.

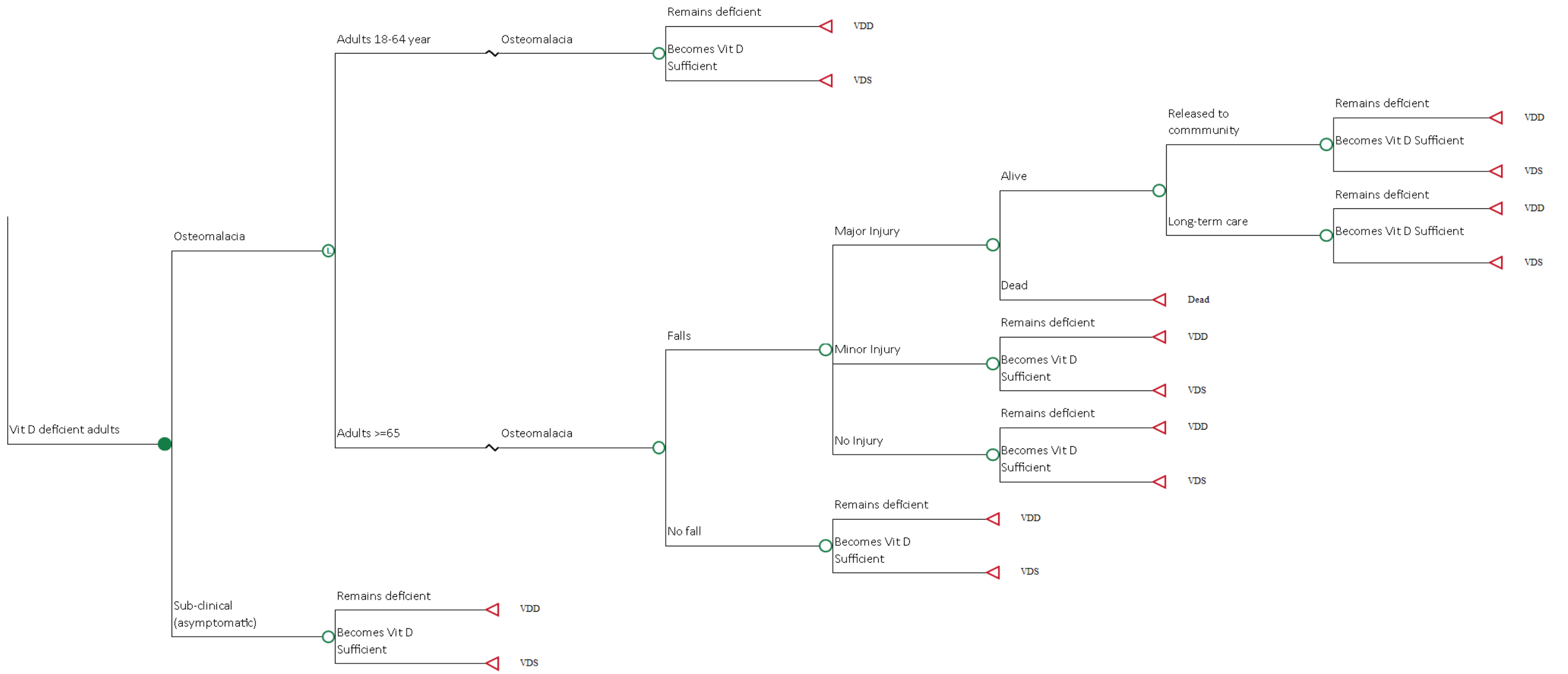


FIGURE 19 – MODEL'S TREE BRANCH WITHIN THE VDD HS FOR ADULTS

Model inputs

1. Population Estimates

The demographic data to populate the model were extracted from the Census 2011(216), and is presented in Figure 20. The modeled population was composed of 49% males, 11.3% were from BAME background and the median age was 39 years, with 22% being children (<18 years).

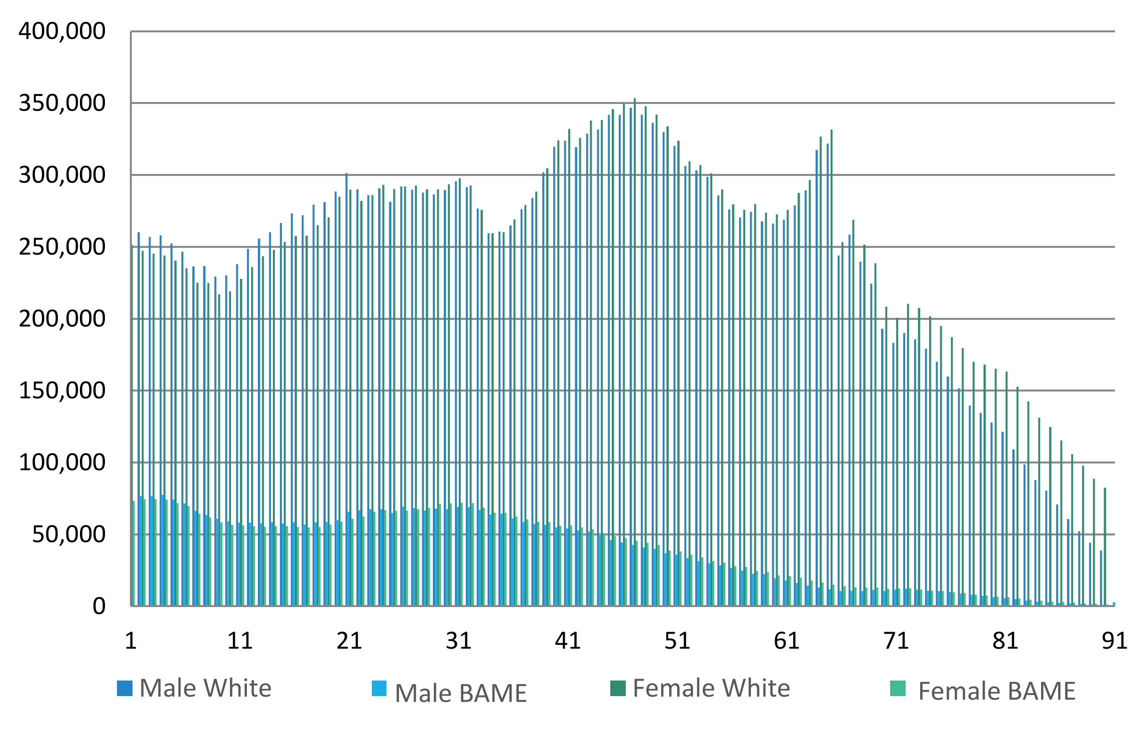


FIGURE 20 - DISTRIBUTION OF ENGLAND AND WALES' POPULATION BY AGE AND SEX

Transition probabilities

1.1. Transition to the VDD HS

A. NO ADDITIONAL INTERVENTION ARM

The TPs from the VDS HS to the VDD HS (Figure 16, B), and for remaining deficient (Figure 16, G) were based on 4-year data from the NDNS, a nation-wide survey of 6,828 individuals. A total of 1502 had their blood tested for serum 25(OH)D, with age ranging from 1.5-90 years. The majority of the participants were from a white ethnic background (N=1329) (Table 9). Individual data were accessed through the UK Data Service in August/September 2016.

TABLE 9 – TOTAL NUMBER OF PARTICIPANTS IN THE NDNS (2014) WHOSE BLOOD SAMPLES WERE ANALYSIS FOR SERUM 25(OH)D.

Ethnic group	Total number (N)	Proportion (%)
White	1329	88.5%
Mixed ethnic group	29	1.93%
Black or Black British	26	1.72%
Asian or Asian British	99	6.60%
Any other group	19	1.25%

The total number of Black or Black British (N=26), Asian or Asian British (N=99) and Mixed Ethnic Group (N=29) was assumed to form the BAME group, making a total of 154 participants, 11.5% of the participants (1). The mean population serum 25(OH)D was 45.8 nmol/L (SD=24 nmol/L). The maximum serum 25(OH)D measured was 156 nmol/L (Figure 21) (1).

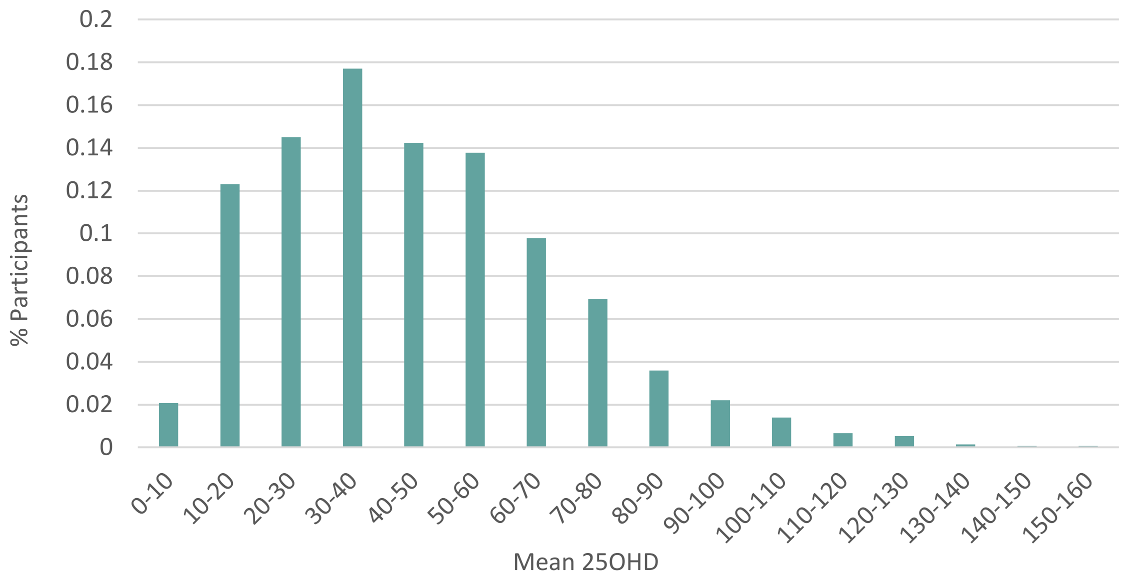


FIGURE 21 – MEAN SERUM 25(OH)D ACROSS PARTICIPANTS OF THE NATIONAL DIET AND NUTRITION SURVEY (NDNS)

The threshold for higher risk of poor bone and muscle health (30nmol/L for children and 50nmol/L for adults) was used to determine the probability of an individual being in the VDD HS, at each cycle (Table 10). (1)

TABLE 10 – VITAMIN D STATUS OF THE POPULATION

Population	Subgroup	Sample size (N)	% below threshold (N)
White ethnic group	1.5-4 year	40	7.5% (3)
	5-18 years, male	201	20.9% (42)
	5-18 years, female	175	20.5% (36)
	19-64 years, male	331	60.4% (200)
	19-64 years, female	429	58.3% (250)
	>65 years, male	86	58.1% (50)
	>65 white female	106	70.1% (75)
BAME group	1.5-18 years, BAM	95	47.4 %(45)
	>18 years, BAME	59	84.7 %(50)

Because of the small sample size of BAME groups, results were divided into two main subgroups: children (0-18 years old) and adults (+19 years old). For the white ethnic group, the data were divided into young children (1.5-4 years), older children (5-18 years; male and female), younger adults (19-64 years; male and female) and older adults (+ 65 years; male and female). In order to validate the rates retrieved from the NDNS compared to other reported rates of VDD in the BAME population, a purposive review of the literature was undertaken, and the results are presented in Table 11.

TABLE 11 – STUDIES REPORTING VDD IN BAME POPULATION

Study	Population and setting	Threshold	% below threshold
Rates used in the model			
NDNS. Bates et al. (1)	154 BAME participants, 95 children and 59 adults. Year-round collection. UK	30nmol/L (children) 50mol/L (adults)	47.4% children and 84.7% adults
Comparators			
Patel et al. (52)	1904 adults aged over 45 years. Participants were grouped into sub-groups: South Asian, Afro-Caribbean. Year-round collection. Birmingham	30 nmol/L	75.7% South Asian and 49% Afro-Caribbean. Adults
O'Neill et al. (219)	Nutrition model for BAME adults. Year-round collection UK	30 nmol/L	49.3%. Adults
Hayden et al. (220)	9936 individuals (White and BAME). Ethnic data from census. Year-round collection. Manchester.	25 nmol/L	69% (in areas where >70% of the population were non-white).
Ford et al. (54)	Mean age 53 years. White (N=317); Black Afro-Caribbean (N=125); South Asian (N=251); others (N=137). September collection. Birmingham	25 nmol/L	11.8% White 31.2 % Black Afro-Caribbean 35.6% South Asian
Lawson et al. (221)	Sample of 618 South Asian (Bangladeshi, Indian and Pakistani) children two years. October-November collection.	25 nmol/L	20% in Bangladeshi; 34% in Pakistani; 25% in Indian. Children

As shown in Table 11 the literature reports prevalence rates of VDD in the BAME groups that are consistently higher than those reported in the white ethnic groups. The estimated risk from the NDNS is higher: 47.4% in children compared to 20-34% (221), and 84.7% in adults compared to 49% and 75.7% (52). Ford et al. report proportions in an even lower range (31.2%-35.6%) than all the other studies since the authors use a lower threshold to define VDD (25nmol/L), and data were collected at the end of the summer, in September, when the prevalence of VDD reaches its lower values (1).

To maintain consistency with the data sources, and because the NDNS data has the advantage of being available at the individual level which allows estimation of risk at different thresholds, the base case risk of VDD in the BAME population was based on data from the NDNS.

B. WHEAT FLOUR FORTIFICATION ARM

In the scenario of wheat flour fortification, it was assumed that the mean daily intake of Vitamin D was increased and therefore the TP to the VDD HS was lower than in the 'no intervention' scenario. The effect of wheat flour fortification depended on: 1) the amount of Vitamin D added to flour, and 2) the population's daily wheat flour intake. The effect of fortifying wheat flour with Vitamin D in the UK was estimated using a published theoretical model (214), that used data from the NDNS up to 2010. At 400IU of VD/100 g of wheat flour, the mean daily Vitamin intake increases by 148-432 IU per day, depending on the age group and sex (215), shown in Table 12.

TABLE 12 – THE IMPACT OF WHEAT FLOUR FORTIFICATION

	No wheat flour fortification				400 IU/ 100 g wheat flour				
	VD intake (IU/d)		Winter serum 25(OH)D (nmol/L)		VD intake (IU/d)		Winter serum 25(OH)D (nmol/L)		
Population	Mean	SD	Mean	95% CI	Mean	SD	Mean	95% CI	Mean difference (nmol/L)
1.5-3, all	100	104	38	[34;42]	252	132	43	[38,50]	5
4-8, all	108	76	38	[34,43]	364	132	48	[41,56]	10
9-49, males	124	96	39	[34,43]	460	192	52	[44,63]	13
9-14 females	104	88	38	[34,42]	388	156	49	[42,58]	11
15-49, females	120	104	39	[34,43]	376	172	49	[41,57]	10
50-64 all	200	152	41	[36,47]	480	220	53	[45,64]	12

Using the increased serum 25(OH)D level estimated by Allen et al. (2015), the corresponding impact on population Vitamin D status was estimated and the proportion with VDD re-calculated, illustrated in the graph below, presented in Figure 22. As it is shown, the effect of wheat flour fortification varied according to the age and sex on the individual, due to differences in the daily wheat flour intake of the groups. There were no data available to differentiate between effect of wheat flour fortification in white ethnic groups and BAME groups.

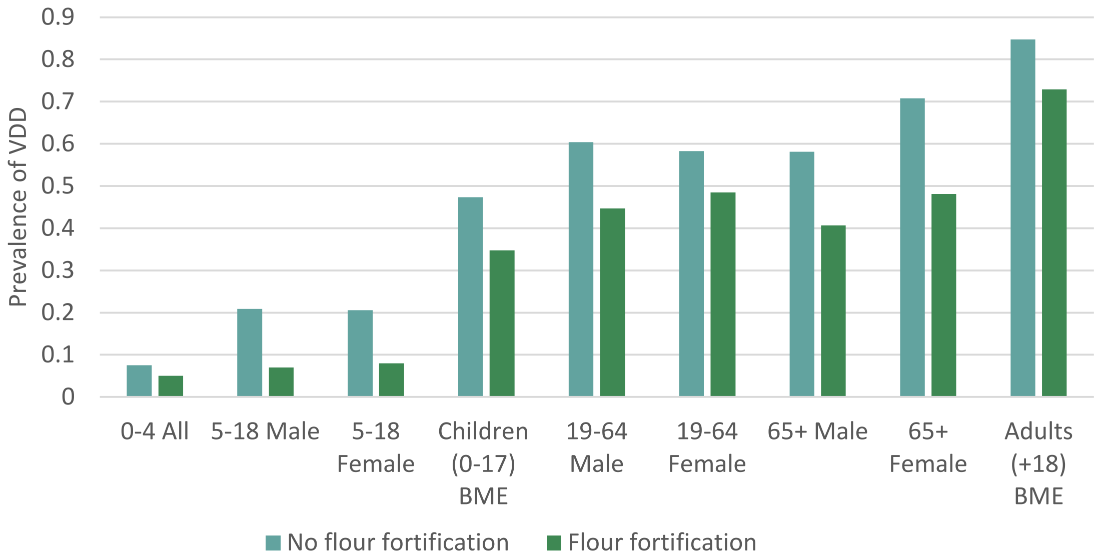


FIGURE 22 - PROPORTION OF THE POPULATION THAT IS VDD (25(OH)D <30NMOL/L) IN THE SCENARIOS OF NO WHEAT FLOUR FORTIFICATION AND WHEAT FLOUR FORTIFICATION

There were no data available on the potential difference of the effect of wheat flour fortification within specific ethnic groups and therefore the same effect was assumed for all.

A. SUPPLEMENTATION ARM

In the supplementation arm, the transition probability to the VDD HS was assumed to be 0 if the individual was taking Vitamin D supplements, and the same as the baseline (no intervention arm) if the individual was not taking supplements.

The probability of an individual taking supplements was defined at the beginning of each cycle. Infants up to 1 year old had 0.5 probability of taking supplements, while all other eligible individuals had a 0.2 probability of taking supplements (222).

B. COMBINATION OF WHEAT FLOUR FORTIFICATION AND SUPPLEMENTATION

The combined scenario of fortification and supplementation assumed an additive effect of both interventions. In the combined scenario, the TP to VDD was the same of that estimated for the wheat flour fortification alone. If the individual is taking supplements, the TP to VDD was assumed to be 0.

1.2. Transition to the Dead HS

VDD had no direct impact on mortality rates and therefore the TPs to the Dead HS were based on all-cause mortality rates of the population. There were two exceptions: an increased mortality was applied for: 1) major injury after a fall (128) and, 2) cardiomyopathy (64). In both cases, increased mortality was assumed to occur in the year in which the event occurs. Increased mortality due to major injury after a fall was dependent on the individuals' age at the time of the fall (128).

1.3. Transitions within the VDD HS

A. RICKETS

The TPs to the Rickets HS were obtained from Callaghan et al. (3), a study that estimated the incidence of rickets in children aged 0-5 years in the UK (table 14).

TABLE 13 – INCIDENCE RATES OF RICKETS IN DIFFERENT GROUPS OF THE POPULATION

Population subgroup	Rickets in healthy population	Rickets in VDD population
White ethnic background	0.0004%	0.005%
African or Afro-Caribbean background	0.095%	0.200%
South Asian background	0.038%	0.080%

Rates were transformed into probabilities using TreeAge Pro's *RatetoProb* function. TP from the VDD HS to rickets was 0.14% in BAME children and 0.053% in children from a white ethnic background.

1.3.1. TRANSITION WITHIN THE RICKTES HS

HYPOCALCEMIC CARDIOMYOPATHY

Dilated cardiomyopathy as a consequence of VDD is a rare event that has only been reported in BAME infants < one year (64). Dilated cardiomyopathy is linked to high mortality rates and life-time morbidity for surviving children. Its treatment requires hospitalization and intensive care (64). The risk of suffering dilated cardiomyopathy if a child is VDD is not known. The model assumes that 1 in 1000 BAME infants with rickets will have cardiomyopathy, based on expert consultation. Using a tracker variable to record the number of cases of cardiomyopathy occurring during the simulation, it was noted that no cardiomyopathy cases were registered. The same happened when the model ran a subgroup analysis limited to BAME children. Following expert consultation, it was determined that the cardiomyopathy arm was to be kept in the model, for its clinical relevancy, but further efforts to find parameter estimates to populate the arm were limited as it was clear that this outcome had a negligible impact upon the final results.

HYPOCALCEMIC SEIZURES

Callaghan et al. report that of 24 children with symptomatic rickets, six presented with hypocalcemic seizures, giving a TP of 0.25 (3).

BONE DEFORMITIES

The most common outcome for children with rickets is poor bone health, which is associated with bone pain and bone deformities. The TP probability of having some sort of bone deformity is $P_{BoneDeformities} = 1 - (P_{Cardiomypathy} + P_{Seizures})$

B. OSTEOMALACIA

The diagnosis of osteomalacia is not straightforward – the symptoms are mainly associated with bone pain and a definite diagnosis is only done through bone biopsy. There are no data on the prevalence of VDD related osteomalacia. The TP to the osteomalacia HS was informed by a study by Priemel et al., which analysed the bone health of German adults using a post-mortem sample (223). Although adults aged over 50 years were overrepresented in this cohort, the reported rate was assumed to apply to all adult populations in the model. In order to estimate the proportion of osteomalacia within the VDD population, it was assumed that all identified cases of osteomalacia in the study were due to VDD. In Germany, the prevalence of serum 25(OH)D <50 nmol/L has been estimated to be 61.6% (224). The TP to osteomalacia from the HS VDD was calculated to be 0.42.

1.3.2. TRANSITION WITHIN THE OSTEOMALACIA HS

OSTEOMALACIA-RELATED FALLS

A systematic review and meta-analysis of observational studies found that the risk of falling is inversely associated with the serum 25(OH)D (odds ratio of 1.44 (95% CI 1.17-1.76) for 25(OH)D < 50 nmol/L (81). Data from the studies included in the review was used to estimate the increased risk of falling due to having serum 25OD < 50 nmol/L (Table 14).

TABLE 14 – INCREASED RISK OF FALL DUE TO VDD

Study	Vitamin D status	Faller (N)	Non-faller (N)	Risk of Fall [95% CI]	Increased risk of being a faller
Suzuki et al. (225)	VDD	95	307	0.24 [0.19;0.28]	0.08
	Non-VDD	380	2102	0.15 [0.14;0.18]	
Beauchet et al. (226)	VDD	78	148	0.35 [0.28;0.41]	0.14
	Non-VDD	57	219	0.21[0.16;0.25]	
Annweiler et al. (227)	VDD	56	188	0.23 [0.18;0.28]	0.13
	Non-VDD	24	225	0.10 [0.06;0.13]	
Total	VDD	229	643	0.26 [0.23;0.29]	0.11
	Non-VDD	461	2546	0.15[0.14;0.16]	

The studies report an increased risk of falling between 0.08-0.14. In the model, it was assumed that being VDD led to an increased risk of falling of 11%. For adults with osteomalacia, the TP to the fall HS was 0.262. It was assumed that the fall HS was associated with a decrement in quality of life due to fear of falling. Additional loss of quality of life may be incurred, depending on the fall outcome.

FALL OUTCOMES

The model follows the conservative approach used by Poole et al. (128) to model the outcomes of falls in the elderly population in the UK. Falling may result in no injury, minor injury or major injury. In the case of a fall with no injury, the model assumed no costs were incurred, and the disutility of fear of falling was applied for one cycle only. Minor and major injuries are associated with disutility and costs. The probability of suffering an injury increased with age, as well as the probability of the injury being major (Table 15). In addition, major injuries could lead to the patient being admitted to long-term care. Long-term care was assumed to last for 6 months.

TABLE 15 – PROBABILITY OF INJURY AFTER A FALL (128)

Age (years)	Minor injury	Major Injury	No injury
65-70	0.024	0.005	1-(0.024+0.005) = 0.971
70-75	0.028	0.009	1-(0.028+0.009) = 0.963
+75	0.058	0.037	1-(0. 058+0.037) = 0.905

Utility

Baseline utility values were based on the UK tariff (228). Each individual entered the model with a baseline utility based on the UK population norms (229). The disutility of VDD states was informed by clinical expert elicitation, as described in Chapter 5. The utility values resulting from the surveys were used to estimate the one-year utility in the diseased HS. The disutility of VDD related outcomes was assumed to be incurred for a finite period of time, which for most clinical outcomes was less than a year. The assumption of the duration was based on the severity of the outcome. For example, seizures were thought to affect patients' utility for a month, asymptomatic VDD would affect the patient for the whole year, and fractures for a maximum of six months. For the rest of the cycle, the patient would have the same utility as at the baseline.

At the beginning of each cycle, individuals start with baseline utility, unless they had suffered a major fall in the previous cycle. After a major fall, it was assumed that individuals would have a fear of falling in the subsequent year, and the corresponding utility value of fear of falling was assigned and they move to the next cycle with a starting utility using a tracker variable in TreeAgePro. The final one-year utility and assumption of the duration of the acute HS are presented in Table 16.

TABLE 16 - ESTIMATED UTILITY PER CYCLE (1 YEAR)

Estimated utility per cycle (1 year)			
Health State	**Acute utility**	**One year utility**	**Assumed duration of acute event**
Active Rickets	0.621	0.811	6 months
Cardiomyopathy	0.465	0.465	1 year
Seizures	0.495	0.958	1 month
Leg deformities	0.758	0.758	6 months
Pain and muscle weakness	0.612	0.806	6 months
Asymptomatic	0.955	0.955	1 year
Children and Adolescents (5-17)			
Active Rickets	0.567	0.783	6 months
Leg deformities	0.708	0.708	1 year
Pain and muscle weakness	0.608	0.804	6 months
Asymptomatic	0.946	0.946	1 year
Young adults (18-64)			
Pain and muscle weakness	0.303	0.652	6 months
Asymptomatic	0.869	0.869	1 year
Adults (over 65)			
Hip fracture + nursing home	-0.051	0.474	6 months
Hip fracture + community	0.201	0.600	6 months
Fear of falling	0.243	0.621	6 months
Minor fracture	0.406	0.703	6 months
Pain and muscle weakness	0.310	0.655	6 months
Asymptomatic	0.766	0.766	1 year

Costs and resource use

Costs were calculated in 2016 Great Britain Pound (GBP). Costs obtained from sources published prior to 2016 were indexed to 2016 GBP using the Unit Cost of Health and Social Care 2016 (230).

Wheat flour fortification

The costs of wheat flour fortification are shared across the milling industry and the public sector, including local and national authorities. The cost structure is country specific and the model was based on the Food Standard Agency (FSA) report of mandatory fortification of wheat flour with folic acid in the UK (231). A summary of the costs used in the model is presented below, in Table 17.

WHEAT FLOUR MILLING INDUSTRY

Four nutrients are currently added to wheat flour in the UK under mandatory regulations - calcium, iron, Vitamin B1 (thiamin) and Vitamin B3 (nicotinic acid). The inclusion of Vitamin D in the group of mandated nutrients would require very few changes to the current programme. The initial set up costs are therefore negligible (231). This information was confirmed by personal communication with international wheat flour fortification specialist, Dr. Helena Pachón, (FFI, June 2015) and UK's main fortificant supplier (Mr. Toby Cusworth, LFI - UK, November 2015).

Currently, the UK mills buy a pre-mix with the mandated nutrients, which is then added to the flour during the milling process. LFI was contacted to provide a quote to add Vitamin D to the mix. For 400IU/100g of wheat flour, a cost of £1.59 per tonne of wheat flour was estimated (Box 3). According to the National Association of British and Irish Millers (NABIM), approximately four million tonnes of wheat flour are produced annually in the UK (232) which translates to a total incremental cost of around £11 million per year. The supplier stated this was an overestimation of the real price. At the time of communication, no mandatory fortification was in place and Vitamin D was only maintained in stock in low amounts to fulfil voluntary fortification of breakfast cereals and some other foods such as bread. Purchase at a national scale is likely to make the unit price drop.

- At the time of communication, LFI (UK) had in stock encapsulated Vitamin D that is only 0.25% active (1/400), used to fortify breakfast cereals. This means that it is necessary to use 400 x 10μg of encapsulated Vitamin D to obtain the effect of 10 μg of pure Vitamin D.
- The required dose of 10μg/100g of wheat flour equates to 100μg/Kg = 100,000μg/tonne = 100 mg/tonne of pure Vitamin D.
- Amount of encapsulated Vitamin D is 100mg x 400 = 40 grams/tonne of flour.
- The encapsulated Vitamin D has a cost of £35 per kg so the ingredient on-cost to treat wheat flour to 10mcg per 100g is £35 x 40 / 1000 = **£1.40/tonne**
- The amount of fortificant added needs to include an overage to account for losses during storage and heat (as when used for baking).
- Considering an overage of 12.5%, the price rises to **£1.57/tonne**

BOX 3- ESTIMATION OF PRICE OF ADDING VITAMIN D PER TONNE OF WHEAT FLOUR

LABELLING

Food labels are required to list all food ingredients and changes to the food's composition would require an update of the label. Until 2014, the Food Labelling

Regulations included a specific exemption on ingredient foods, which included wheat flour with the mandated added four nutrients and stated that these do not need to include an ingredient list on the label (233). In 2014, FSA revoked this exemption and established that, from 13 December 2014, all ingredients must be listed in the wheat flour's label (234). It is therefore likely that under the current regulations, labels would need to be updated with the new Vitamin D content. Moreover, products containing wheat flour, such as cakes, biscuits and bread, might have to have their labels updated as well.

In the case of wheat flour fortification with folic acid (231), it was suggested that a threshold would be determined in terms of labelling requirements, which meant that products containing wheat flour might not need to change the label, if the amount of the added nutrient is below a pre-specified threshold. Moreover, it has also been noted that the costs of updating labels can be minimal if enough time is allowed for the industries to implement the changes, since the food industry already has a labelling updating cycle. If that is the case, the new content could be introduced in the label at the normal time of re-labelling, without incurring any extra costs. Such point has been made regarding the coloured-code front-of-package labels (235).

Nonetheless, the labelling costs were estimated for a sensitivity analysis. Re-labelling costs have been estimated to be £2000 - £5000 per stock keeping unit (SKU) (235), whilst the British Retail Consortium (BRC) has provided an estimate of £1000 for each SKU that does not renew the label frequently.

There are 500,000 SKUs in biscuits and cakes alone. At £1000 per label, and assuming all of these would incur labelling costs, a total initial cost of £500,000,000, which leads to an average initial cost of £8.90 per person. This is an overestimation and it is not clear how this initial cost would pass on to the consumers. The cost will be considered in a scenario analysis, assuming an initial cost per person of £8.90 (GBP 2007), which is £10.70 (GBP 2015).

TRADE

About 2% of the UK produced wheat flour is exported each year, and around 65% of this is destined to the Irish market. Bread exports account for 2.9 % of the production and 11% of the production of cakes and biscuits. It is not fully understood how mandatory fortification of wheat flour with Vitamin D would affect trade. Although previous consultation with food industry representatives has highlighted concerns that consumers from other countries may avoid purchasing UK products if the labels mention it has been fortified (231), there is no data to support claims that fortification would have a negative impact on trade. Because of the lack of data and the uncertainty regarding the direction of the effect of fortification on trade, such effects will not be considered in the analyses.

Government costs

If wheat flour fortification was implemented, the government would need to assure the industries were complying and the Vitamin was added at the required amounts.

The FSA has previously surveyed the UK's Local Authorities Coordinators of Regulatory Services (LACORS), who provided an estimate of 100-200 samples that would be analysed per year in the case of a new fortification policy for folic acid (231). The costs for such a monitoring scheme were estimated to be £10,000 (GBP 2007) per year. Inflating to 2015 prices, the costs of enforcement is £12,383. An additional

£2,000,000 initial cost was assumed to be for a national wide campaign to inform the public about a new fortification policy.

TABLE 17 – ESTIMATED COST OF WHEAT FLOUR FORTIFICATION IN THE UK

	Total cost	**Source**
Vitamin D fortificant	£6,280,000	Personal communication with LFI, ltd.
Enforcement	£12,383	FSA (230, 231)
National campaign	£2,000,000	Brown et al. (236)

Consumer costs

Although consumer costs were not directly out into the model, they were considered in terms of potential increase in price and loss of consumer choice:

PRICE INCREMENT

An increased cost in wheat flour production is likely to translate to an increased price for the consumer. Assuming that all of the industry cost of wheat flour fortification is shifted onto the consumer, the price increase can be estimated using the average wheat flour consumption per person per year. In 2008/2009, 74kg of wheat flour were consumed per person per year, including in bread, cakes and biscuits (232).

Assuming all the flour consumed was produced in the UK and is wheat flour, at the price of £0.00157/ kg of flour, each person can expect to pay an extra £0.12 per year. The average household is made-up, on average, of 2.4 people, which gives an incremental annual cost of £0.29 per household.

CONSUMER CHOICE

Adding a nutrient to a staple food, consumed by the general population, limits consumers' choice for those who do not benefit from the intervention i.e., those who are Vitamin D sufficient. This is regarded in the literature as a cost incurred by these consumers which can be incorporated into the cost of the intervention. Using a rough estimate, Dalziel et al. (163), assumed that the loss of consumer choice for fortifying wheat flour with folic acid was one $1 (Australian dollar) per consumer. In a previous UK economic evaluation of wheat flour fortification with folic acid, it has been argued that since only wheat flour is being fortified, leaving wholemeal flour unfortified, consumers can still opt to buy unfortified flour (231), and therefore the cost of the loss of consumer choice was not considered within the VDD model.

Supplementation scheme

Supplements

UNIT COST OF SUPPLEMENTS

The price of the supplements for the older adults (800IU Vitamin D) was £10.8 per 60 dose pack (237). The price of Vitamin D drops and tablets for the rest of the population (400IU) were estimated on the basis of the price of the healthy start vitamins in the UK. Both Healthy Start's drops and tablets come in 56 dose packages, with a unit price of £1.38 and £0.74, respectively.

Distribution

The distribution of Vitamin D supplements are assumed to be mainly pharmacy –led and the costs were based on a similar programme run in Lewisham. As is the case for vaccination services, it was assumed that the NHS would contract pharmacies to manage the program, making them responsible for distributing the vitamins and managing stocks. Pharmacies receive a £75 incentive at enrolment and a £0.30 incentive per pack of Vitamin distributed.

Monitoring

The Lewisham's programme was monitored through an electronic card system and the same structure was assumed for a national programme in the model. Each Vitamin D beneficiary receives an electronic card (£0.60) and each pharmacy has a card reader installed (£38.80). Software is installed in each pharmacy at the cost of £6000 for purchase software license and £2000 every year thereafter for renewal.

The card system allows for easy identification of eligible individuals. Moreover, data on the uptake and characteristics of supplement takers is recorded.

Training

Lewisham local authority provides in loco training to pharmacists. Because staff in the pharmacies changes frequently, ideally, training with be provided annually (Gwenda Scott & Smita Hanciles, personal communication, September 2016). It has been suggested that a training video would be a more suitable vehicle to provide training to pharmacists, which would result in a one-off cost of producing the video, instead of recurrent cost of training. The video production was assumed to cost £2500, based on an online quote (Creation video UK, September 2016; Studio Rossiter UK, September 2016).

Cost of rickets

The cost of rickets was informed by Zipitis et al. (238), who estimated the average cost per patient for treating rickets in the UK. The estimation was done through a retrospective search of medical records, and the final cost included hospital expenses and the cost of investigations. The total cost per case was £3,088.60, indexed to 2016 price. This was applied to any child who was in the rickets HS. An additional £10,000 cost was computed if the child moved to the cardiomyopathy HS. The cost of cardiomyopathy was informed by expert consultation as there were no studies on the costs of infant hypocalcemic cardiomyopathy.

Cost of falls

The cost of fall related injuries were retrieved from Poole et al. (128). The study provides a mean cost for a major injury and minor injury. Minor injury after a fall had costs associated with seeking medical assistance, treatment and recovery. For major injuries, the same type of cost was considered, and mainly attributed to hip fractures. Major injury can result in six-month long-term admission. The costs of falls are summarized in Table 18. Poole et al. takes a conservative approach to estimate the burden of unintentional falls in the UK, which was deemed appropriate for this model.

TABLE 18 – COSTS ASSOCIATED WITH FALL EVENTS IN THE SIMULATION MODEL

Resource/Event	Cost (GBP 2016)	Source
Minor fall no injury		
65-69	£466.20	Poole et al. (128)
70-74	£476.43	Poole et al. (128)
75+	£472.34	Schuffham et al. (85) Poole et al. 2015 (128)
Major fall		
65-69	£2,827.89	Schuffham et al. (85) Poole et al. 2015 (128)
70-74	£3,683.62	Schuffham et al. (85) Poole et al. 2015 (128)
75+	£3,616.14	Schuffham et al. (85) Poole et al. 2015 (128)
Long-term care (6 months)	£16,754.69	Schuffham et al. (85) Poole et al. 2015 (128)

Discounting

Costs and benefits are discounted at 3.5% rate, as recommended by NICE (89). Discount rates were subjected to one-way sensitivity analysis.

Sensitivity analyses

The model parameters described so far were used to inform the base case analysis. In order to study the robustness of the base case results and to investigate how key model assumptions impacted such results, a series of sensitivity analyses were undertaken. These included scenario analyses, where one parameter was changed to create a new possible scenario; one-way sensitivity analyses where one parameter was varied at a time, in order to investigate how the cost-effectiveness results varied according to that specific parameter, and finally, a probabilistic sensitivity analysis (PSA) using distributions instead of expected values to test the uncertainty around the parameters, as well as the overall decision uncertainty. The sensitivity analyses are described in detail below:

Deterministic sensitivity analyses

SCENARIO A: INCREASED BAME POPULATION

Symptomatic VDD is more frequently reported in urban areas in the UK where the BAME population is more prominent, when compared to the national estimates (78, 239). In this scenario, Birmingham's BAME population is used to inform the setting with higher BAME. According to the 2011 Census (216), 41% of the population in Birmingham is from a BAME group.

SCENARIO B: DISUTILITY OF ASYMPTOMATIC VDD

A scenario analysis where asymptomatic VDD was not considered to have an impact on the individual's HRQoL.

SCENARIO C: DISCOUNT RATE

In NICE's methodological recommendation for the development of public health guidance, it is suggested a discount rate of 3.5% for the base case, and that this value is tested in a sensitivity analysis (89). To conform to the guidelines, a discount rate of 1.5% was modelled in a sensitivity analysis.

SCENARIO D: TIME HORIZON

A shorter time horizon, of 5 and 10 years, were modelled in a sensitivity analysis, to compare the model results for short-term and long-term outcomes.

SCENARIO E: COST OF RE-LABELLING WHEAT FLOUR AND FLOUR-BASED PRODUCTS

As mentioned before, there is a possibility that changing the wheat flour content, will lead to an increased cost for the manufacturers that have to re-label their products. A worst-case scenario analysis, using a high cost of re-labelling of £10.7 per person was undertaken.

SCENARIO F: PUBLIC SECTOR PERSPECTIVE

For estimation of the ICER from a public-sector perspective, a separate analysis was undertaken considering only the public costs, i.e., the cost of the Vitamin D fortificant were excluded.

One-way deterministic analysis

UPTAKE OF SUPPLEMENTS

The uptake of supplements was varied from 0% to 100%, at intervals of 10%. Although the high uptake values (>50%) are unlike to be observed in the population, the analysis intends to inform how the uptake influences the cost-effectiveness of the alternatives, and can ultimately provide an uptake threshold to those interventions providing supplements.

EFFECTIVENESS OF WHEAT FLOUR FORTIFICATION

The effectiveness of flour fortification in reducing the probability of VDD was varied from 0 (no effect) to 50% reduction, at intervals of 5%.

Probabilistic Sensitivity Analysis (PSA)

PSA was done by randomly sampling from each of the parameter distributions and calculating the expected cost and expected QALYs in each intervention arm. A total of 1000 replications were undertaken in order to obtain the distribution of the costs and effectiveness of the programmes. Transition probabilities, costs and utilities parameters were described as probability distributions within the model. The choice of distribution followed Briggs et al. (110) – costs were assigned gamma distributions and probability parameters beta distributions. Utility parameters close to 0 were transformed using the decrement utility transformation method suggested by Briggs (D=1-U) (110). In this case, gamma distributions were used to fit the decrement. TreeAge Pro allows distributions to be defined by a number of inputs including alternative inputs such as the mean and standard error when others are not available from the literature. The full list of distributions used in the model is presented in Appendix 13.

The probabilistic sensitivity analysis outcome will be presented in a CE plane, showing the scatter plot of the 1000 Monte Carlo simulations for each intervention as well as in a CEAC.

Value of Information (VoI)

There is a great deal of uncertainty around the model parameters described above, in terms of the risk of VDD, effectiveness of the interventions and costs. If decision makers decided to implement the most cost-effective alternative, under the currently available evidence, there would be a chance that the wrong decision will be made, and there would be an expected opportunity cost, i.e., expected costs in terms of health benefits and resources forgone. Instead, decision makers can decide to invest in further research to reduce uncertainty, delaying decisions until more evidence is available. The maximum amount decision makers should be willing to pay for new research in the context of VDD was calculated using the expected value of perfect information (EVPI) analysis. The analysis followed the nonparametric approach described by Briggs et al. (p.174). The EVPI estimates the expected cost of current uncertainty, which has been quantified previously in the PSA. For each of the PSA iterations, the expected net benefit of each option is calculated. For a given cost-effectiveness threshold, the EVPI is determined by the difference between the expected net benefit with perfect information and the expected net benefit with current information (110).

Intuitively, the optimal decision under the existing evidence is the intervention that results in the maximum expected net-benefit:

$$max_j E_\theta NB(j,\theta)$$

where j is the number of alternative interventions with unknown parameters θ. With perfect information, the decision maker would know the outcome for each uncertainty (each iteration of the PSA), and could therefore would chose the optimal j given a particular value of θ.

$$max_j NB(j,\theta)$$

However, since θ is not known, the expected value of a decision done with perfect information is the average of the maximum net-benefit over the joint distribution of θ.

$$E_\theta max_j \; NB(j, \theta)$$

Therefore, to estimate the EVPI, first the maximum benefit is calculated for each of the PSA iterations. Then, the mean over the resulting maximum net-benefit is estimated. The EVPI for an individual patient is then the difference between the expected value of the decision made with perfect information about the uncertain parameters θ, and the decision made with the currently available evidence.

$$EVPI = \; E_\theta max_j \; NB(j, \theta) - \; max_j E_\theta NB(j, \theta)$$

This results in the individual EVPI, which was then used to estimate the EVPI for the population. Population EVPI is calculated using the individual EVPI, the total number of individuals affected by the information (incidence of VDD), and the anticipated lifetime of the interventions:

$$EVPI \times \sum_{t=1}^{T} \frac{I_t}{(1+r)^t}$$

where I = incidence in period, t = period, T = total number of periods for which information from research would be useful and r = discount rate.

Population size was estimated based on data from the NDNS (1). It was assumed that the information would be valued for 5-10 years, taking examples from other countries where the nutrition interventions were reassessed. The discount rate used was 3.5%, in order to be consistent with the discount used in the model's base case analysis.

Presentation of Results

The results are presented in the flowing chapter. For the base case and the scenario analyses, alternatives were compared according to their incremental cost-effectiveness ratio (ICER), calculated in terms of the additional cost per QALY gained and following standard decision rules that allow comparison between multiple competing options (91):

I) 'No intervention' alternative was used a s the comparator, for being the current policy in the UK;

II) The other alternatives compared were ranked from the least costly to the most expensive;

III) The alternatives that were costlier and less effective than any of the comparators were eliminated due to being <u>dominated</u>, and their ICER was therefore not estimated;

IV) The ICER for all remaining alternatives was then estimated. If an alternative had a higher ICER than any of the comparators that were lower down the ranking, then that alternative was excluded for <u>extended dominance</u>;

V) After excluding all dominated alternatives, incremental costs and effects were re-calculated for the remaining options with respect to the previous most cost-effective option on the list.

Results will be presented graphically through an incremental cost effectiveness plane. Moreover, ICERs will be estimated using the cost-effectiveness decision rule described by (91), where alternatives are ranked by increasing cost and, after the dominated alternatives are excluded, the incremental costs and benefits of the remaining options are estimated with respect to the previous option on the list. Alternatives are dominated if they are more expensive and produce fewer benefits than any other alternative on the list.

The base case will be presented for two different settings: England and Wales, where approximately 11% of the population is BAME, and Birmingham based scenario, where 41% of the population is BAME. The results will be presented in term of cost per QALY gained and cost per case of VDD prevented.

One-way sensitivity analysis results will be presented in term of an acceptability curve, using £20,000 as a threshold.

For each strategy, the results were reported as the average costs and benefits per person. The results of the deterministic, one-way sensitivity analysis of uptake rates and wheat flour fortification effects were presented in terms of the NMB. Estimation of the NMB was done using a WTP threshold of £20,000. The NMB is the increase in effectiveness multiplied by the WTP threshold, less the increase in cost. For each value of the parameter varied, the NMB of each intervention was calculated, and interventions compared with each other. The most cost-effective was assumed to be the one with the higher NMB.

Discussion

A decision analytic model was developed based on the evidence gathered in previous chapters, as well as expert consultation. Consideration was given to the population's demographic characteristics and the current nutritional status of relevant sub-groups. The alternatives compared had a probability of improving the population nutritional status.

The complexity of the decision problem and the limited data to populate the model led to a number of important assumptions, discussed in this section.

Overall, a conservative approach was chosen when making assumptions regarding interventions to prevent VDD, since the literature reports that both supplementation and food fortification tend to be highly cost-effective interventions to prevent MNDs. When no data was available, the worst case was chosen for the base case.

The model followed a health state transition structure, which meant that at the end of each cycle, the individuals would end up in one of the health states: VDD, VDS or dead. Children suffering rickets would only be allowed to move to VDS HS or dead, since it was assumed that treatment with high dose Vitamin D would be administered within one year. In all other terminal nodes, the TPs to the VDD were not affected by the terminal health state.

Regarding supplementation programmes, it was challenging to model the uptake of supplements. Previous economic evaluations tend to assume a 100% uptake, which was considered inappropriate following experts' advice and reports from the Healthy Start supplementation programme (240, 241). Therefore, the model used data from Lewisham Public Health, which reported an uptake of 20% among pregnant women and children, and 50% among infants up to one year. Additionally, consideration was given to the adherence to the supplementation programme. It seemed unlikely that eligible individuals would take their supplements daily, during the whole period, which for some, namely the BAME subgroup, would be lifetime. Because there was no data on adherence to Vitamin D supplements, individuals were allowed to drop out at the end of each cycle. Taking supplements was defined at the beginning of each cycle, which meant that those taking supplements in one cycle may not take supplements in the following cycle. In reality, behaviours towards supplements are likely to be more complex. For example, it has been hypothesised that those with a predisposition to start taking supplements are more likely to follow the recommendations while those that never took supplements are less likely to ever start taking them.

While it is known that different instruments produce different utility values for the same health state, models generally source utility values from a variety of primary and secondary studies(242). Combining utility values from different instruments to inform the utility of a particular HS is not ideal, and meta-regression analyses have been done in the past to deal with the heterogeneity(243). In this model, the child HS utility values applied were estimated using the proxy version of the CHU9D questionnaire, while the proxy version of the EQ5D-5L questionnaire was used to estimate the adult HS utility values. As explained in chapter 5, there are no preference-based quality of life questionnaires appropriate for the entire life course therefore this is a valid approach to model a population strategy that targets both children and adults. In order to reduce uncertainty about how different utility vales would have affected the results, these were tested in the PSA analysis. The costing methods also took a conservative perspective: the costs of flour fortification have been overestimated since current estimates are more likely to apply to small scale markets that are currently in place. The same applies to the costs of the supplementation programme. Moreover, other delivery methods of supplements exist, that are likely to be less resourceful. For example, the Healthy Start vitamins are distributed, at a national level, through health visitors, child centres and primary care units, which distribute the vitamins for free. The reason why the pharmacy –led scheme was chosen was two-fold. Firstly, it was based on the Lewisham programme, the same programme informed the uptake parameters in the model. For consistency, it was assumed that those uptakes would only be achieved if a similar effort was made in term of resources use to deliver the supplements. Moreover, although potentially cheaper, the current distribution scheme has been mentioned as highly ineffective, reaching a very limited proportion of the eligible population (244).

IMPORTANT MESSAGES FROM THIS CHAPTER

- An individual-level model was developed to simulate the prevention of VDD under four different scenarios, including current policies, as well as supplementation and food fortification policies;
- The model was built to simulate the UK population, and characteristics considered included age, sex, and ethnicity;
- A 90-year time horizon and 1-year cycle length were chosen for the base case;
- Interventions were compared using a societal perspective in terms of cost/QALY, as well as cost per case of VDD prevented;
- Costs and benefits were discounted at a 3.5% discount rate;
- Sensitivity analyses were planned to test the main model assumptions: population, discount rate, time-horizon, initial cost of fortification, perspective and effectiveness parameters;
- A PSA analysis, and a VoI were designed to further explore the model uncertainty.

CHAPTER 7

COST-EFFECTIVENESS OF FOUR STRATEGIES TO PREVENT VITAMIN D DEFICIENCY

This chapter presents the results of the decision analytic model developed in the previous chapter. The chapter is organised into four main sections providing results for 1) the base case analysis; 2) the deterministic sensitivity analyses, which includes the results of the scenario analyses, and the results of the one-way sensitivity analyses; 3) the probabilistic sensitivity analysis, and; 4) the value of information analysis.

The ICERs of the four alternatives compared – no intervention, flour fortification, supplementation, and combined - were calculated following recommended methods for comparison of the cost-effectiveness of multiple alternatives (91). The results of both the base case and scenario A analyses were presented in terms of cost per QALY, as well as the cost per additional case of VDD prevented. Judgement about the cost-effectiveness of the interventions was based on the WTP threshold of £20,000 - £30,000 per QALY, which, among other considerations, is the threshold recommended by NICE to indicate cost-effectiveness of an intervention (174).

The results of the one-way sensitivity analyses testing the uptake rates and the effect of wheat flour fortification within a range of parameters were presented in terms of the

NMB, using the WTP of £20,000. The results of the PSA were presented using CE planes, whereby scatter plots show the results of the PSA analysis for each strategy, compared to the current UK scenario, the 'no intervention' alternative. Additionally, a cost-effectiveness acceptability curve (CEAC) is presented, which shows the probability of each intervention being cost-effective at different values of the decision maker's WTP for a unit of outcome. Lastly, the results of the VoI analysis are presented in terms of the individual and population EVPI, based on the cost-effectiveness thresholds of £20,000. Additionally, the magnitude of EVPI for different WTP values is presented graphically.

Base case analysis

Cost-utility analysis

The results for the base case CUA (Table 19) show that flour fortification was the dominant alternative, for resulting in more QALYs and fewer costs than the no intervention alternative. The combined strategy was cost-effective, with an ICER of £9.50 per QALY. Supplementation alone resulted in a ICER of £135 per QALY, which is greater than the combined strategy ICER, and less effective. The rule of extended dominance applies and policy makers should rule out supplementation alone.

TABLE 19 – RESULTS OF THE COST-UTILITY ANALYSIS FOR THE BASE CASE

Strategy	Mean Cost (£)	Incremental Cost (£)	Effectiveness (QALYs)	Incremental Effectiveness (QALY)	ICER (Cost/QALY)
No intervention	4.02	0.00	0.54	0.00	Dominated
Flour fortification	2.90	-1.12	0.57	0.03	Dominant
Combined	4.40	0.38	0.58	0.04	9.50
Supplementation	5.37	1.35	0.55	0.01	135

The results were plotted onto the CE plane presented in Figure 23. In this depiction, all alternatives were compared to the status quo, the no intervention scenario.

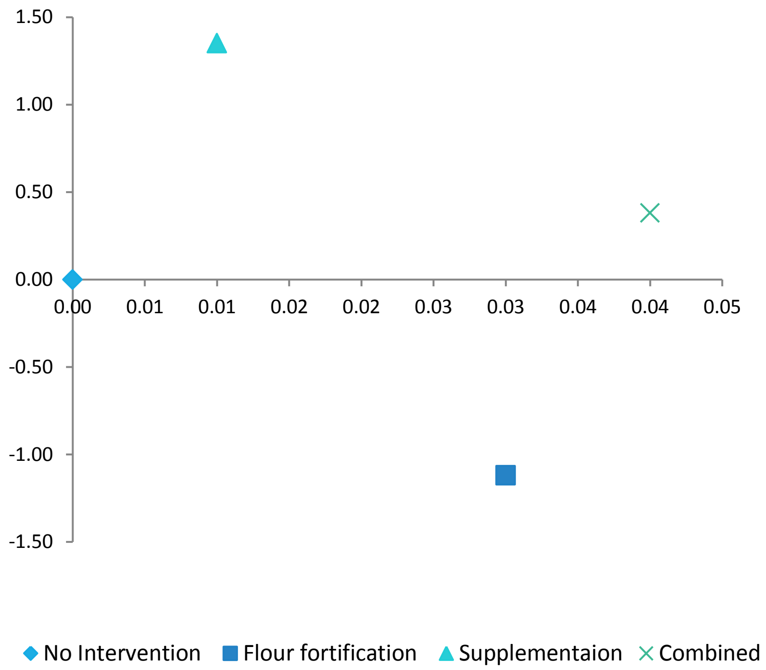


FIGURE 23 – COST-EFFECTIVENESS PLANE OF THE RESULTS OF THE BASE CASE ANALYSIS

Cost-effectiveness analysis

The results of the CEA showed that the combined strategy was the most cost-effective alternative, with an ICER of £1.8 per additional case of VDD prevented (Table 20). It shows that wheat flour fortification dominated both 'no intervention' and supplementation, as it prevented more cases of VDD and was less costly. Supplementation alone resulted in an ICER £22.5 per QALY, and has for the previous CUA results, extended dominance applies since the combined strategy has a lower ICER and more effective.

TABLE 20 – RESULTS OF THE COST-EFFECTIVENESS ANALYSIS FOR THE BASE CASE

Strategy	Mean Cost (£)	Incremental Cost (£)	Total cases	Prevented cases	ICER (cost/ case prevented)
No intervention	4.02	0	0.68	0	Dominated
Flour fortification	2.9	-1.12	0.51	0.17	Dominant
Combined	4.4	0.38	0.47	0.21	1.81
Supplementation	5.37	1.35	0.62	0.06	22.50

* INCREMENTAL EFFECTIVENESS WAS MEASURED IN TERMS OF ADDITIONAL CASE OF VDD PREVENTED. THE ICER IS PRESENTED IN TERMS OF COST PER ADDITIONAL CASE OF VDD PREVENTED.

Deterministic sensitivity analyses

As described in Table 21, a series of sensitivity analyses were undertaken to test the main assumptions relating to A) the composition of the population in terms of the ethnic groups; B) the disutility associated with the asymptomatic VDD heath state (HS), C) alternative discount rates, D) alternative assumptions relating to the cost of updating the food labels of the fortified wheat flour and products containing fortified flour, and E) the perspective; by taking a public sector perspective, instead of the societal perspective assumed in the base case.

TABLE 21 – DESCRIPTION OF THE SCENARIOS MODELLED IN THE ONE-WAY SENSITIVITY ANALYSIS

Scenario	Element tested	Assumption tested	Assumption made
A	Risk of VDD	Population at risk of VDD	Increased the number of individuals in the population from a BAME background, a group at a higher risk for VDD
B	Disutility	Disutility of being in the asymptomatic HS	No disutility assumed for the HSs of asymptomatic VDD
C	Discounting	Discount rate for costs and benefits	1.5% for costs and benefits
D	Time horizon	Time horizon	5 and 10 years
E	Costs	Costs of updating food labels	An initial cost per person added to the cost of the wheat flour fortification strategy.
F	Perspective	Public sector perspective	Industry costs not included

Scenario analyses

A. BAME population

In scenario A, the ethnic profile of the population was changed to simulate a population with a higher proportion of BAME individuals – 41% compared to 11% in the base case. Under this scenario, the ranking order of the strategies changed (Table 21) and this time the combined strategy was the most expensive alternative. Supplementation alone resulted in an ICER of £42.5 per QALY when compared to ‘no intervention’. Nonetheless, the ‘no intervention’ and supplementation alone alternatives were both dominated by wheat flour fortification, as were more expensive and less effective. The combined strategy was cost-effective, with an ICER of £17.6 per QALY.

TABLE 23 – RESULTS OF THE COST-UTILITY ANALYSIS FOR SCENARIO A

Strategy	Mean Cost (£)	Incremental Cost (£)	Effectiveness (QALYs)	Incremental Effectiveness (QALY)	ICER (£/QALY)
No intervention	4.46	0	0.52	0	-
Flour fortification	3.96	-0.5	0.55	0.03	Dominant
Supplementation	5.31	0.85	0.54	0.02	42.5
Combined	5.34	0.88	0.57	0.05	17.6

The CEA showed that the combined strategy had a low ICER of £3.52 per case prevented (Table 22).

TABLE 22 - RESULTS OF THE COST-EFFECTIVENESS ANALYSIS FOR SCENARIO A

Strategy	Mean Cost (£)	Incremental Cost (£)	Effectiveness (Total cases per person)	Incremental Effectiveness*	ICER*
No intervention	4.46	0	0.79	0	-
Flour fortification	3.96	-0.5	0.62	0.17	Dominant
Supplementation	5.31	0.85	0.68	0.11	7.73
Combined	5.34	0.88	0.54	0.25	3.52

* INCREMENTAL EFFECTIVENESS WAS MEASURED IN TERMS OF ADDITIONAL CASE OF VDD PREVENTED. THE ICER IS PRESENTED IN TERMS OF COST PER ADDITIONAL CASE OF VDD PREVENTED.

B. Disutility of asymptomatic VDD

The utility parameters used in the model were based on results of the proxy elicitation exercise described in chapter five. For both the child and adult population, the results of the survey suggest that clinicians associate some disutility with low serum 25(OH)D levels, otherwise asymptomatic. For this analysis, no disutility was assumed for asymptomatic VDD.

The results, presented in Table 23, show that by varying the utility in this manner, the combined strategy has no longer a benefit over wheat flour fortification..

TABLE 23 - RESULTS OF THE COST-UTILITY ANALYSIS FOR SCENARIO B

Strategy	Mean Cost (£)	Incremental Cost (£)	Effectiveness (QALYs)	Incremental Effectiveness (QALY)	ICER (Cost/QALY)
No intervention	4.02	0	0.59	0	-
Flour fortification	2.9	-1.12	0.61	0.02	Dominant
Combined	4.4	0.38	0.61	0.02	19
Supplementation	5.37	1.35	0.59	0	Dominated

C. Discount rate

At a lower discount rate of 1.5% for both costs and QALYs, the strategy recommendation from the model did not change, and the 'combined' strategy was the most cost-effective intervention, at a slightly higher ICER of £12.40 per QALY (Table 24).

TABLE 24 - RESULTS OF THE COST-UTILITY ANALYSIS FOR SCENARIO C

Strategy	Mean Cost (£)	Incremental Cost (£)	Effectiveness (QALYs)	Incremental Effectiveness (QALY)	ICER
No intervention	5.18	0	0.82	0	-
Flour fortification	3.67	-1.51	0.86	0.04	Dominant
Combined	5.8	0.62	0.87	0.05	12.4
Supplementation	7.06	1.88	0.83	0.01	188

D. Time horizon

Shorter time horizons than the 90 years used for the base case were tested in a sensitivity analysis. The overall results did not change – the combined strategy was the most cost-effective option (£43/QALY for 5 years and £17.5/QALY for 10 years). A shorter time horizon of 5 years resulted in a different ranking order regarding the mean cost of the alternatives - the combined strategy was the most expensive intervention.

TABLE 25 - RESULTS OF THE COST-UTILITY ANALYSIS FOR SCENARIO D

Strategy	Mean Cost (£)	Incremental Cost (£)	Effectiveness (QALYs)	Incremental Effectiveness (QALY)	ICER
5-year time horizon					
No intervention	1.85	0	0.54	0	-
Flour fortification	1.82	-0.03	0.57	0.03	Dominant
Supplementation	3.13	1.28	0.55	0.01	128
Combined	3.57	1.72	0.58	0.04	43
10-year time horizon					
No intervention	2.52	0	0.54	0	-
Flour fortification	1.42	-1.1	0.57	0.03	Dominant
Combined	3.22	0.7	0.58	0.04	17.5
Supplementation	3.44	0.92	0.55	0.01	92

E. Label cost

An alternative assumption was made regarding the initial cost of wheat flour fortification. In the base case, the cost of changing food labels to include Vitamin D was assumed to be £0. In this analysis, an approximate conservative estimate was used of £10.7 per person in the first year. It assumes all wheat flour producers, as well as manufacturers of foods containing wheat flour such as cakes and biscuits would incur an additional cost to update the product's label. Under this scenario, no intervention was the cheapest (Table 26). The combined strategy was the most cost-effective intervention, with an ICER of £277.0 per QALY. Supplementation resulted in the lowest ICER of £135.0 per QALY. The least cost-effective intervention was wheat flour fortification, with an ICER of £319.3.

TABLE 26 - RESULTS OF THE COST-UTILITY ANALYSIS FOR SCENARIO E

Strategy	Mean Cost (£)	Incremental Cost (£)	Effectiveness (QALYs)	Incremental Effectiveness (QALY)	ICER (£/QALY)
No intervention	4.02	0	0.54	0	-
Supplementation	5.37	1.35	0.55	0.01	135
Flour fortification	13.6	9.58	0.57	0.03	319.3
Combined	15.1	11.08	0.58	0.04	277

Public sector perspective

In scenario E, the analysis was undertaken from a public-sector perspective, which excluded all costs falling outside the public authorities' scope, namely the costs incurred by the food industry. The costs considered in this analysis included NHS costs of treating VDD related complications, the Local Authorities' costs of running the supplementation programmes, the flour fortification enforcement costs, and the cost of a national campaign to promote supplementation.

The combined strategy resulted in an ICER of £6.5 per QALY, (Table 27), and as expected, the average cost of the interventions including flour fortification, was lower.

TABLE 27 - RESULTS OF THE COST-UTILITY ANALYSIS FOR SCENARIO F

Strategy	Mean Cost (£)	Incremental Cost (£)	Effectiveness (QALYs)	Incremental Effectiveness (QALY)	ICER (£/QALY)
No intervention	4.05	0	0.54	0	-
Flour fortification	2.81	-1.24	0.57	0.03	Dominant
Combined	4.31	0.26	0.58	0.04	6.5
Supplementation	5.37	1.32	0.55	0.01	132

One-way sensitivity analyses

One-way sensitivity analyses were performed on the main effectiveness parameters – the uptake rate of supplements and the effectiveness of wheat flour fortification. These parameters were considered critical to the model results, and due to the high level of uncertainty surrounding them, they were explored separately.

Uptake rate

Monte Carlo simulations were repeated for uptake rates between 0 - 100%, at 10% intervals. FIGURE 24 shows that the NMB varies with each uptake rate, using the WTP threshold of £20,000 per QALY. The results show that the combined strategy is consistently the preferred alternative. It is only when the uptake of supplements is 60% or above that the NMB of the 'supplementation' alternative is greater than the NMB of 'flour fortification'.

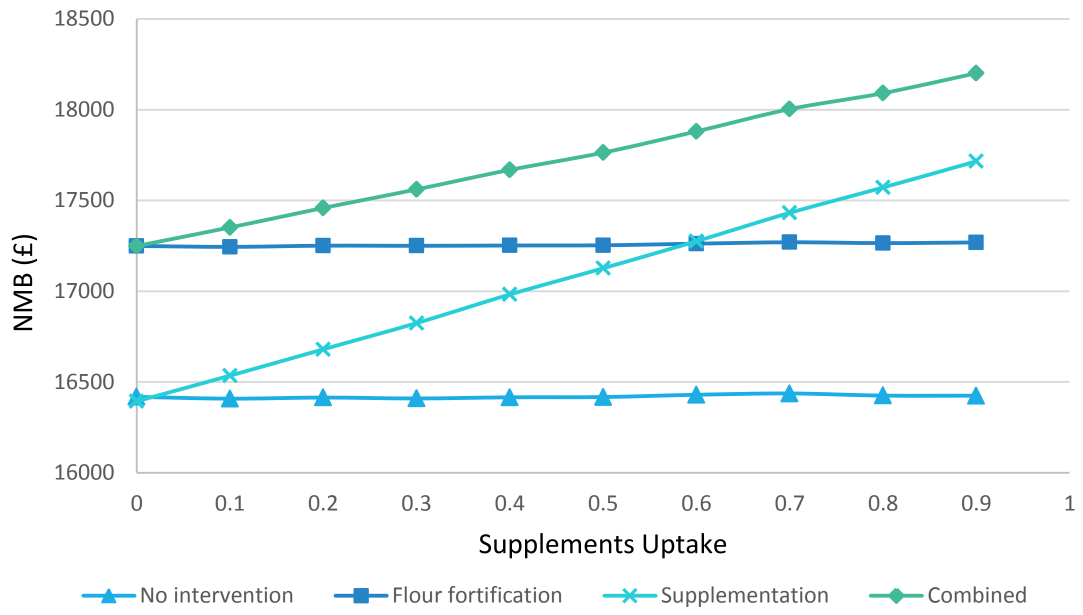


FIGURE 24 - NMB OF FOUR STRATEGIES TO PREVENT VDD ACCORDING TO THE UPTAKE RATE OF SUPPLEMENTS

Flour fortification effect

In the base case, wheat flour fortification reduces the probability of a person being deficient by 2.5% to 20%, depending on the age group. For the one-way sensitivity analysis, the overall effect of wheat flour fortification was varied, from 0-50% at 5% intervals. The results are plotted in FIGURE 25. As expected, the NMBs of wheat flour fortification and combined strategies increase with the increase of wheat flour fortification effectiveness. The combined strategy is consistently the optimal strategy. From an effectiveness of just around 7.5%, the flour fortification strategy emerges as the preferred strategy, compared to the supplementation strategy.

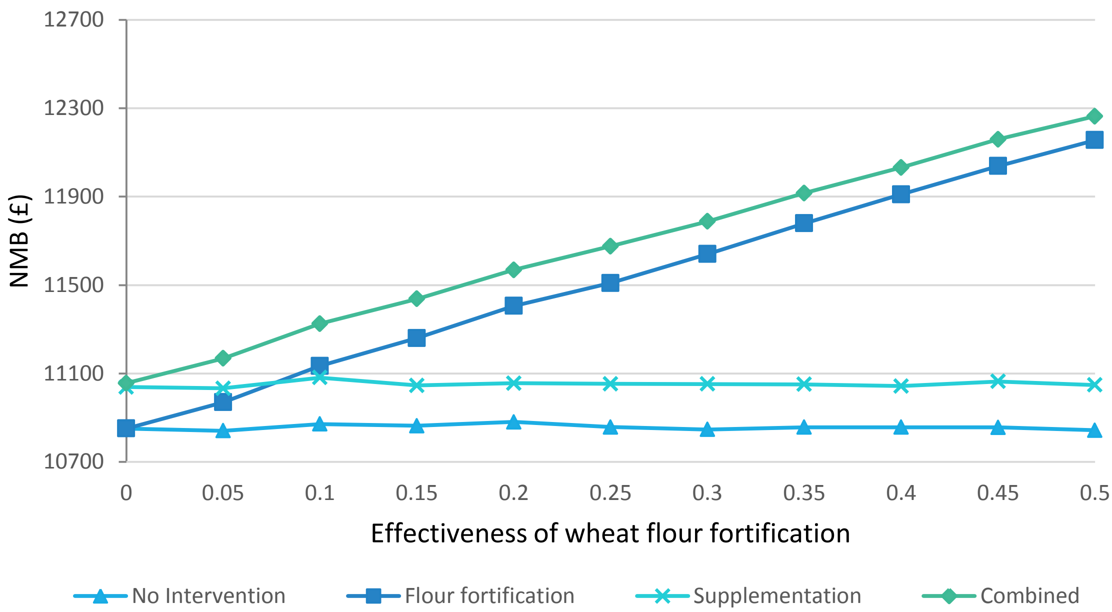


FIGURE 25 - NMB OF FOUR STRATEGIES TO PREVENT VDD ACCORDING TO THE EFFECTIVENESS OF WHEAT FLOUR FORTIFICATION

Probabilistic Sensitivity Analysis

A PSA was carried out to explore the overall decision uncertainty arising from the parameters' uncertainty. Second-order Monte Carlo simulation was repeated 1000 times, with cost, effectiveness and TPs being drawn from probability distributions. The results are presented in Figure 26, as the incremental cost and effectiveness of each proposed alternatives, when compared to the no intervention scenario.

The simulations gave results that are on the right of the y axis for all interventions, which shows considerable certainty that alternatives would result in more QALYs than the no intervention alternative. Regarding cost parameters, there is more uncertainty, particularly regarding the costs of supplementation. For all alternatives, the results cross the x axis. Nonetheless, incremental costs of flour fortification tend to favour the conclusion that flour fortification is potentially cost-saving as compared to no intervention. On the other hand, expected values for the supplementation and combined scenarios are more concentrated in the NE quadrant, meaning that these interventions are likely to result in some additional costs. All ICERs calculated on the basis of the PSA values are below £20,000 per QALY.

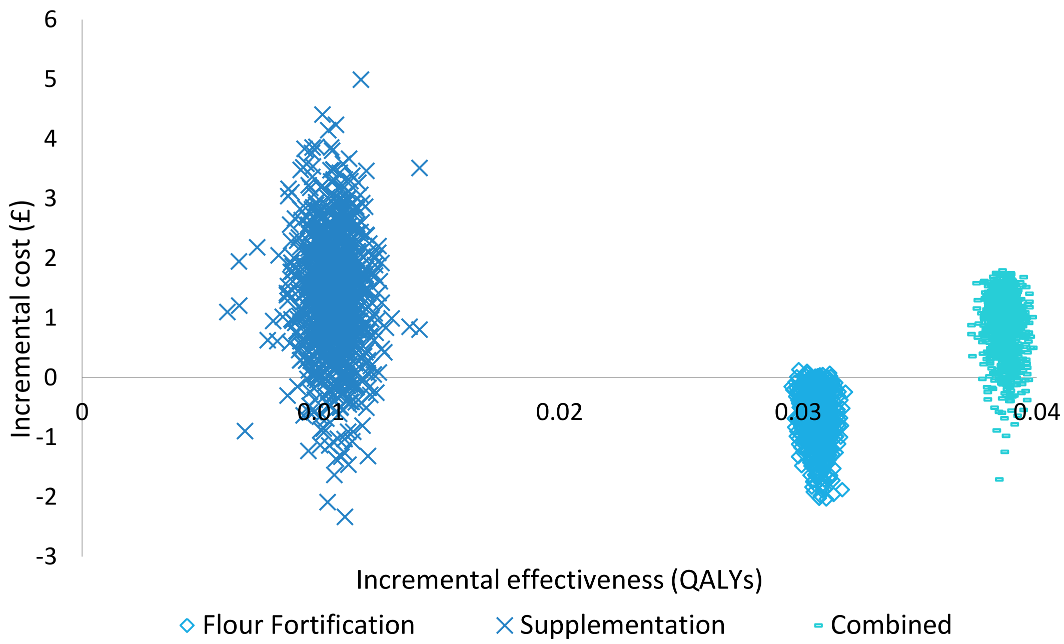


FIGURE 26 – Incremental cost-effectiveness scatter plot

The overall uncertainty around the decision, when all alternatives are compared, is reflected in the CEACs presented in Figure 27. For WTP values below £200/QALY, wheat flour fortification is the preferred alternative. For higher WTP thresholds, there is certainty that the combined strategy is the most cost-effective.

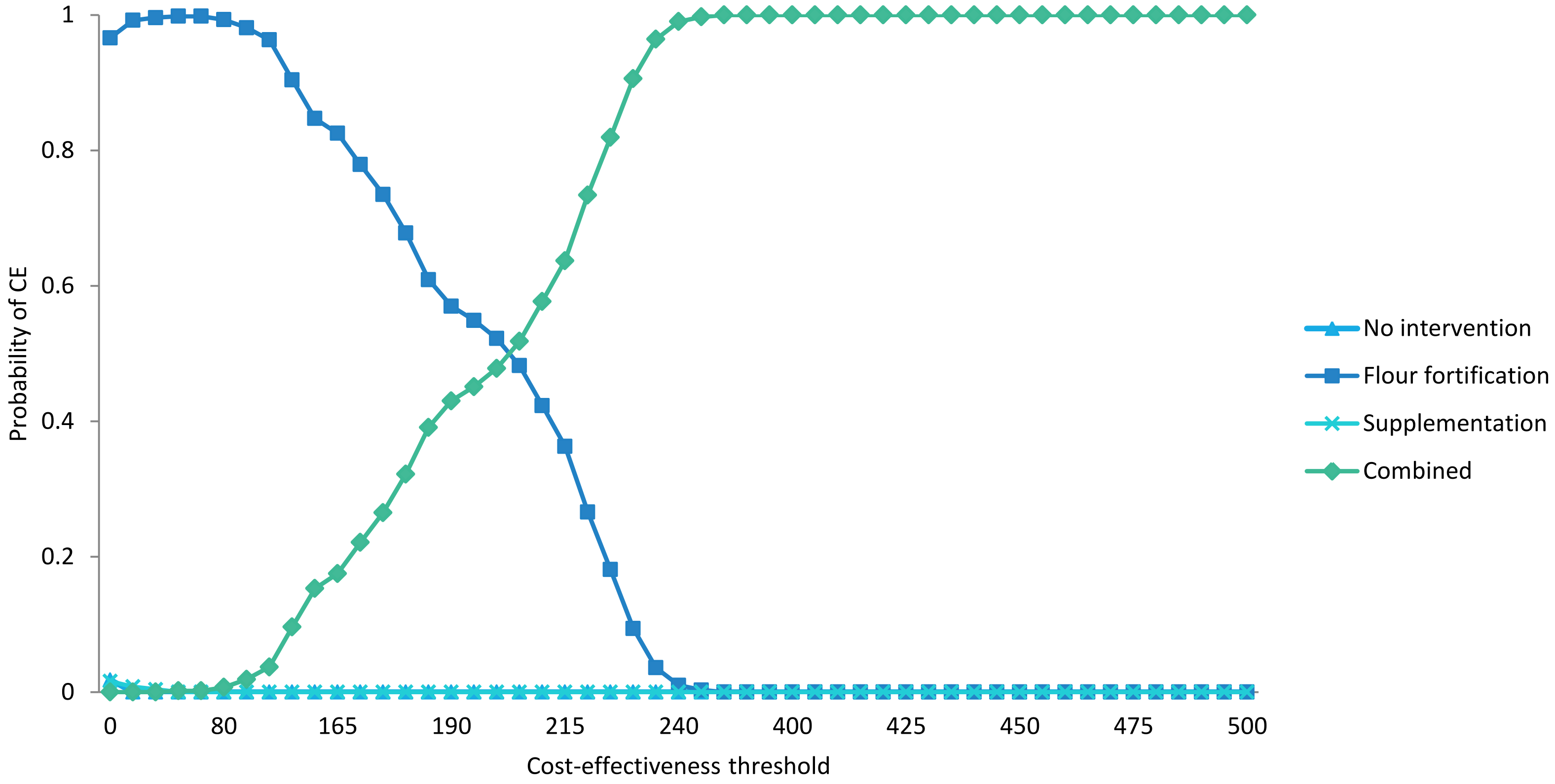


FIGURE 27 – CEAC SHOWING THE PROBABILITY OF ALTERNATIVES TO PREVENT VDD BEING COST-EFFECTIVE AT INCREASING ACCEPTABILITY THRESHOLDS

Expected Value of Perfect Information (EVPI)

Using the output of the PSA, an EVPI analysis was undertaken to estimate the expected cost of the current uncertainty, in order to see if further research would be potentially worthwhile or should be ruled out (110).

The result was the EVPI surrounding the decision as a whole for each time the decision is made, representing the EVPI for an individual. The individual EVPI estimates were used to estimate the population EVPI, which is more relevant to inform research prioritisation decisions. The population benefiting from the interventions was calculated over a 10-year time horizon. Overall, in the UK, 24% of children and 62% of adults are at risk of developing VDD. The population was discounted by an annual 3.5% rate. The population EVPI for different cost-effectiveness thresholds is shown in Figure 28.

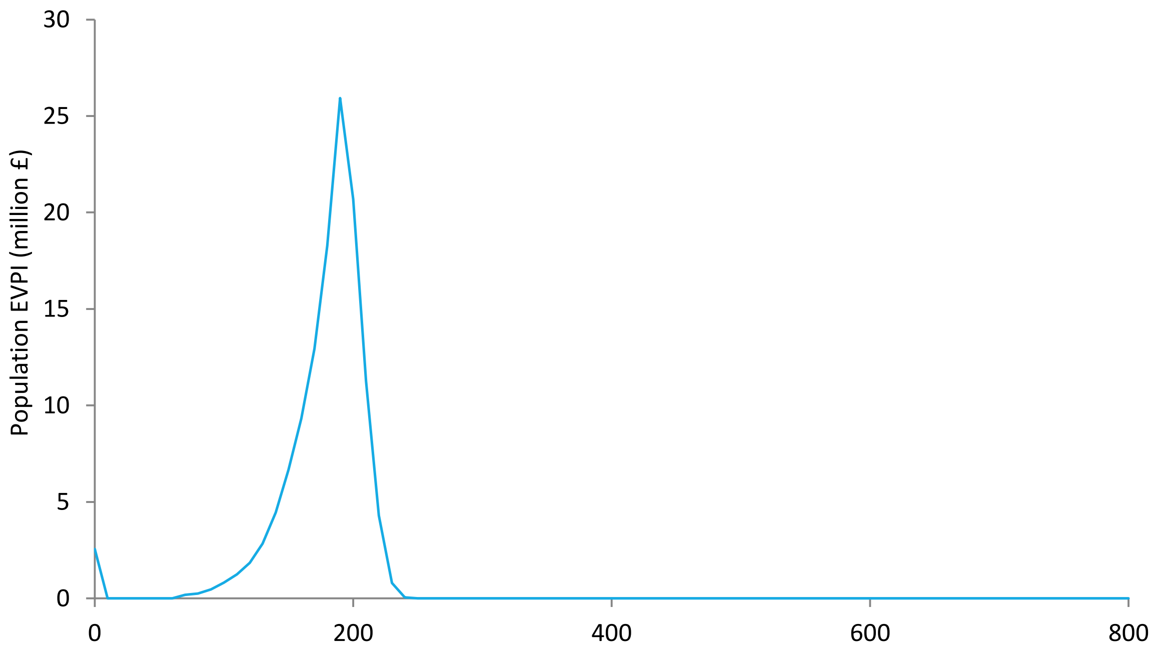


FIGURE 28 - Population EVPI for the prevention of VDD

When there is decision uncertainty, which is around the ICER, there is a value to the consequence of decision error (opportunity loss) (110). Therefore, and as it can be seen in the graph, the population EVPI peaks around the ICER of the combined strategy (£150-£200) and is zero for higher cost-effectiveness thresholds. Over a ten-year time horizon, the population EVPI reaches a maximum of £26 million at a cost-effectiveness threshold of £190/QALY, and £0 at £20,000/QALY.

Summary of findings

Deterministic analyses, including the base case and the sensitivity analyses showed that some interventions including flour fortification were preferred. In the base case, the combined strategy was the most cost-effective alternative, with an ICER of £9.5/QALY. Under NICE's recommended cost-effectiveness threshold of £20,000-£30,000, the 'combined' strategy would be highly cost-effective. For WTP values below £9.5/QALY, wheat flour fortification would be the preferred alternative. The interventions are still cost-effective, with an ICER of £42.5/QALY in populations with a higher proportion of individuals from a BAME background.

The scenario analyses showed the results were robust with the combined strategy being the most cost-effective intervention in practically all scenarios modelled. Uncertainty around the potential costs of changing the labels of the fortified foods, meant that, from a societal perspective, the supplementation alternative may be preferred if the costs of labelling are high. From the public-sector perspective, labelling costs do not affect the cost-effectiveness results.

One-way sensitivity analysis on the uptake rate of supplements showed that, at a WTP of £20,000 per QALY, the combined strategy was the one resulting in higher NMB, across all range of uptake values tested. Moreover, the analysis has shown that high uptake rates need to be achieved (above 60%) for the NMB of supplementation to be higher than that of wheat flour fortification.

An additional one-way sensitivity analysis was done to test the effectiveness of the wheat flour fortification parameter. The results showed that the NMB was higher for the combined strategy across all modelled effectiveness rates. Wheat flour fortification alone resulted in higher NMB than supplementation for an overall effect of approximately 10% risk reduction.

Using the conventional cost-effectiveness, threshold of £20,000 per additional QALY, the result of the PSA showed there was no decision uncertainty, and the combined strategy was the most cost-effective. At lower thresholds, particularly around the ICER (£100-250), more decision uncertainty was observed. Such results are reflected in the VoI analysis undertaken. For cost-effectiveness thresholds around the ICER the population EVPI peaked with a maximum of £26 million. At a threshold of £20,000, the population EVPI is zero.

CHAPTER 8

DISCUSSION

Introduction

The primary aim of this thesis was to estimate the cost-effectiveness of preventing VDD in the UK, using a decision analytic model to compare the cost-effectiveness of four alternative strategies for preventing population VDD in the UK. For this purpose, data was generated to populate a computer simulation model and the model parameters were derived from a combination of published literature, primary data collection, and consultation with clinical experts. The economic evaluation results reflect the costs and benefits of preventing VDD. The uncertainty surrounding the results was fully explored and reported to help inform policy recommendations, as well as to plan future research.

The motivations for undertaking the research in this thesis came from the rising concerns about the high prevalence of VDD (3, 51, 245); the reports of symptomatic cases in UK urban areas (64, 150); and NICE's recommendations (6), which called for research on the costs and benefits of strategies to prevent VDD.

Vitamin D is essential for healthy bones in children and adults, as it maintains adequate levels of calcium and phosphorus in the body. VDD causes poor bone mineralisation and muscle weakness, which in older adults, when added to frail HSs, results in an increased risk of falls. BAME groups are at a higher risk for VDD, and present lower mean serum 25(OH)D, on average, than white ethnic groups. The prevention of VDD is under the spotlight in the UK and the recent report from the Scientific Advisory Committee on Nutrition (SACN) (14) recommends year-round daily intake of 400 IU of Vitamin D from dietary sources for all persons aged above 1 year old, and 380-400 IU for infants up to one year old. The report acknowledges the difficulty of achieving such daily intakes from natural food sources alone, and suggests that the government should give consideration to strategies for the UK population to achieve the recommended intake (14). SACN recommendations have been criticised by clinicians and local public health authorities for the lack of guidance on such strategies, leaving space for debate on how these population intake rates are to be achieved. As was shown in the literature reviews presented in chapters three and four of this thesis, both supplementation and food fortification programmes are likely to be effective and cost-effective ways of improving the populations' nutritional status, including the Vitamin D status.

This chapter starts by revisiting the aims of this thesis and discusses its findings within the context of the wider literature. The chapter continues by reflecting on the methods used, highlighting the main strengths and limitations of the approach. The final sections elaborate on what the implications are for current policy making, as well as suggestions for future research.

Summary of the findings

This section reports the main findings of the thesis and discusses them in relation to current available evidence.

Literature reviews

A systematic review of published economic evaluations of VDD prevention strategies was presented in Chapter 3. The results showed that, while there is growing interest in evaluating interventions to prevent VDD, the evaluations are still limited in their scope, missing important groups of the population such as children and dark skinned populations, primarily due to the lack of available data. As a result, most analyses focused on the supplementation of older adults with Vitamin D to prevent falls and fractures, and compared either different supplementation strategies or supplementation against no intervention (127-129, 132-136, 138, 141). Besides being easily identifiable and measurable outcomes, the focus on VDD prevention in older adults may be explained by the relevance of the health outcomes modelled; since falls and fractures in the elderly are an important cause of morbidity and increased mortality, preventing them has the potential of being cost-effective, even if small effects are achieved. Vitamin D in combination with calcium is marketed and reimbursed in many countries as a co-adjuvant in the prevention and treatment of bone disease, mainly osteoporosis, which explains the predominance of economic evaluations in this area, as well as the availability of trial-based analysis funded by the pharmaceutical industry. The systematic review also raised concerns regarding the generalisability of trial data to national settings, in terms of the uptake of supplements and the costs of the programmes.

In general, the review results showed that the following gaps exist in the current available literature:

- Evaluation of relevant population strategies, with consideration of food fortification policies, as well as supplementation;
- Inclusion of costs and outcomes that are relevant to all groups of the population affected by VDD;
- CUAs that produce results that can be used by decision makers, by comparing with other public health programmes. Importantly, the lack of CUAs comparing population strategies to prevent VDD has been attributed to the dearth of utility values of VDD HSs (130, 131);
- Realistic estimations of the effectiveness of population interventions, particularly the coverage of relevant interventions.

A further literature review was undertaken with the main focus on model-based economic evaluations of both supplementation and food fortification strategies to prevent MNDs. The aim was to gather knowledge on the design of the model, the relevant parameters and the necessary statistical analyses. Other non-model based analyses, as well as costing studies, were considered. The review found that few models have been developed. The existing economic evaluations indicated that strategies are likely to be cost-effective, and food fortification has the potential to be cost-saving. Moreover, the review was fruitful in terms of providing insights into the cost structure of the programmes, as well as identifying relevant sensitivity analyses, and challenges, not only to researchers, but also to policy makers.

Health-Related Quality of Life of Populations with VDD

As mentioned, one of the main findings of the systematic review presented in chapter three was the dearth of evidence on the utility associated with VDD HS. In order to fill this gap in the literature, an expert elicitation exercise was undertaken, which is presented in chapter 5. The aim was to estimate the disutility of having VDD, and make these estimates available to be used in CUAs of interventions to address VDD.

Using two different preference-based multi-attribute questionnaires (the CHU9D and the EQ-5D), two separate surveys were developed and administered to two separate groups of experts: childhood VDD experts and adult VDD experts. A total of 48 clinical experts, highly specialised in VDD, responded to the surveys – 38 provided utility values for the children's HSs and 10 for the adults' HSs. The respondents were able to assess the patient quality of life experienced within the described HS and rank the HSs according to their preferences. The results of the surveys showed that experts have lower preferences for VDD HSs, when compared to full health, including asymptomatic VDD.

It was interesting to find that the 'asymptomatic' VDD HS, the most common health state for those with VDD, is thought to negatively affect HRQoL, i.e., clinical experts do not think that asymptomatic VDD is truly asymptomatic; rather, there is a subclinical manifestation of VDD. Looking closely at the results of the surveys, it can be seen that the attributes leading to such disutility arise from 'having a little bit of pain', and 'feeling a little bit tired', in children and having pain and anxiety/depression in adults, as well as lower mobility in older adults. These are interesting findings if put in context with the wider research on VDD, that is focused on the impact of VDD on health outcomes beyond bone health (246, 247). Nonetheless, these findings do not go without a note of caution: the attributes deriving the results, namely pain, tiredness, anxiety and mobility, may not be the result of VDD, but rather the cause since these symptoms would potentially reduce individual's time spent outdoors and therefore exposure to sunlight. In general, the findings of this thesis are in line with the few cross-sectional studies that have assessed HRQoL for low serum 25(OH)D levels (188-190), stating that low 25(OH)D is associated with lower HRQoL of individuals. The findings from the expert elicitation survey in this thesis contribute further to the literature by quantifying the decrement in HRQoL in utility terms.

The estimated utility of some HSs can be compared with the literature focusing on similar HSs. For example, published utility values for osteoporotic fractures are available from healthy older women at risk of hip fractures (197), patients with a hip fracture (248), and within other published literature reviews (194, 195). The utility values elicited in this thesis were generally lower than those reported in the literature, particularly for the 'fear of falling' HS. Interpretation of the values may need to consider two fundamental aspects of the methods used:

a) Proxy elicitation: there is evidence that different respondent groups attribute different utility to the same HSs. A well-described phenomenon is the ability of patients to adapt to a disability state, which results in a higher utility value, when compared to estimates from proxies, who tend to discount the states more than the patients themselves (249). Moreover, greater disagreement has been found for the nonphysical parameters of the preference-based questionnaires (185), which explains the greater variability observed for the fear of falling HS.

b) Time, in terms of the time frame of the HS, as well as in how respondents perceive it, is also likely to impact on the results. The HS's description and the survey's design aimed to estimate the utility values for a hypothetical patient on the day they sought medical assistance. This might have been perceived as if the patient was in the most severe period of the HS, which would have explained why medical attention was sought. Therefore, studies providing utility values for one-year would potentially result in higher utilities, which are linked to the healing process and adaptation.

Moreover, more reliable results would have potentially been obtained with a larger sample size.

Building a decision analytic model to evaluate VDD

Chapter six described the methods used to build a decision analytic model to estimate the cost effectiveness of preventing VDD in the UK population. VDD is a dynamic condition where people can easily move between deficient and sufficient HSs, as a result of their sunlight exposure or diet changing. In order to account for such transitions, a state-transition model was considered the most suitable design to simulate VDD in the population. The population of interest was a representative sample of the whole UK population, with varied risk of VDD depending on demographic characteristics - age, sex and ethnicity - as well as behaviours – such as supplement uptake. In order to account for the heterogeneity within the UK population, an individual patient simulation model was deemed the most appropriate. A long time horizon was used and costs and benefits were discounted at the same rate, 3.5%, as recommended by NICE. Data from the latest NDNS was used to determine the risk of being deficient by age group, sex and ethnicity.

Cost-effectiveness of preventing VDD

The model compared four alternative strategies: 1) wheat flour fortification; 2) supplementation of at-risk groups; 3) a combined strategy of both wheat flour fortification and supplementation of at-risk groups; and 4) no intervention. For each scenario, the mean costs and benefits were estimated for a 90-year time horizon, and analysed taking a societal perspective. The results of the base case analysis showed that the combined strategy was the most cost-effective alternative, and wheat flour fortification alone was cost saving when compared to no intervention, and supplementation alone. These findings place wheat flour fortification with Vitamin D close to other fortification strategies to prevent population MNDs, which are generally depicted as highly cost-effective or cost saving, as demonstrated in Chapter four.

Uncertainty analyses

The results were robust when tested under different assumptions using deterministic sensitivity analyses. The combined strategy was the most cost-effective alternative under a range of scenarios that included a higher number of individuals at-risk in the population, a higher discount rate, inclusion of food re-labelling costs, and a lower discount rate of 1.5%.

The results from the PSA showed that there was some uncertainty around input parameters, particularly relating to the costs. Such uncertainty is reflective of the lack of cost data for the hypothetical scenarios compared. Nonetheless, the PSA resulted in low decision uncertainty: out of 1000 simulations, the combined strategy was always the most cost-effective alternative at a willingness to pay threshold of £20,000. For low WTP, below £150/QALY, flour fortification is the most cost-effective option.

The low decision uncertainty meant that the VoI was zero at a WTP value of £20,000. At lower WTP, closer to the ICER (£100-£200/ QALY), there was some decision uncertainty that resulted in high population EVPI. The results show that the current uncertainty around the decision to prevent VDD does not justify investment in future research and therefore the VOI analysis further supports the adoption of a combined strategy of wheat flour fortification and supplementation.

Reflection on the approaches taken

The following section summarises reflections on the methodological approach taken within the thesis. Many of the strengths highlighted are closely related to potential limitations, and therefore a narrative summary follows.

UTILITY DATA SOURCES

In this thesis, the utility values were elicited from a sample of experts. For the first time, utility of several VDD HSs was estimated, including rickets and osteomalacia-related outcomes, as well as low serum 25(OH)D with no clinically evident manifestation. The use of a sample of clinical experts, typically a hard-to-reach group, was made possible through network sampling of health professionals with an interest in VDD. Their views are well informed and, because most have treated more than one case of VDD, the results are likely to reflect clinical perception of HRQoL for an average patient. However, the limitations of such an approach should be acknowledged. The discussion around who is 'best placed' to provide utility values is ongoing (250), and it is an important debate since different groups are likely to provide different utility values

(185). For public resource allocation decisions, NICE recommends that the general public should be the preferred source of preferences (174).

INTERVENTIONS

This is the first economic evaluation to compare wide coverage Vitamin D population strategies: supplementation of all at-risk groups, including older adults, and wheat flour fortification. Moreover, this is the first economic evaluation to consider a strategy of a combination of supplementation and food fortification. The intent was to open the debate for new ways of tackling VDD, since the current policies have been shown to be ineffective.

Some limitations arise from modelling hypothetical scenarios. These are linked to the lack of evidence on the effectiveness and costs of each, which means that parameters need to be based on assumptions and modelled data rather than population data from interventional studies. Additionally, a simplifying assumption was made regarding the costs and effects of the combined alternative. It has been assumed that these parameters were additive, whilst in reality it is likely that interaction effects, which could not be predicted in this analysis, will impact both the effectiveness and costs of a combination programme. For example, people's behaviour towards Vitamin D may change: wheat flour fortification might make individuals more aware of the importance of taking supplements, or, in contrast, it may be that it would reduce the uptake of supplements if individuals thought that the necessary Vitamin D had already been derived through the intake of fortified foods.

Voluntary fortification of foods by industry was not considered in the model, although it is in place in some countries, and it has been considered in economic evaluations of

MNDs prevention. The advantages of voluntary fortification lie in the lower public costs associated with enforcement of the regulation, and the maintenance of the consumer's freedom to choose, since some companies will choose to opt out. Nonetheless, the reason to exclude voluntary fortification within the analysis was linked to its important caveats when it comes to tackling MNDs. Its success as a public health measure depends on the industries' willingness to adopt fortification (251, 252). Additionally, the amount added is left to the industry's judgement and such flexibility leads to difficulties in monitoring and measuring impact, as well as lack of sustainability, since it is not guaranteed that fortification practices will be maintained over time (252). Additional issues have to deal with access to fortified foods. Voluntary fortified foods are typically more expensive than the non-fortified options, as it is currently the case of iodised salt, which creates inequities, leaving those in lower socio-economic groups at a greater disadvantage (231).

MODEL DEVELOPMENT

A model is a simplification of reality and there will always be some loss of information when a model developer translates reality into a series of definitive pathways. While oversimplification of reality is not desirable, the challenge with modelling complex interventions is finding the balance between incorporating all relevant pathways and interactions, without overcomplicating the model structure. In this thesis, the model development was enriched by consultation with experts from a variety of backgrounds, at different stages. These included local public health authorities that have developed interventions to prevent VDD, as well as modellers with experience in MNDs analyses. The insights gathered from researchers and decision makers during the development of the model highlighted the challenges faced by different stakeholders. For example, local authorities struggle with the implementation of the Healthy Start supplementation scheme, since the funding from the Department of Health covers the costs of the vitamins only, and neglected costs relating to staff, distribution and monitoring. Several other important issues that have been raised in this thesis come directly from the modelling process, which involves multidisciplinary teams in the discussion on what is relevant. Such process reiterates the value of decision analytic modelling as a method to evaluate public health strategies, where discussions and judgments are fundamental. Moreover, by discussion, the model parameters can reflect the views of a group of experts and go some way to overcoming issues of a lack of data or publication bias.

In order to utilise the different available data sources, this thesis took a pragmatic approach to evaluate policies to prevent population VDD, bridging different sources of evidence, including recently published systematic reviews, reports from local authorities and expert opinion. It is acknowledged that NICE's methodological guidelines (89) recommend that effectiveness data should be sourced from systematic reviews. Published systematic reviews synthesising the costs and effectiveness of strategies to prevent VDD in children (130, 253) and adults (81, 148, 191) were used to inform the model. No further review to inform model parameters was undertaken within this thesis, since the available syntheses had been published recently between 2014 and 2015, which is within the time frame of this project.

The model assumes a societal perspective in relation to the costs, and efforts were made to understand how the changes in the costs of food production would affect the final cost to the consumer. When fortifying a staple food such as flour, it is important to make sure that price changes do not have the unintended consequence of creating inequalities, by reducing the access of low-income groups. The research undertaken in this thesis showed that it is unlikely that wheat flour fortification would have a noticeable impact on the price of flour, or on the price of products that contain flour. Nonetheless, there is uncertainty regarding the costs of re-labelling flour and products with flour, and how these costs would be handled by food industries. Learning from other countries, namely Australia, where folic acid fortification of wheat flour has been mandated, labelling was mentioned as a potential issue prior to implementation, though it did not have any impact on prices after implementation. In the UK, a study focusing on the costs of wheat flour fortification with folic acid concluded that industries would incorporate label changes in their normal update cycle and therefore, no additional costs would be incurred (231).

The use of an individual patient simulation model is a strength of this work. The model allowed the heterogeneity of the population to be incorporated, pathways to be easily distinguished for adults and children, and different threshold values for defining VDD to be applied, without having to generate multiple HSs. Although the dichotomy of defining a population as deficient and non-deficient may at first seem a narrow definition of the problem, individual characterisation of each simulated trial allows the complexity of VDD to be incorporated without complicating the presentation of the model.

Population

There are concerns about the current UK policies not reaching the groups at risk that would benefit more from VDD preventive programmes. An important group is the dark skinned population that constitutes around 10% of the whole UK population (216) and have a higher risk of being deficient throughout the year. Although the analyses did not incorporate a formal equity analysis, by applying different weights to QALYS, it is the first economic evaluation to include the dark skinned population as a group within the simulated trials. Moreover, a scenario analysis considered geographic areas where a higher proportion of the population is dark skinned (urban areas such as Birmingham, where 40% of the population is from a BAME background) and aimed to provide insight into how results vary in such regional settings. Nonetheless, an assumption had to be made in terms of the effectiveness of the strategies within each group of the population. It was assumed that the uptake rates for supplementation would be the same among these different ethnic groups. It was also assumed that the effect of wheat flour fortification would be the same, but it is likely that different ethnic groups have different daily consumption patterns for flour. However, no data on such variability could be found in the literature. The model did account for differences in supplementation uptake rates and food consumption in terms of sex, and age. Infants are not likely to eat wheat flour based foods, particularly in their first year of life, and therefore the effectiveness was lower in this group. Moreover, data from Lewisham showed that the uptake of supplements is higher in the first year of life, which was also accounted for in the model.

Time horizon

It seems important, in the context of VDD, to model prevention through a long time horizon, since intervention to prevent VDD will potentially have a wider benefit and impact on costs over time. To capture the long term effects of each alternative, a long time horizon was selected for the base case analysis. However, VDD is a dynamic condition that changes with peoples' lifestyles and attitudes towards the sun, as well as seasonal light availability. Because VDD frequently captures the media interest and public attention, more foods are being voluntarily fortified, including breakfast cereals, mushrooms, yogurts, and cheeses. This is changing the diet profile of the population, and is therefore likely to impact on the population's daily intake of Vitamin D, and therefore reduce the prevalence of VDD, which will potentially reduce the effectiveness of a VDD population strategy over time.

Costs

The model has some limitations in terms of the cost parameters. The price of Vitamin D supplements was based on the price of the Healthy Start drops and tablets. It is likely that the available vitamins are currently more expensive than if this program was to be offered at a national level. The price of supplements for the older adult population was retrieved from the BNF. The currently available Vitamin D tablets at 800IU are expensive, compared to other supplements. It can therefore be argued that the price of supplements was overestimated within the model. If that is the case, other things being equal, the supplementation intervention would be more cost-effective.

Regarding the costing of the supplementation programme, the approach taken was not only thorough, but based on a scenario where a comprehensive public health programme was implemented. The example was taken from Lewisham, a borough that has reported the highest uptake of the Healthy Start vitamins in the UK. Lewisham provides supplements through community pharmacies using an electronic card system, and has developed software to monitor the programme. The costs of rolling out the programme to a national level were estimated by multiplying the costs in Lewisham by the number of local authorities in England and Wales. There are some issues with this approach: it is likely that, if the programme is rolled out at a national level, better prices could be negotiated with several providers and distributers achieving economies of scale. At the same time, the costs incurred by Lewisham, may not be the same within other local authorities, due to differences in organisation and structure.

Other models of delivering supplements have been considered in previous economic evaluations. For example, the Healthy Start vitamins scheme, at a national level is distributed by health visitors and general practitioners, which cuts the distribution costs to a minimum (130, 253). However, less resource-intensive supplementation programmes have reported lower uptake rates (240, 241).

Value of Information

An important contribution of this work is that it offers further evidence on how uncertainty may be tackled from a decision maker's perspective, through a value of perfect information (EVPI) analysis. The results can be used to further inform decisions under uncertainty, and suggest that it may be worthwhile to undertake research to reduce such uncertainty. However there seems to be low decision uncertainty with this model, which resulted in low EVPI at the recommended cost-effectiveness threshold of £20,000/QALY.

Implications for policy making

Decision making under uncertainty

The decision of what interventions to fund falls to the policy-maker and it is desirable that, in order to make the right decision, evidence is available in terms of the implications of each choice. This is generally why evidence-based decision making has been advocated. Even so, evidence-based decisions are prone to uncertainty and the choice requires value judgements that may be weak or strong judgements, depending on the evidence available.

Fortification is likely to be cost-saving and importantly, an attractive policy to public authorities since the majority of the costs are borne by the private sector. If decision-makers are looking for a cost-saving answer to the VDD issue, fortification alone is able to prevent cases of VDD at lower cost than the current scenario – 'no intervention'. Nonetheless, it is likely that a more efficient policy can be achieved at some cost, by implementing a supplementation strategy in combination with a fortification policy, in order to reach those who would not benefit from fortification.

Indeed, the series of cost-effectiveness analysis, including sensitivity analyses presented in this thesis, showed that the combined strategy is likely to be highly cost-effective. The ICER of the combined strategy was consistently low, which makes the combined strategy an appealing alternative.

The following subsections discuss issues related to the hypothetical decision to implement one of the alternative strategies.

Preventing Vitamin D Deficiency

The research presented in this thesis suggested that a strategy that combines wheat flour fortification and supplementation of the at-risk groups is likely to be a highly cost-effective way of preventing VDD in the UK. Moreover, the uncertainty analysis showed that the 'no intervention' scenario, which reflects the current UK status, is consistently the least preferred option.

Such results should prompt decision-makers to take action towards improving the population's Vitamin D status. Important considerations should focus on what should be offered – Public Health England has suffered budget cuts in recent years and programmes such as the supplementation programme suggested in this thesis, although cost-effective when in combination with wheat flour fortification, may have prohibitively high set-up costs. If this is the case, wheat flour fortification, and potentially other fortification options, should be considered.

When planning a new policy to prevent VDD, it is useful to look at examples from other countries. Sweden is generally referred to as a case of success when it comes to polices to prevent VDD since it reports the highest mean population serum 25(OH)D in Europe, despite being a high latitude country (37). A combination of milk and spreadable fats fortification, supplementation, and majority of the population being of white ethnic background have been mentioned as factors contributing to this result (37). Nonetheless, there are concerns that the policies might not be reaching the dark skin populations. It has been noted migrant women had lower serum 25(OH)D, and had lower intake of milk (50, 254), showing the importance of carefully choosing a food vehicle that reaches the population of interest. It has also been noted that the uptake of supplements is lower in dark skin populations.

The current UK supplementation programme, which is part of the Healthy Start scheme, has been referred to as a missed opportunity ((244)) mainly due to the low uptake rates observed across the country. It does not seem likely that making supplements available *per se* will successfully improve the population nutritional status. Interventions that require a high level of agency, as it is the case of a supplementation programme are likely to be less effective and less equitable than interventions requiring lower levels of agency. The case for this has been well described by Adams et al. (255), who give the example of folic acid supplementation versus folic acid fortification. With this in mind, the model developed in this thesis considered a resourceful supplementation programme that relied on pharmacies to distribute the supplements, and a software and electronic card system to monitor it. This approach is thought to achieve 20% uptake in the adult population, and 50% in infants up to one year. Nonetheless, the one-way sensitivity analysis of the uptake of supplements showed that the combined strategy results in higher NMB for uptake rates starting from 10%. It might be that a less resourceful supplementation programme may be implemented in combination with wheat flour fortification.

Prior to implementation, it seems important to adequately define the population of interest and how it can be reached. It seems also important to plan, and execute, the monitoring of a supplementation programme.

Ethical considerations

Although not a topic that is obviously within the scope of this thesis, some ethical considerations appeared during the model development that should contribute to this discussion. It is important to consider the ethical aspects of the public health interventions under consideration in order to design strategies that align with the population's needs, while respecting moral principles, such as equity, non-maleficence and autonomy. The strategies proposed in the thesis were tailored to improve the general population's health by improving its Vitamin D status. Special attention has been given to British groups at higher risk, including children, dark skinned populations, and the elderly. Targeting these groups could lead to greater health equity, as they are frequently disadvantaged and are vulnerable to lower income and/or lower educational attainment compared to other social groups in the UK. However, providing a targeted supplementation programme, for example, to all groups with dark skin, might result in stigmatisation and consequently lower Vitamin D supplement uptake by this group of interest. This has been observed in Scotland, where one of the reasons for the low uptake of the Healthy Start vitamins among low income groups, who are eligible for free vitamins, was stigma associated with being poor (240).

Another issue that should be considered has to do with consumer choice. Mandatory fortification of wheat flour would mean that there would not be any wheat flour available in the UK that would be free of Vitamin D, unless exceptions are made. In Australia, mandatory fortification of wheat flour exempts organic flour, leaving the consumer with the option to opt-out. Even so, organic flour tends to be more expensive, which means that lower income groups are left without an option. Given the benefits to the entire population of Vitamin D fortification, however, policy-makers may consider lower consumer choice a worthy trade-off for greater health and lower rates of VDD.

The costs of the loss of consumer choice have been explored in a few economic evaluations of mandatory food fortification. As mentioned in chapter four, Dalziel et al. (163) assumed that each person in the population incurred a one-dollar cost due to the loss of choice. This has prompted interesting work aiming at understanding consumers' preferences towards mandatory fortification, in terms of what compensation people might be willing to accept if mandatory fortification with folic acid was implemented (256).

In the UK, where mandatory fortification of flour with folic acid has previously been considered, a report from the FSA concluded that, because all non-wheat flour types would be exempted, the issue was not relevant (231). There is resistance to other mass public health interventions, such as water fluoridation (257).

Future Research

The research developed within this thesis makes a valuable contribution to the existing body of literature, but also serves to outline recommendations for future research.

As has been highlighted in the literature, more and better data are needed on ethnic minority groups in order to design new interventions that successfully reach those in need. It has been particularly challenging to assess the impact of the interventions without knowing, for example, uptake rates, food consumption and daily intakes. This is an important consideration in terms of coverage and consequent population effectiveness of wheat flour fortification. More data on flour fortification with Vitamin

D is likely to become available in the future. After the national micronutrient survey in Jordan, it was found that around 60% of women and 19% of children had VDD, a new flour fortification policy was introduced in the country and the next national micronutrient survey will provide population data on the effectiveness of the intervention. Notwithstanding, transferability of the results to other settings depends on the comparability of, among other things, the flour intakes of the populations (258, 259).

In terms of methods, it would be interesting for an economic study to consider the impact of food fortification from a macroeconomic perspective. Industry has raised concerns in the past about how enforcement or restriction of food composition may affect exports. Although only a small share of the wheat flour produced in the UK is exported, mainly to Ireland, a considerable proportion of products containing wheat flour such as biscuits and cakes are exported (NABIM, 2017).

Moreover, considering the previous point regarding the loss of consumer choice in the case of mandatory fortification, it would be valuable to undertake a discrete choice experiment (DCE) to understand general public preferences towards methods of delivery. This is distinctly relevant in the UK due to resistance to mandatory fortification policies, including flour fortification with folate and water fluoridation (260-262). The media seem to have a special interest in reporting research related to VDD, and therefore the public might have preconceptions in terms of the value of interventions to prevent VDD (5).

Future research on VDD could benefit from taking a broad perspective. VDD is a complex issue that involves sociodemographic determinants such as geography, age, ethnicity, lifestyle and cultural/religious traditions. Some advocate that individuals should be persuaded to spend more time outdoors in order to take advantage of sunlight exposure as a source of Vitamin D. Nonetheless, such messages directly conflict with public health messages towards the use of sunscreen to avoid sun burn and skin cancer. Systems approach to such public health issues, as well as realist reviews of the literature, might be a helpful way of conducting future research, acknowledging that public health research faces a different set of challenges requiring different research methods.

Conclusion

This thesis developed a decision analytic model to estimate the cost-effectiveness of preventing population VDD, and raised pertinent questions to be addressed in future research. The research has made several original and relevant contributions to the literature on modelling VDD, both in terms of the methodological approach, as well as of the information made available to inform policy makers.

APPENDICES

Appendix 1 – MEDLINE Search strategy

1 exp Vitamin D/

2 exp Cholecalciferol/

3 exp ergocalciferols/ or exp dihydrotachysterol/ or exp 25-hydroxyVitamin d 2/

4 exp Hydroxycholecalciferols/

5 Vitamin D?.tw,ot.

6 (cholecalciferol$ or calcifediol$ or calcitriol$ or dihydrotachysterol$ or hydroxyvitamin$ d?).tw,ot.

7 (alfacalcidol$ or alphacalcidol$ or colecalciferol$).tw,ot.

8 or/1-7

9 Economics/

10 "costs and cost analysis"/

11 Cost allocation/

12 Cost-benefit analysis/

13 Cost control/

14 Cost savings/

15 Cost of illness/

16 Cost sharing/

17 Health care costs/

18 Drug costs/

19 Hospital costs/

20 Health expenditures/

21 (fiscal or financial or finance or funding).tw.

22 Value of life/

23 Exp economics, hospital/

24 Exp economics, medical/

25 Economics, nursing/

26 Economics, pharmaceutical/

27 Exp "fees and charges"/

28 Exp budgets/

29 (low adj cost).mp.

30 (unit adj cost$).mp.

31 (economic$ or pharmacoeconomic$ or price$ or pricing).tw.

32 Or/9-31

33 8 and 32

34 Limit 33 to animals

35 Limit 33 to humans

36 34 not 35

37 33 not 36

Appendix 2 – Characteristics of the studies evaluating supplementation with Vitamin D alone and Vitamin D in combination with calcium

Study	Population and setting	Interventions	Type of EE and method	Perspective	Time horizon	Clinical outcome	Measure of benefit	Results
Frick et al., 2010, (132)	Community dwelling individuals over 65 years. USA	Vitamin D (800IU); Medical management of psychotropic drugs; Tai chi, Muscle and balance exercise; Home modifications multifactorial individualised programmes for all the population; Multifactorial individualised programmes for those with high risk of falling.	Cost-utility. Base case incremental analysis	Health Care Service	9 years	Fall related hip fracture	Cost per QALY	Taking into account feasibility considerations, Vitamin D supplementation and home modifications were the most cost-effective. Home modifications cost more $14,794 per QALY than Vitamin D.
Lee et al. 2013, (133)	Community dwelling individuals age 65 to 80 years. USA	Population screening for VDD; Universal supplementation. After screening, VDD individuals were assumed to be supplemented with 1000IU of Vitamin D if 25OHD was between 15–25 ng/mL and 2000-4000IU if 25OHD<15 ng/mL.	Cost-utility. Markov model	Payer perspective	3 years	Falls	Net Monetary Benefit using WTP of $50000/QALY.	Population screening was the preferred alternative for women (NMB 224$ for women and NMB $298 for men, when compared with universal supplementation (NMB 189$ in women and NMB $260 in men). The benefits were more evident for the older group (80 years old): population screening had a NMB of $563 in women and $703 in men, while universal supplementation resulted in NMB of $428 in women and $571 in men.

Study	Population and setting	Interventions	Type of EE and method	Perspective	Time horizon	Clinical outcome	Measure of benefit	Results
Poole et al. 2014 (129)	Population over 65 years. UK	Vitamin D alone (800IU); Current care	Cost-effectiveness Markov model	Health and Social Care Services	1 year	Hip fracture	Cost per avoided hip fracture	Intervention was cost-saving, with a net saving of £22M. For women aged 75-79 years, annual savings were 8.2M while for women aged 85 and over the savings were 131M, due to increased incidence of hip fracture with age.
Zarca et al. 2014 (136)	Individuals over 65 years. France	Universal supplementation with high-dose Vitamin D; Universal supplementation followed by 25OHD test (after three months); 25OHD test followed by treating those VDD; No intervention.	Cost-utility analysis	Health Care Service	Lifetime	Hip fracture	Cost per QALY	Universal supplementation with high-dose Vitamin D was dominated by the both interventions Universal supplementation followed by 25OHD test (€5.219/QALY) and 25OHD test followed by treating those VDD (€9.104/QALY).
Filby et al. 2014 (130)	Pregnant and breastfeeding women, children aged less than five years, adults over 65 years, dark skinned population. UK	Universal provision of Vitamin D; 25OHD test followed by treatment	Cost-consequence analysis	Health Care Service	1 year	-	Cost per extra person taking supplements and cost per averted case of VDD	Universal supplementation was cost-saving in comparison with testing the whole population. Incremental cost of testing women, children, people aged over 65y and dark skinned sub-group was £10 million, £21 million, £25 million and £160 million, respectively.

Study	Population and setting	Interventions	Type of EE and method	Perspective	Time horizon	Clinical outcome	Measure of benefit	Results
Poole et al. 2015 (128)	Individuals over 60 years. UK	Vitamin D alone (800IU); Current care	Cost-utility analysis. Markov model	National health and social care services	5 years	Falls	Cost per QALY	Supplementation for those aged over 60 years had an ICER of £19,759/QALY. Supplementing those aged over 65 years dominated current care by being cost-saving and leading to increased QALYs.
Church et al. 2015 (135)	Elderly population (over 84 years) living in residential care facilities. Australia	Vitamin D supplementation (800IU); Medication review; Multifactorial intervention. Each was compared against the 'no intervention' scenario.	Cost-utility analysis. Markov model	Health care Service	Lifetime	Falls	Cost per QALY.	Vitamin D supplementation and medication review were both cost-saving, compared to 'no intervention'. ICER for medication review relative to Vitamin D supplementation was AU$2442/QALY.
Patil et al. 2016 (138)	Home dwelling elderly women aged between 70-80 years. Finland	Vitamin D (800IU); Vitamin D (800IU) + exercise; Exercise alone.	Cost-effectiveness Trial-based analysis	Societal	2 years	Medically assisted falls	Medically attended injurious falls per person year	Supplementation with Vitamin D alone was dominated and excluded from analysis. ICERs of €221 for no intervention, €708 for exercise only and €3820 for Vitamin D and exercise.

NC – not clear; **EE** – Economic Evaluation; **WTP** – Willingness to pay; **NMB** –Net Monetary Benefit; **M** – Million; **ICER** – Incremental Cost Effectiveness Ratio; **AU** – Australian Dollars **BMI –** Body Mass Index; **LRNI** – Lower Reference Nutrient Intake;

Appendix 3 – Characteristics of the studies evaluating supplementation with Vitamin D in combination with calcium and other nutrients

Study	Population and setting	Interventions	Type of EE and method	Perspective	Time horizon	Clinical outcome	Measure of benefit	Results
Torgerson et al. 1995 (127)	Elderly Women (i) living in the community (ii) in nursing homes, (iii) with low BMI in nursing homes. UK	Oral supplementation with Vitamin D (800IU) and calcium (1.2g); Annual parenteral Vitamin D (300,000IU)	Cost-effectiveness. Trial-based analysis	National Health Service	3 years	Fractures	Cost per averted fracture (all fractures and hip fracture)	For women living in the community, the cost per averted fracture with parenteral Vitamin D was £946 for all fractures and£ £2,317 for hip fractures. With oral supplements, the cost per averted fracture was 14,420£ and 22,379£ for hip fractures. Targeting to those with low BMI and those in nursing homes reduced the costs.
Willis et al. 2002 (139)	Women aged between 50-90 years. Sweden	Supplementation with Vitamin D (800IU) and calcium (1.2g); no intervention	Cost-utility. Markov model	National Health and Social Welfare Service	Until patients were 90 years old	Hip fractures	Cost per QALY	Intervention was cost-saving for those aged 70 years. Intervention was cost-effective (SEK 7,740/QALY) for younger women at high risk of hip-fractures.
Lilliu et al. 2003 (141)	Elderly women in nursing homes Belgium, France, Germany, Netherlands, Spain, Sweden, and the UK.	Supplementation with Vitamin D (800IU) and calcium (1.2g); no intervention	Cost-effectiveness. Trial based analysis	National Health Care Service	3 years	Hip fractures	Cost per avoided hip fracture	Costs in placebo group were higher for all countries. Overall, the net benefit ranged between £79,000 and £711,000 per 1000 women.

Study	Population and setting	Interventions	Type of EE and method	Perspective	Time horizon	Clinical outcome	Measure of benefit	Results
Church et al. 2011 (134)	Individuals over 65 years living in the community and in residential care. Australia	Community dwelling: Tai-chi; Home hazard assessment; Exercise, multiple interventions; Cataract surgery; Psychotropic medication withdrawal; Cardiac pacing. Residential care: Hip protectors; Supplementation with Vitamin D and calcium; Multiple interventions; Medical reviews.	Cost-utility and cost-effectiveness. Markov model	National Health Care Service (authors state a societal perspective when possible)	10 years	Falls	Cost per QALY	Community dwelling: Most cost-effective were Tai chi, home hazard assessment and group exercise. Residential care: The most cost-effective intervention was medication review, followed by supplementation with Vitamin D and calcium.
Filby et al. 2015 (131)	Pregnant women, women planning to become mothers, infants, and young children. UK	Vitamin D provided in a multivitamin preparation. Scenario 1: Current targeted supplementation based on income; Universal supplementation (no income restrictions). Scenario 2: Universal supplementation (extended to all women planning a pregnancy, and children between 4-5 years); current targeted supplementation based on income.	Cost-effectiveness and cost-utility. Base case incremental analysis.	Public sector (local authority, central government and the National Heath Care Service) and societal	Lifetime	Pregnancy affected by a neural tube defects, symptomatic VDD or LRNI for Vitamin A and C in each subgroup	Cost per QALY	Scenario 1: universal offering scheme was not cost-effective, ICER of £620,898. Universal scheme in scenario 2 was likely to be cost-effective effective for any subgroup combinations that includes ‘women planning a pregnancy and before 10 weeks pregnant’, ICER of £6,528.

NC – not clear; **EE** – Economic Evaluation; **WTP** – Willingness to pay; **NMB** –Net Monetary Benefit; **M** – Million; **ICER** – Incremental Cost Effectiveness Ratio; **AU** – Australian Dollars **BMI –** Body Mass Index; **LRNI** – Lower Reference Nutrient Intake;

Appendix 4 - Characteristics of the studies evaluating food fortification

Characteristics of included studies								
Study	**Population and setting**	**Interventions**	**Type of EE and method**	**Perspective**	**Time horizon**	**Clinical outcome**	**Measure of benefit**	**Results**
Sandmann et al. 2015 (140)	Women over 65 years. Germany	Bread fortification with Vitamin D (800IU) + calcium (200mg); No food fortification.	Cost-effectiveness Analytic model (not specified)	Societal	10 years and 35 years	Fractures	Cost per avoided fracture	Bread fortification with Vitamin D and calcium was cost saving
Ethgen et al. 2015 (142)		Dairy fortification with Vitamin D (800IU) + calcium (200mg); No food fortification.	Cost-utility analysis. Markov model	Health sector	Lifetime	Fractures	Cost per Life year gained	Fortified dairy was cost-effective from 70 years on in the general population and from 60 years on in patients at increased risk of osteoporotic fractures
Hiligsmann et al. 2017 (137)	Population over 60 years. France	Dairy fortification with Vitamin D (800IU) + calcium (200mg); No food fortification.	Cost-utility analysis. Markov microsimulation model	Health sector	Lifetime	Fractures	Cost per QALY	Fortified dairy was cost-effective in women over 70 years and in men over 80 years

Appendix 5 - Quality assessment checklist

	Poole 2014 (129)	Lee 2013 (133)	Church 2011 (134)	Frick 2010 (132)	Torgerson 1995 (127)	Lilliu 2003 (141)	Willis 2002 (139)	Zarca 2014 (136)	Filby 2014 (130)	Poole 2015 (128)	Sandmann 2015 (140)	Patil 2016 (138)	Church 2015 (135)	Filby 2015 (131)	Hilisgmann (2017) (137)	Ethgen (2015) (142)
Study Design																
Research question is stated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Economic relevance of research question is stated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
The viewpoint(s) of the analysis is clearly stated and justified	✓	x	x	x	x	x	✓	x	x	✓	x	✓	✓	✓	✓	✓
Rationale for the choice of the alternatives compared is reported	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	X
Alternatives being compared are clearly described	✓	NC	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	x	✓
Type of economic evaluation is stated	x	✓	✓	✓	✓	✓	✓	✓	✓	x	x	✓	✓	x	x	✓
Choice of type of economic evaluation is justified	x	x	✓	x	x	x	x	x	✓	x	x	x	✓	x	x	✓
Data collection																
Source(s) of effectiveness estimates is stated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Details of the design and results of the effectiveness study are given	NA	X	NA	NA	✓	✓	✓	NA	X	NA	NA	✓	NA	NA	NA	NA
Details of the methods of synthesis or meta-analysis of estimates given	✓	NA	✓	✓	NA	NA	NA	X	NA	✓	X	NA	✓	✓	✓	✓
Primary outcome measure(s) for the economic evaluation is clearly stated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Methods used to value HSs and other benefits are stated	NA	✓	✓	✓	NA	NA	x	x	NA	NA	NA	NA	✓	✓	x	✓

	Poole 2014 (129)	Lee 2013 (133)	Church 2011 (134)	Frick 2010 (132)	Torgerson 1995 (127)	Lilliu 2003 (141)	Willis 2002 (139)	Zarca 2014 (136)	Filby 2014 (130)	Poole 2015 (128)	Sandmann 2015 (140)	Patil 2016 (138)	Church 2015 (135)	Filby 2015 (131)	Hilisgmann (2017) (137)	Ethgen (2015) (142)
Details of the subjects from whom valuations were obtained are given	NA	X	✓	✓	NA	NA	x	x	NA	NA	NA	NA	x	✓	✓	✓
Productivity changes (if included) are reported separately	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Relevance of productivity changes to the study question is discussed	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	✓	NA	NA	NA	NA	NA
Quantities of resources are reported separately from their unit cost	x	x	x	x	✓	x	✓	X	✓	x	x	✓	x	✓	x	x
Methods for the estimation of quantities and unit costs are described	x	x	✓	✓	✓	✓	✓	✓	✓	x	✓	✓	✓	✓	✓	✓
Currency and price data is recorded	x	x	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	✓	✓	✓
Were details of price adjustments for inflation or currency conversion given	✓	✓	✓	✓	x	✓	✓	✓	✓	✓	✓	NA	✓	✓	✓	✓
Details of any model used are given	✓	✓	✓	✓	x	NA	✓	✓	✓	✓	✓	NA	✓	x	✓	✓
Justification for the choice of model used and the key parameters are stated	x	x	✓	x	x	NA	✓	x	✓	X	X	NA	✓	x	x	x
Analysis and interpretation of results																
Time horizon of cost and benefits is stated	✓	✓	✓	✓	X	✓	✓	✓	NA	✓	✓	✓	x	x	✓	✓
The discount rate is stated	NA	✓	✓	✓	✓	X	✓	✓	NA	NA	x	x	✓	✓	✓	✓
The choice of discount rate is justified	NA	x	✓	✓	x	NA	x	x	NA	NA	NA	NA	x	✓	x	x
An explanation is given if cost or benefits were not discounted	NA	NA	NA	NA	NA	x	NA	NA	NA	NA	x	x	NA	NA	NA	NA
The details of statistical test(s) and confidence intervals are given for stochastic data	NA	✓	✓	✓	x	NA	✓	✓	✓	NA	x	x	✓	✓	NA	NA

	Poole 2014 (129)	Lee 2013 (133)	Church 2011 (134)	Frick 2010 (132)	Torgerson 1995 (127)	Lilliu 2003 (141)	Willis 2002 (139)	Zarca 2014 (136)	Filby 2014 (130)	Poole 2015 (128)	Sandmann 2015 (140)	Patil 2016 (138)	Church 2015 (135)	Filby 2015 (131)	Hilisgmann (2017) (137)	Ethgen (2015) (142)
The approach to sensitivity analysis is described	X	✓	✓	✓	X	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓
Choice of variables for sensitivity analysis is justified	NA	✓	✓	x	NA	✓	x	✓	✓	NA	✓	✓	x	✓	✓	✓
Ranges over which the parameters were varied are stated	NA	✓	✓	✓	NA	✓	✓	✓	✓	NA	✓	✓	✓	✓	✓	✓
Relevant alternatives are compared	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Incremental analysis is reported	✓	✓	✓	✓	x	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Major outcomes are presented disaggregated as well as aggregated	✓	x	✓	✓	✓	x	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
The answer to the study question is given	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Conclusions follow from the data reported	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Conclusions are accompanied by the appropriate caveats	✓	x	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

NA - Not applicable; NC – Not clear

Appendix 6 - Summary characteristics of analysis based on decision analytic models

Study	Micronutrient	Type of EE and analytic framework	Country	Population	Interventions	Effectiveness data sources	Benefits	Perspective	Cost data	Time horizon	Discount
Monahan et al. (157)	Iodine	CEA. Decision tree	UK	Pregnant women: mild to moderate iodine-deficient population	Iodine supplementation vs no supplementation	Based on a systematic review	IQ point gained in the offspring.	Health service and societal	Market price for supplement prices, health and public health services costs previous cost study. Literature on the costs of preterm birth and healthcare costs taken from various published sources.	Lifetime	3.5% costs
Rabovskaja et al. (156)	Folic Acid	CEA and CUA. Decision tree	Australia	Pregnant women	Mandatory fortification vs voluntary folic acid fortification and voluntary supplementation	Effectiveness based on a previous model-based study.	QALYs, LYG, avoided NTD cases,	Societal	Based on FSANZ report and included industry and regulatory costs to the government. Annual recurrent costs from the National food agency	Lifetime	5% (o% and 7% in sensitivity analysis)
Bentley et al. (155)	Folic acid	CUA. Markov model	United States	Women 15-44 years. Analysis done but ethnic groups	Fortification of enriched grains with different amounts of folic acid (140, 350 or 700 mcg/100g) vs. no fortification	Several sources: previous CEA, food standards reports and interventional studies	QALYs	NC	Previous economic studies	NC	3%

Appendix 7 - Summary characteristics of analysis based on traditional cost-effectiveness methods

Study	Micronutrient	Type of EE and analytic framework	Country	Population	Interventions	Effectiveness data sources	Benefits	Perspective	Cost data	Time horizon	Discount
Jentik et al. (263)	Folic acid	CUA	Netherlands	Pregnant women	Fortification of wheat flour vs. no fortification	Estimation based on survey data and previous CEA	QALYs	Societal	Related to NTDs: total hospital care, travel and parking costs for parents, paramedic care, wheelchair, house adaptations, special education, productivity losses	Lifetime	4% costs 1.5% benefits
Dalziel et al. (163)	Folic acid	CUA	Australia and New Zeeland	Pregnant women	Promoting the use of supplements among pregnant women vs extending voluntary fortification vs promoting consumption of folate-rich foods vs mandatory folic acid fortification of wheat flour	Primary study	DALYs	NC	Based on resource use data from a primary study and on national published data. Costs were related with programme administrators, health professionals, materials, folic acid supplements, fortificant, training, equipment and supplies. Included loss of consumer choice assumed to be $1.	10 years	Costs and outcomes discounted at 5% per annum, 0% used in sensitivity analyses

Study	Micronutrient	Type of EE and analytic framework	Country	Population	Interventions	Effectiveness data sources	Benefits	Perspective	Cost data	Time horizon	Discount
FSANZ (166)	Iodine	CBA	Australia and New Zealand	Children aged 0-14 years	Mandatory fortification of iodised salt and reduction of the voluntary iodine fortification threshold	Literature review	Net benefits	Societal	Government costs of implementing and enforcing mandatory fortification (training staff, administration, complaints, auditing); Industry costs (machinery, labelling, iodine, analytical testing) and health care costs. Sources included survey to the industries and national authorities.	15 years	Benefits at 1.55% and costs at 3.3%

Study	Micronutrient	Type of EE and analytic framework	Country	Population	Interventions	Effectiveness data sources	Benefits	Perspective	Cost data	Time horizon	Discount
FSANZ (165)	Folic acid	CBA	Australia and New Zealand	Pregnant women	Mandatory white bread making wheat flour and all bread making flour	Literature review	Net benefits	Societal	The costs of mandatory fortification include the in-principle costs to consumers of reduced choice (although this was not estimated for this project), the costs to government of administering and enforcing mandatory fortification and the costs to industry of fortifying their product. The costs of monitoring the policy were not included based on FSANZ advice	40 years	Benefits at 1.55% and costs at 3.3%
Postma et al. (158)	Folic Acid	CEA	Netherlands	Women in child-bearing age	Supplementation	National data	Life-year gained	Societal	Direct costs only. Sourced from national data and US data. Health costs related to NTDs included admissions, surgical procedures and follow-up. Institutionalisation of children with NTD. Educational costs also included	Lifetime	3%

Study	Micronutrient	Type of EE and analytic framework	Country	Population	Interventions	Effectiveness data sources	Benefits	Perspective	Cost data	Time horizon	Discount
Goodall et al. (162)	Iodine	CEA	Australia and New Zealand	Whole population	Mandatory bread fortification	Literature review. Modelled according to national consumption data and prevalence data	Preventing one person from having an iodine level below 50µg/l	Societal	From previous published economic evaluation	10 years	Costs and benefits at 5%
Moore et al. (160)	Fluoride	CUA	Australia and New Zealand	Whole population	Water fortification	Literature review	QALYs	Medical and Public Health Perspective	Capital, maintenance and fluoride costs Two national databases (Minister of Health and Private water plants	20 years	3.5% to 8%
Baltussen et al. (161)	Iron	CUA	Four sub regions: Africa, South America, Europe and Southeast Asia	Pregnant women and new-borns	Iron supplementation vs iron fortification	Primary data and literature review	DALYs	Societal	Thorough cost estimation provided in supplemental tables. Resources used: administration and planning, monitoring and evaluation, legislation, media, enforcement and food inspection.	10 years	NC
Phillips et al. (159)	Vitamin A	CEA	Guatemala	Women of child bearing age and children up to six years old	Sugar fortification vs. supplementation vs. Food production and education programme	Secondary data from donors databases	Cost per person achieving adequate Vitamin A	Societal	Cost data from expenditure records, and unit cost calculation. Donated goods were also valuated and included in the analysis.	NC	10%

Appendix 8 – Invitation letter template

Dear members of the European Working Group on Bone,

I am currently doing a PhD, supervised by Dr. Wolfgang Högler, on the costs and benefits of preventing VDD and its complications.

As part of my PhD, I am collecting data on the health-related quality of life of children with Vitamin D deficiency. This information will be used to inform an economic evaluation on preventing Vitamin D deficiency.

As experts on rickets and other health outcomes of Vitamin D deficiency, I would like to invite you to complete the following questionnaire. The task will take approximately 15 minutes and it is of extreme importance for the success of this research.

To participate, please follow the link:

http://goo.gl/forms/CKucIEA0C4

Additionally, I kindly ask you to forward this email to other experts outside the Consensus group whom you feel share your expertise on rickets and Vitamin D deficiency and will be able to contribute.

Please make sure to copy me into the forwarded email.

Please note: We are using a questionnaire that has been specifically designed for the paediatric population. Unfortunately, this questionnaire has been only validated for children above 5 years. If you feel that some of the questions do not apply to the younger children, then answer with your best guess. For example, you may feel it is impossible to determine if an infant is feeling annoyed. In this case, I ask you to think about the best approximate situation, e.g. feeling irritable.

I thank you in advance for your collaboration.

Kind regards,

Magda

Appendix 9 – The CHU9D questionnaire

ESTIMATING THE QUALITY OF LIFE OF CHILDREN WITH VITAMIN D DEFICIENCY

This questionnaire is part of a PhD project in Health Economics that aims to estimate the cost effectiveness of interventions to prevent HRQoL (VDD) in the UK.

With this questionnaire we intend to estimate the utility- based quality of life (QoL) of children with Vitamin D deficiency.

What is utility-based QoL? Worldwide, public health decision makers are faced with funding constraints and economic evaluation can assist with decision making by providing information on the comparative costs and consequences of alternative uses of health care budgets. Within economic evaluation, it is conventional practice to measure the consequences of a service/treatment using the unit of 'Quality-Adjusted Life Years' (QALYs). QALYs combine the length of life with quality of life (QoL), which is measured using a preference-based function whereby more weight is given to certain dimensions of QoL e.g. 'having no pain' might be seen as more important than 'being able to do usual activities'.

There is a lack of evidence in the literature about the utility-based QoL of a person with rickets and other conditions caused by VDD. I need this information to conduct a comprehensive economic evaluation of interventions to prevent VDD and its complications in the UK. We are asking you to complete this questionnaire because you are an expert in the field and we would very much appreciate you taking the time to answer the following questions. There are no right or wrong answers and all responses will be taken into account.

What we ask you to do:

In the following pages we ask you to complete two different types of tasks:

Task 1 asks you to rank health states related to VDD according to their severity. This will help us understand VDD and its consequences better.

Task 2 presents a questionnaire designed to understand the QoL associated with each health state. This questionnaire has been developed specifically for a paediatric population and will allow us to estimate the QALYs lost in each health state. Each scenario is hypothetical so we ask you to think as if you have seen in your practice a patient with the described health state **today**.

The questionnaire is divided in **two parts**. The **first part** asks about **infants and young children (0-4 years)** and the **second part** about **older children (5-18 years)**. For each age group, we have defined the relevant health states that you need to consider for a child with Vitamin D deficiency. This resulted in **six health states** for younger children and **four health states** for older children.

We welcome any comments and queries regarding this questionnaire. If you have some, please contact Magda Aguiar:

Thank you for your collaboration!

PART 1: Infants and young children (0-4 years old)

Task 1. Ranking health states by severity

Please rank the following 6 states, giving the **value '1' to the 'best'** state and the value **'6' to the 'worst'** state.

States	**Children from 0 to 4 years old**
A. The patient is Vitamin D deficient [25(OH)D <30nmol/L]. The child presents with hypocalcemic **cardiomyopathy**. The condition requires hospital care, including ventilation and inotropic support	
B. The patient is Vitamin D deficient [25(OH)D <30nmol/L]. The child presents with **hypocalcemic seizures** and requires hospitalisation	
C. The patient is Vitamin D deficient [25(OH)D <30nmol/L]. The child has **active rickets,** diagnosed through X-ray, and presents with skeletal abnormalities such as bowed legs, swollen ankles and/or deformed chest	
D. The child presents with **leg deformities** following active rickets (rickets healed in deformity). If not continuously supplemented with Vitamin D for life, the child may require surgery to correct deformities, and may develop active rickets again	
E. The patient is Vitamin D deficient [25(OH)D <30nmol/L]. The child presents with **pain and muscle weakness** and may show signs of **delay in motor milestones** and **poor growth**	
F. The patient is Vitamin D deficient, confirmed by serum concentration of [25(OH)D <30nmol/L]. The child may be in a pre-rickets state but nonetheless, the child is **asymptomatic**	

Task 2. Child Health Utility 9D (CHU9D) questionnaire

Instructions

These questions ask about how your patient is **today.** For each question, read all the choices and decide which one is most like your patient **today**.

Then put a tick in the box next to it like this ☑. Only tick **one** box for each question. Some questions have extra guidance with them as your patient is less than 5 years of age.

Example

Today the child feels quite upset so I will tick this box.

Upset

☐ The child doesn't feel upset today

☐ The child feels a little bit upset today

☐ The child feels a bit upset today

☑ The child feels quite upset today

☐ The child feels very upset today

Now please think about the presented HS and answer the rest of the questions below:

A. Consider the scenario in the box below, for a child aged between 0-4 years old with **cardiomyopathy (Health State A)**

The patient is severely Vitamin D deficient [25(OH)D <30nmol/L]. The child presents with hypocalcaemic **cardiomyopathy**. The condition requires hospital care, including ventilation and inotropic support.

1. Worried

☐ The child doesn't feel worried today

☐ The child feels a little bit worried today

☐ The child feels a bit worried today

☐ The child feels quite worried today

☐ The child feels very worried today

2. Sad

☐ The child doesn't feel sad today

☐ The child feels a little bit sad today

☐ The child feels a bit sad today

☐ The child feels quite sad today

☐ The child feels very sad today

3. Pain

☐ The child doesn't have any pain today

☐ The child has a little bit of pain today

☐ The child has a bit of pain today

☐ The child has quite a lot of pain today

☐ The child has a lot of pain today

4. Tired

☐ The child doesn't feel tired today

☐ The child feels a little bit tired today

☐ The child feels a bit tired today

☐ The child feels quite tired today

☐ The child feels very tired today

5. Annoyed

☐ The child doesn't feel annoyed today

☐ The child feels a little bit annoyed today

☐ The child feels a bit annoyed today

☐ The child feels quite annoyed today

☐ The child feels very annoyed today

6. School Work/Homework (such as reading, writing, doing lessons)

If your patient is at preschool/nursery/kindergarten, then please think about that. If your patient didn't go today because of their health and they usually would have, please tick the last option "The child can't do their schoolwork/homework today". If today is not a day they usually would have gone, then please think about how you think they would have been had they gone. If your patient does not go to preschool/nursery/kindergarten, then please think about whether they have had any problems with activities such as colouring, looking at books/reading, and concentrating, as appropriate for their age.

☐ The child has no problems with their schoolwork/homework today

☐ The child has a few problems with their schoolwork/homework today

☐ The child has some problems with their schoolwork/homework today

☐ The child has many problems with their schoolwork/homework today

☐ The child can't do their schoolwork/homework today

7. Sleep

☐ Last night the child had no problems sleeping

☐ Last night the child had a few problems sleeping

☐ Last night the child had some problems sleeping

☐ Last night the child had many problems sleeping

☐ Last night the child couldn't sleep at all

8. Daily routine (things like eating, having a bath/shower, getting dressed)

Please think about this question in terms of eating, drinking, toileting, washing and teeth cleaning, as appropriate for their age.

☐ The child has no problems with their daily routine today

☐ The child has a few problems with their daily routine today

☐ The child has some problems with their daily routine today

☐ The child has many problems with their daily routine today

☐ The child can’t do their daily routine today

9. Able to join in activities (things like playing out with their friends, doing sports, joining in things)

Please think about this question in terms of the activities your patient would usually be doing today.

☐ The child can join in with any activities today

☐ The child can join in with most activities today

☐ The child can join in with some activities today

☐ The child can join in with a few activities today

☐ The child can join in with no activities today

Part 3: About your practice

1. What is your speciality:

____

2. In which country do you practice:

____

3. How many cases of Rickets have you seen in the past two years:

____

Appendix 10 – EQ-5D Questionnaire

ESTIMATING THE QUALITY OF LIFE OF ADULTS WITH VITAMIN D DEFICIENCY

This questionnaire is part of a PhD project in Health Economics that aims to estimate the cost-effectiveness of interventions to prevent Vitamin D deficiency (VDD) in the UK.

With this questionnaire we intend to estimate the utility- based quality of life (QoL) of people with Vitamin D deficiency.

What is utility-based QoL? Worldwide, public health decision makers are faced with funding constraints and economic evaluation can assist with decision making by providing information on the comparative costs and consequences of alternative uses of health care budgets. Within economic evaluation, it is conventional practice to measure the consequences of a service/treatment using the unit of 'Quality-Adjusted Life Years' (QALYs). QALYs combine the length of life with quality of life (QoL), which is measured using a preference-based function whereby more weight is given to certain dimensions of QoL e.g. 'having no pain' might be seen as more important than 'being able to do usual activities'.

There is a lack of evidence in the literature about the utility-based QoL of a person with osteomalacia and other conditions caused by VDD. I need this information to conduct a comprehensive economic evaluation of interventions to prevent VDD and its complications in the UK.

We are asking you to complete this questionnaire because you are an expert in the field and we would very much appreciate you taking the time to answer the following questions. There are no right or wrong answers and all responses will be taken into account.

What we ask you to do:

In the following pages we ask you to complete two different types of tasks:

Task 1 asks you to rank health states related to VDD according to their severity. This will help us understand VDD and its consequences better.

Task 2 presents a questionnaire designed to understand the QoL associated with each health state. This questionnaire has been developed specifically for a paediatric population and will allow us to estimate the QALYs lost in each health state. Each scenario is hypothetical so we ask you to think as if you have seen in your practice a patient with the described health state **today**.

The questionnaire is divided in **two parts**. The **first part** asks about **young adults (from 19 to 60 years)** and the **second part** about **older adults (over 60 years)**. For each age group, we have defined the relevant health states that you need to consider for a person with Vitamin D deficiency. This resulted in **two health states** for young adults and **six health states** for older adults.

We welcome any comments and queries regarding this questionnaire. If you have some, please contact Magda Aguiar:

Thank you for your collaboration!

Task 1. Ranking health states by severity

Please rank the following 6 states, giving the **value '1' to the 'best'** state and the value **'6' to the 'worst'** state.

States	**Young adults (19-60 years)**
A. The patient is Vitamin D deficient [25(OH)] <30nmol/L]. He/she presents with diffuse bone pain and muscle weakness**,** elevated ALP and secondary hyperparathyroidism. The muscles affected are mostly thighs, shoulders and main trunk of the body. Physical activities, such as climbing stairs or getting up from a chair without using the arms for support, may be limited. The patient has consequently been diagnosed with **osteomalacia**.	
B. The patient has osteomalacia. He/she presents with localised bone pain, diagnosed as **pseudofracture (Looser zone**). The patients reports that the pain is persistent during day and night and shows sign of distress.	
G. The patient is Vitamin D deficient [25(OH)] <30nmol/L**]**. The patient is considered to be **asymptomatic**.	

Task 2. The EQ-5D questionnaire

PART 1: Young adults (19 to 60 years old)

Under each heading, please tick the ONE box that you think best describes your patient's health TODAY.

The patient is Vitamin D deficient [25(OH)] <30nmol/L]. He/she presents with ***diffuse bone pain and muscle weakness,*** *elevated ALP and secondary hyperparathyroidism. The muscles affected are mostly thighs, shoulders and main trunk of the body. Physical activities, such as climbing stairs or getting up from a chair without using the arms for support, may be limited. The patient has consequently been diagnosed with* ***osteomalacia****.*

MOBILITY

No problems in walking about ❑
Slight problems in walking about ❑
Moderate problems in walking about ❑
Severe problems in walking about ❑
Unable to walk about ❑

SELF-CARE

No problems washing or dressing him/herself ❑
Slight problems washing or dressing him/herself ❑
Moderate problems washing or dressing him/herself ❑
Severe problems washing or dressing him/herself ❑
Unable to wash or dress him/herself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

No problems doing his/her usual activities ❑
Slight problems doing his/her usual activities ❑
Moderate problems doing his/her usual activities ❑
Severe problems doing his/her usual activities ❑
Unable to do his/her usual activities ❑

PAIN / DISCOMFORT

No pain or discomfort ❑
Slight pain or discomfort ❑
Moderate pain or discomfort ❑
Severe pain or discomfort ❑
Extreme pain or discomfort ❑

ANXIETY / DEPRESSION

Not anxious or depressed ❑
Slightly anxious or depressed ❑
Moderately anxious or depressed ❑
Severely anxious or depressed ❑
Extremely anxious or depressed ❑

Task 3: About your practice

1. What is your speciality:

____

2. In which country do you practice:

____

3. How many cases of Osteomalacia have you seen in the past two years:

____

Appendix 11 – Results from the CHU9D

Cardiomyopathy		
CHU9D Dimension	Level	0-4 year old
Worried	Level 1	2.6%
	Level 2	0.0%
	Level 3	7.9%
	Level 4	23.7%
	Level 5	65.8%
Sad	Level 1	2.6%
	Level 2	0.0%
	Level 3	13.2%
	Level 4	26.3%
	Level 5	57.9%
Pain	Level 1	5.3%
	Level 2	18.4%
	Level 3	23.7%
	Level 4	31.6%
	Level 5	21.1%
Tired	Level 1	0.0%
	Level 2	10.5%
	Level 3	26.3%
	Level 4	63.2%
	Level 5	0.0%
Annoyed	Level 1	2.6%
	Level 2	2.6%
	Level 3	23.7%
	Level 4	47.4%
	Level 5	23.7%
School Work/Homework	Level 1	0.0%
	Level 2	7.9%
	Level 3	10.5%
	Level 4	7.9%
	Level 5	73.7%
Sleep	Level 1	7.9%
	Level 2	10.5%
	Level 3	23.7%
	Level 4	34.2%
	Level 5	23.7%
Daily routine	Level 1	2.6%
	Level 2	5.3%
	Level 3	2.6%
	Level 4	15.8%
	Level 5	73.7%
Able to join in activities	Level 1	2.6%
	Level 2	5.3%
	Level 3	2.6%
	Level 4	15.8%
	Level 5	73.7%

Hypocalcemic seizures		
CHU9D Dimension	Level	0-4 year old
Worried	Level 1	2.6%
	Level 2	2.6%
	Level 3	5.3%
	Level 4	26.3%
	Level 5	63.2%
Sad	Level 1	5.3%
	Level 2	2.6%
	Level 3	10.5%
	Level 4	36.8%
	Level 5	44.7%
Pain	Level 1	7.9%
	Level 2	15.8%
	Level 3	28.9%
	Level 4	31.6%
	Level 5	15.8%
Tired	Level 1	0.0%
	Level 2	7.9%
	Level 3	18.4%
	Level 4	34.2%
	Level 5	39.5%
Annoyed	Level 1	2.6%
	Level 2	2.6%
	Level 3	26.3%
	Level 4	47.4%
	Level 5	21.1%
School Work/Homework	Level 1	0.0%
	Level 2	2.6%
	Level 3	13.2%
	Level 4	15.8%
	Level 5	68.4%
Sleep	Level 1	2.6%
	Level 2	15.8%
	Level 3	28.9%
	Level 4	39.5%
	Level 5	13.2%
Daily routine	Level 1	2.6%
	Level 2	7.9%
	Level 3	5.3%
	Level 4	39.5%
	Level 5	44.7%
Able to join in activities	Level 1	2.6%
	Level 2	15.8%
	Level 3	28.9%
	Level 4	39.5%
	Level 5	13.2%

Active rickets			
CHU9D Dimension	Level	0-4 year old	5-18 years old
Worried	Level 1	2.6%	0.0%
	Level 2	18.4%	13.2%
	Level 3	47.4%	28.9%
	Level 4	28.9%	21.1%
	Level 5	2.6%	36.8%
Sad	Level 1	0.0%	2.6%
	Level 2	26.3%	10.5%
	Level 3	55.3%	31.6%
	Level 4	15.8%	28.9%
	Level 5	2.6%	26.3%
Pain	Level 1	5.3%	0.0%
	Level 2	10.5%	18.4%
	Level 3	42.1%	34.2%
	Level 4	28.9%	21.1%
	Level 5	13.2%	26.3%
Tired	Level 9	5.3%	0.0%
	Level 1	10.5%	15.8%
	Level 2	42.1%	26.3%
	Level 3	28.9%	44.7%
	Level 4	13.2%	13.2%
Annoyed	Level 1	5.3%	0.0%
	Level 2	18.4%	15.8%
	Level 3	52.6%	31.6%
	Level 4	18.4%	23.7%
	Level 5	5.3%	28.9%
School Work/Homework	Level 1	7.9%	5.3%
	Level 2	36.8%	21.1%
	Level 3	34.2%	42.1%
	Level 4	10.5%	21.1%
	Level 5	10.5%	10.5%
Sleep	Level 1	18.4%	18.4%
	Level 2	36.8%	13.2%
	Level 3	39.5%	50.0%
	Level 4	2.6%	10.5%
	Level 5	2.6%	7.9%
Daily routine	Level 1	5.3%	5.3%
	Level 2	34.2%	18.4%
	Level 3	44.7%	47.4%
	Level 4	10.5%	21.1%
	Level 5	5.3%	7.9%
Able to join in activities	Level 1	0.0%	2.6%
	Level 2	26.3%	7.9%
	Level 3	28.9%	42.1%
	Level 4	34.2%	18.4%
	Level 5	10.5%	28.9%

Leg deformities			
CHU9D Dimension	**Level**	**0-4 year old**	**5-18 years old**
Worried	Level 1	26.3%	10.5%
	Level 2	36.8%	21.1%
	Level 3	31.6%	31.6%
	Level 4	5.3%	31.6%
	Level 5	0.0%	5.3%
Sad	Level 1	28.9%	5.3%
	Level 2	44.7%	31.6%
	Level 3	21.1%	28.9%
	Level 4	5.3%	31.6%
	Level 5	0.0%	2.6%
Pain	Level 1	28.9%	15.8%
	Level 2	36.8%	39.5%
	Level 3	28.9%	34.2%
	Level 4	5.3%	7.9%
	Level 5	0.0%	2.6%
Tired	Level 9	28.9%	18.4%
	Level 1	44.7%	47.4%
	Level 2	21.1%	21.1%
	Level 3	2.6%	10.5%
	Level 4	2.6%	2.6%
Annoyed	Level 1	15.8%	23.7%
	Level 2	65.8%	21.1%
	Level 3	15.8%	39.5%
	Level 4	2.6%	13.2%
	Level 5	0.0%	2.6%
School Work/Homework	Level 1	36.8%	34.2%
	Level 2	47.4%	34.2%
	Level 3	10.5%	26.3%
	Level 4	2.6%	2.6%
	Level 5	2.6%	2.6%
Sleep	Level 1	63.2%	36.8%
	Level 2	31.6%	47.4%
	Level 3	2.6%	10.5%
	Level 4	2.6%	2.6%
	Level 5	0.0%	2.6%
Daily routine	Level 1	34.2%	28.9%
	Level 2	55.3%	39.5%
	Level 3	5.3%	21.1%
	Level 4	5.3%	7.9%
	Level 5	0.0%	2.6%
Able to join in activities	Level 1	0.0%	7.9%
	Level 2	55.3%	34.2%
	Level 3	39.5%	47.4%
	Level 4	5.3%	7.9%
	Level 5	0.0%	2.6%

Pain and muscle weakness			
CHU9D Dimension	**Level**	**0-4 year old**	**5-18 years old**
Worried	Level 1	13.2%	5.3%
	Level 2	21.1%	5.3%
	Level 3	15.8%	39.5%
	Level 4	47.4%	44.7%
	Level 5	2.6%	5.3%
Sad	Level 1	13.2%	5.3%
	Level 2	13.2%	10.5%
	Level 3	26.3%	42.1%
	Level 4	42.1%	34.2%
	Level 5	5.3%	7.9%
Pain	Level 1	7.9%	7.9%
	Level 2	15.8%	0.0%
	Level 3	28.9%	44.7%
	Level 4	36.8%	34.2%
	Level 5	10.5%	13.2%
Tired	Level 9	5.3%	5.3%
	Level 1	21.1%	7.9%
	Level 2	23.7%	50.0%
	Level 3	39.5%	26.3%
	Level 4	10.5%	10.5%
Annoyed	Level 1	5.3%	5.3%
	Level 2	31.6%	7.9%
	Level 3	26.3%	52.6%
	Level 4	28.9%	26.3%
	Level 5	7.9%	7.9%
School Work/Homework	Level 1	7.9%	7.9%
	Level 2	23.7%	23.7%
	Level 3	36.8%	50.0%
	Level 4	18.4%	13.2%
	Level 5	13.2%	5.3%
Sleep	Level 1	10.5%	13.2%
	Level 2	42.1%	28.9%
	Level 3	31.6%	47.4%
	Level 4	10.5%	10.5%
	Level 5	5.3%	0.0%
Daily routine	Level 1	10.5%	94.7%
	Level 2	23.7%	5.3%
	Level 3	36.8%	0.0%
	Level 4	23.7%	0.0%
	Level 5	5.3%	0.0%
Able to join in activities	Level 1	7.9%	84.2%
	Level 2	10.5%	15.8%
	Level 3	31.6%	0.0%
	Level 4	44.7%	0.0%
	Level 5	5.3%	0.0%

Asymptomatic			
CHU9D Dimension	**Level**	**0-4 years**	**5-18 years**
Worried	Level 1	94.7%	89.5%
	Level 2	5.3%	10.5%
	Level 3	0.0%	0.0%
	Level 4	0.0%	0.0%
	Level 5	0.0%	0.0%
Sad	Level 1	89.5%	86.8%
	Level 2	10.5%	13.2%
	Level 3	0.0%	0.0%
	Level 4	0.0%	0.0%
	Level 5	0.0%	0.0%
Pain	Level 1	73.7%	78.9%
	Level 2	23.7%	21.1%
	Level 3	2.6%	0.0%
	Level 4	0.0%	0.0%
	Level 5	0.0%	0.0%
Tired	Level 9	73.7%	60.5%
	Level 1	23.7%	39.5%
	Level 2	2.6%	0.0%
	Level 3	0.0%	0.0%
	Level 4	0.0%	0.0%
Annoyed	Level 1	86.8%	86.8%
	Level 2	10.5%	10.5%
	Level 3	2.6%	2.6%
	Level 4	0.0%	0.0%
	Level 5	0.0%	0.0%
School Work/Homework	Level 1	84.2%	86.8%
	Level 2	15.8%	10.5%
	Level 3	0.0%	2.6%
	Level 4	0.0%	0.0%
	Level 5	0.0%	0.0%
Sleep	Level 1	94.7%	94.7%
	Level 2	5.3%	5.3%
	Level 3	0.0%	0.0%
	Level 4	0.0%	0.0%
	Level 5	0.0%	0.0%
Daily routine	Level 1	92.1%	94.7%
	Level 2	7.9%	5.3%
	Level 3	0.0%	0.0%
	Level 4	0.0%	0.0%
	Level 5	0.0%	0.0%
Able to join in activities	Level 1	84.2%	84.2%
	Level 2	13.2%	15.8%
	Level 3	2.6%	0.0%
	Level 4	0.0%	0.0%
	Level 5	0.0%	0.0%

Appendix 12 – Results from the EQ-5D questionnaire

Hip fracture nursing home		
EQ-5D Dimension		**65+**
Mobility	Level 1	0.0%
	Level 2	0.0%
	Level 3	10.0%
	Level 4	50.0%
	Level 5	40.0%
Self-care	Level 1	0.0%
	Level 2	0.0%
	Level 3	30.0%
	Level 4	40.0%
	Level 5	30.0%
Usual activity	Level 1	0.0%
	Level 2	0.0%
	Level 3	10.0%
	Level 4	20.0%
	Level 5	70.0%
Pain / Discomfort	Level 1	0.0%
	Level 2	10.0%
	Level 3	50.0%
	Level 4	40.0%
	Level 5	0.0%
Anxiety / Depression	Level 1	0.0%
	Level 2	0.0%
	Level 3	10.0%
	Level 4	70.0%
	Level 5	20.0%

Hip fracture community		
EQ-5D Dimension		**65+**
Mobility	Level 1	0.0%
	Level 2	10.0%
	Level 3	10.0%
	Level 4	80.0%
	Level 5	0.0%
Self-care	Level 1	10.0%
	Level 2	30.0%
	Level 3	30.0%
	Level 4	30.0%
	Level 5	0.0%
Usual activity	Level 1	0.0%
	Level 2	10.0%
	Level 3	60.0%
	Level 4	30.0%
	Level 5	0.0%
Pain / Discomfort	Level 1	0.0%
	Level 2	30.0%
	Level 3	40.0%
	Level 4	30.0%
	Level 5	0.0%
Anxiety / Depression	Level 1	0.0%
	Level 2	40.0%
	Level 3	50.0%
	Level 4	0.0%
	Level 5	10.0%

Minor fracture		
EQ-5D Dimension	**Level**	**65+**
Mobility	Level 1	0.0%
	Level 2	10.0%
	Level 3	70.0%
	Level 4	20.0%
	Level 5	0.0%
Self-care	Level 1	10.0%
	Level 2	30.0%
	Level 3	30.0%
	Level 4	30.0%
	Level 5	0.0%
Usual activity	Level 1	0.0%
	Level 2	10.0%
	Level 3	60.0%
	Level 4	30.0%
	Level 5	0.0%
Pain / Discomfort	Level 1	0.0%
	Level 2	30.0%
	Level 3	40.0%
	Level 4	30.0%
	Level 5	0.0%
Anxiety / Depression	Level 1	0.0%
	Level 2	40.0%
	Level 3	50.0%
	Level 4	0.0%
	Level 5	10.0%

Fear falling		
EQ-5D Dimension	**Level**	**65+ years**
Mobility	Level 1	0.0%
	Level 2	10.0%
	Level 3	50.0%
	Level 4	40.0%
	Level 5	0.0%
Self-care	Level 1	10.0%
	Level 2	20.0%
	Level 3	50.0%
	Level 4	20.0%
	Level 5	0.0%
Usual activity	Level 1	0.0%
	Level 2	10.0%
	Level 3	40.0%
	Level 4	40.0%
	Level 5	10.0%
Pain / Discomfort	Level 1	10.0%
	Level 2	30.0%
	Level 3	40.0%
	Level 4	20.0%
	Level 5	0.0%
Anxiety / Depression	Level 1	0.0%
	Level 2	0.0%
	Level 3	30.0%
	Level 4	30.0%
	Level 5	40.0%

Looser Zone			
EQ-5D Dimension	**Level**	**19-64 years**	**65+ years**
Mobility	Level 1	60.0%	0.0%
	Level 2	20.0%	10.0%
	Level 3	0.0%	50.0%
	Level 4	0.0%	30.0%
	Level 5	0.0%	10.0%
Self-care	Level 1	80.0%	0.0%
	Level 2	20.0%	40.0%
	Level 3	0.0%	30.0%
	Level 4	0.0%	30.0%
	Level 5	0.0%	0.0%
Usual activity	Level 1	70.0%	0.0%
	Level 2	20.0%	20.0%
	Level 3	10.0%	30.0%
	Level 4	0.0%	50.0%
	Level 5	0.0%	0.0%
Pain / Discomfort	Level 1	80.0%	0.0%
	Level 2	20.0%	10.0%
	Level 3	0.0%	20.0%
	Level 4	0.0%	60.0%
	Level 5	0.0%	10.0%
Anxiety / Depression	Level 1	70.0%	0.0%
	Level 2	30.0%	10.0%
	Level 3	0.0%	50.0%
	Level 4	0.0%	40.0%
	Level 5	0.0%	0.0%

Pain and Muscle Weakness			
EQ-5D Dimension	**Level**	**19-64 years**	**65+ years**
Mobility	Level 1	0.0%	0.0%
	Level 2	0.0%	0.0%
	Level 3	60.0%	50.0%
	Level 4	40.0%	50.0%
	Level 5	0.0%	0.0%
Self-care	Level 1	10.0%	0.0%
	Level 2	0.0%	10.0%
	Level 3	40.0%	50.0%
	Level 4	50.0%	40.0%
	Level 5	0.0%	0.0%
Usual activity	Level 1	0.0%	0.0%
	Level 2	0.0%	20.0%
	Level 3	40.0%	30.0%
	Level 4	60.0%	40.0%
	Level 5	0.0%	10.0%
Pain / Discomfort	Level 1	0.0%	0.0%
	Level 2	10.0%	10.0%
	Level 3	40.0%	50.0%
	Level 4	50.0%	40.0%
	Level 5	0.0%	0.0%
Anxiety / Depression	Level 1	10.0%	0.0%
	Level 2	0.0%	40.0%
	Level 3	60.0%	20.0%
	Level 4	30.0%	40.0%
	Level 5	0.0%	0.0%

Asymptomatic			
EQ-5D Dimension	**Level**	**19-64 years**	**65+ years**
Mobility	Level 1	60.0%	30.0%
	Level 2	40.0%	70.0%
	Level 3	0.0%	0.0%
	Level 4	0.0%	0.0%
	Level 5	0.0%	0.0%
Self-care	Level 1	80.0%	70.0%
	Level 2	20.0%	30.0%
	Level 3	0.0%	0.0%
	Level 4	0.0%	0.0%
	Level 5	0.0%	0.0%
Usual activity	Level 1	70.0%	30.0%
	Level 2	20.0%	60.0%
	Level 3	10.0%	10.0%
	Level 4	0.0%	0.0%
	Level 5	0.0%	0.0%
Pain / Discomfort	Level 1	70.0%	40.0%
	Level 2	20.0%	60.0%
	Level 3	10.0%	0.0%
	Level 4	0.0%	0.0%
	Level 5	0.0%	0.0%
Anxiety / Depression	Level 1	0.0%	60.0%
	Level 2	40.0%	30.0%
	Level 3	20.0%	10.0%
	Level 4	40.0%	0.0%
	Level 5	0.0%	0.0%

Appendix 13 – Model Inputs

A.1 Transitions to the VDD health state

Population group (Age, sex, ethnicity)	Deterministic (point estimate)	Probabilistic (distribution)	Source
No intervention arm			
1.5-4 years, all, white	0.075	Beta	NDNS (1)
5-18 years, male, white	0.21	Beta	NDNS (1)
5-18 years, female, white	0.21	Beta	NDNS (1)
19-64 years, male, white	0.6	Beta	NDNS (1)
19-64 years, female, white	0.58	Beta	NDNS (1)
>65 years, male, white	0.58	Beta	NDNS (1)
>65 years, female, white	0.71	Beta	NDNS (1)
1.5-17 years, all, BAME	0.47	Beta	NDNS (1)
18 years, all, BAME	0.85	Beta	NDNS (1)
Flour fortification arm			
1.5-4 years, all, white	0.05	Beta	Estimated based in Allen's model (214)
5-18 years, male, white	0.07	Beta	Estimated based in Allen's model (214)
5-18 years, female, white	0.08	Beta	Estimated based in Allen's model (214)
19-64 years, male, white	0.45	Beta	Estimated based in Allen's model (214)
19-64 years, female, white	0.48	Beta	Estimated based in Allen's model (214)
>65 years, male, white	0.41	Beta	Estimated based in Allen's model (214)
>65 years, female, white	0.48	Beta	Estimated based in Allen's model (214)
1.5-17 years, all, BAME	0.35	Beta	Estimated based in Allen's model (214)
18 years, all, BAME	0.73	Beta	Estimated based in Allen's model (214)

A.2. Transitions within the VDD health state

Health State	Deterministic (point estimate)	Probabilistic (distribution)	Source
Rickets			
White ethnicity	0.00053	Beta	Callaghan et al. (3)
BAME	0.0014	Beta	Callaghan et al. (3)
Hypocalcemic seizures	0.25	Beta	Callaghan et al. (3)
Poor Bone Health	0.5	Beta	Callaghan et al. (3)
Cardiomyopathy	0.001	Beta	Assumption
Osteomalacia	0.42	Beta	Priemel et al. (223)
Falls if VDD	0.11	Beta	Estimated based on Suzuki et al. (225), Annweiler et al. (227) and Beauchet et al. (226)
Minor injury after fall			
65-69 years	2.4	Beta	Poole et al. (128)
70-74 years	2.8	Beta	Poole et al. (128)
75+ years	5.8	Beta	Poole et al. (128)
Major injury after fall			
65-69 years	0.5	Beta	Poole et al. (128)
70-74 years	0.9	Beta	Poole et al. (128)
75+ years	3.7	Beta	Poole et al. (128)

B. Utilities

Infants and Young children (0-4)			
Health State	**Deterministic (point estimate)**	**Probabilistic (distribution)**	**Source**
Active Rickets	0.62	Beta	Primary data collection
Cardiomyopathy	0.46	Beta	Primary data collection
Seizures	0.49	Beta	Primary data collection
Leg deformities	0.76	Beta	Primary data collection
Pain and muscle weakness	0.61	Beta	Primary data collection
Asymptomatic	0.95	Beta	Primary data collection
Children and Adolescents (5-17)			
Active Rickets	0.57	Beta	Primary data collection
Leg deformities	0.71	Beta	Primary data collection
Pain and muscle weakness	0.61	Beta	Primary data collection
Asymptomatic	0.95	Beta	Primary data collection
Young adults (18-64)			
Looser zone	0.31	Beta	Primary data collection
Pain and muscle weakness	0.3	Beta	Primary data collection
Asymptomatic	0.87	Beta	Primary data collection
Adults (over 65)			
Hip fracture + nursing home	-0.05	Gamma*	Primary data collection
Hip fracture + community	0.2	Gamma*	Primary data collection
Fear of falling	0.24	Beta	Primary data collection
Minor fracture	0.41	Beta	Primary data collection
Looser zone	0.23	Beta	Primary data collection
Pain and muscle weakness	0.31	Beta	Primary data collection
Asymptomatic	0.77	Beta	Primary data collection

* Negative utility transformation method was applied

C.1. Costs

Item	Deterministic (point estimate)	Probabilistic (distribution)	Source
Clinical outcomes			
Cardiomyopathy (per case)	10,000.00	Gamma	Assumption
Long-term Care (per case)	16,755.00	Gamma	Poole et al. (128)
Major Injury (per case)	2,827.89	Gamma	Poole et al. (128)
Minor Injury (per case)	466.20	Gamma	Poole et al. (128)
Rickets (per case)	3,088.60	Gamma	Zipitis et al. (238)
Flour fortification related costs			
Enforcement	12,383.00	Gamma	FSA (231)
Labelling (per person)	10.70	Gamma	FSA (231)
Vitamin D Fortificant	1.57	Gamma	Consultation
Supplementation programme related costs			
National campaign	2,000,000.00	Gamma	Brown et al. (236)
Electronic card	0.60	Gamma	Lewisham cost report
Electronic card reader	38.80	Gamma	Lewisham cost report
Pharmacy Enrolment	75.00	Gamma	Lewisham cost report
Pharmacy incentive (per supplement dispensed)	0.30	Gamma	Lewisham cost report
Software Annual License	2,400.00	Gamma	Lewisham cost report
Software Purchase	6,000.00	Gamma	Lewisham cost report
Training video	2,500.00	Gamma	Lewisham cost report
Child supplements	8.99	Gamma	Healthy Start Vitamin
Older adults' supplements	43.20	Gamma	BNF (237)
Younger adults' supplements	4.82	Gamma	Healthy Start Vitamin

REFERENCES

1. Bates B, Lennox A, Prentice A, Bates C, Page P, Nicholson S, et al. National Diet and Nutrition Survey Results from Years 1, 2, 3 and 4 (combined) of the Rolling Programme (2008/2009 – 2011/2012). Public Health Engand and Food Standards Agency; 2014. Report No.: 1910535338.

2. Bates B, Lennox A, Prentice A, Bates C, Page P, Nicholson S, et al. National Diet and Nutrition Survey Results from Years 5 and 6 (combined) of the Rolling Programme (2012/2013 – 2013/2014) Public Health Engand and the Food Standards Agency

2016.

3. Callaghan AL, Moy R, Booth IW, Debelle G, Shaw NJ. Incidence of symptomatic vitamin D deficiency. Archives of Disease in Childhood. 2006;91(7):606-7.

4. Högler W. Complications of vitamin D deficiency from the foetus to the infant: One cause, one prevention, but who's responsibility? Best Practice & Research Clinical Endocrinology & Metabolism. 2015;29(3):385-98.

5. Caulfield T, Clark MI, McCormack JP, Rachul C, Field CJ. Representations of the health value of vitamin D supplementation in newspapers: media content analysis. BMJ open. 2014;4(12):e006395.

6. National Institute for Health and Care Excellence (NICE). Vitamin D: increasing supplement use among at-risk groups. 2014.

7. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS) statement. Cost Effectiveness and Resource Allocation. 2013;11(1):6.

8. Ovesen L, Brot C, Jakobsen J. Food contents and biological activity of 25-hydroxyvitamin D: a vitamin D metabolite to be reckoned with? Annals of Nutrition and Metabolism. 2003;47(3-4):107-13.

9. Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. Am J Physiol Renal Physiol. 2005;289(1):F8-28.

10. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism. 2011;96(7):1911-30.

11. Deluca HF. Historical overview of vitamin D. Feldman D, Wesley Pike J, Adams JS. 2011;1.

12. Allen LH. Guidelines on food fortification with micronutrients. Guidelines on food fortification with micronutrients: World Health Organization. Dept. of Nutrition for Health and Development; 2006.

13. Gouni-Berthold I, Krone W, Berthold HK. Vitamin D and cardiovascular disease. Curr Vasc Pharmacol. 2009;7(3):414-22.

14. Scientific Advisory Committee on Nutrition (SACN). Vitamin D and Health. Public Health England; 2016.

15. Holick MF. Vitamin D Deficiency. New England Journal of Medicine. 2007;357(3):266-81.

16. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. The American journal of clinical nutrition. 2006;84(1):18-28.

17. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, et al. Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. Journal of Clinical Endocrinology and Metabolism. 2016;101(2):394-415.

18. Department of Health. Nutrition and bone health: with particular reference to calcium and vitamin D. Report of the Subgroup on Bone Health, Working Group on the Nutritional Status of the Population of the Committee on Medical Aspects of the Food Nutrition Policy. London; 1998. Report No.: 0300-8045.

19. Institute of Medicine (IOM). Dietary reference intakes for calcium and vitamin D: National Academies Press; 2011.

20. Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? Br J Nutr. 2003;89(5):552-72.

21. McCollum EV, Simmonds N, BeckerJE SP. Studies on experimental rickets. XXI. An experimental demonstration of the existence of a vitamin which promotes calcium deposition. J Biol Chem. 1922;53.

22. Mozoåowski W. Jäccaron; drzej Sniadecki (1768–1838) on the Cure of Rickets. Nature. 1939;143:121-.

23. Palm T. The geographic distribution and etiology of rickets. Practitioner. 1890;45(270-279):321-42.

24. Rajakumar K, Greenspan SL, Thomas SB, Holick MF. Solar ultraviolet radiation and Vitamin D. Journal Information. 2007;97(10).

25. Chesney RW. Theobald palm and his remarkable observation: how the sunshine vitamin came to be recognized. Nutrients. 2012;4(1):42-51.

26. Morii H, Lund J, Neville P, DeLuca H. Biological activity of a vitamin D metabolite. Archives of Biochemistry and Biophysics. 1967;120(3):508-12.

27. Whiting S, Calvo M, Stephensen C. Current Understanding of Vitamin D Metabolism, Nutritional Status, and Role in Disease Prevention. In: Carol J. Boushey MGF, Linda M. Delahanty, editor. Nutrition in the Prevention and Treatment of Disease: Academic Press; 2008. p. 937-67.

28. Stamp TC, Haddad JG, Twigg CA. Comparison of oral 25-hydroxycholecalciferol, vitamin D, and ultraviolet light as determinants of circulating 25-hydroxyvitamin D. Lancet. 1977;1(8026):1341-3.

29. Jakobsen J, Knuthsen P. Stability of vitamin D in foodstuffs during cooking. Food chemistry. 2014;148:170-5.

30. G R, Gupta A. Fortification of foods with vitamin D in India. Nutrients. 2014;6(9):3601-23.

31. The Spreadable Fats (Marketing Standards) and the Milk and Milk Products (Protection of Designations) (England) Regulations 2008 2008 No. 1287 (2008).

32. The Spreadable Fats, Milk and Milk Products (Scotland) Regulations 2008 2008 No. 216 (2008).

33. Spreadable Fats (Marketing Standards) and the Milk and Milk Products (Protection of Designations) Regulations (Northern Ireland), No. 239 (2008).

34. The Spreadable Fats (Marketing Standards) and the Milk and Milk Products (Protection of Designations) (Wales) Regulations, 1341 (2008).

35. Pearce S, Cheetham TD. Diagnosis and management of vitamin D deficiency. Bmj. 2010;340(7738):142-7.

36. Calvo MS, Whiting SJ, Barton CN. Vitamin D fortification in the United States and Canada: current status and data needs. The American journal of clinical nutrition. 2004;80(6):1710S-6S.

37. Spiro A, Buttriss JL. Vitamin D: An overview of vitamin D status and intake in Europe. Nutrition Bulletin 2014;39(4):322-50.

38. Driscoll Jr R, Meredith S, Sitrin M, Rosenberg I. Vitamin D deficiency and bone disease in patients with Crohn's disease. Gastroenterology. 1982;83(6):1252-8.

39. Young AR. Some light on the photobiology of vitamin D. Journal of Investigative Dermatology. 2010;130(2):346-8.

40. Holick MF. McCollum Award Lecture, 1994: vitamin D--new horizons for the 21st century. The American journal of clinical nutrition. 1994;60(4):619-30.

41. Hoteit M, Al-Shaar L, Yazbeck C, Bou Sleiman M, Ghalayini T, El-Hajj Fuleihan G. Hypovitaminosis D in a sunny country: Time trends, predictors, and implications for practice guidelines. Metabolism. 2014.

42. Christie FT, Mason L. Knowledge, attitude and practice regarding vitamin D deficiency among female students in Saudi Arabia: a qualitative exploration. International Journal of Rheumatic Diseases. 2011;14(3):22-9.

43. Ozkan B, Doneray H, Karacan M, Vancelik S, Yildirim ZK, Ozkan A, et al. Prevalence of vitamin D deficiency rickets in the eastern part of Turkey. Eur J Pediatr. 2009;168(1):95-100.

44. G R, Gupta A. Vitamin D Deficiency in India: Prevalence, Causalities and Interventions. Nutrients. 2014;6(2):729-75.

45. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. The American journal of clinical nutrition. 2000;72(3):690-3.

46. NICE. NICE guidelines [PH11]. National Institute for Health and Clinical Excellence 2008.

47. Cashman KD, Dowling KG, Skrabakova Z, Gonzalez-Gross M, Valtuena J, De Henauw S, et al. Vitamin D deficiency in Europe: pandemic? The American journal of clinical nutrition. 2016;103(4):1033-44.

48. Hilger J, Friedel A, Herr R, Rausch T, Roos F, Wahl DA, et al. A systematic review of vitamin D status in populations worldwide. British Journal of Nutrition. 2014;111(1):23-45.

49. Granlund L, Ramnemark A, Andersson C, Lindkvist M, Fhärm E, Norberg M. Prevalence of vitamin D deficiency and its association with nutrition, travelling and clothing habits in an immigrant population in Northern Sweden. European journal of clinical nutrition. 2016;70(3):373.

50. Andersson Å, Björk A, Kristiansson P, Johansson G. Vitamin D intake and status in immigrant and native Swedish women: a study at a primary health care centre located at 60 N in Sweden. Food & Nutrition Research. 2013;57(1):20089.

51. Hyppönen E, Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. The American journal of clinical nutrition. 2007;85(3):860-8.

52. Patel JV, Chackathayil J, Hughes EA, Webster C, Lip GY, Gill PS. Vitamin D deficiency amongst minority ethnic groups in the UK: a cross sectional study. Int J Cardiol. 2013;167(5):2172-6.

53. van der Meer IM, Middelkoop BJC, Boeke AJP, Lips P. Prevalence of vitamin D deficiency among Turkish, Moroccan, Indian and sub-Sahara African populations in Europe and their countries of origin: an overview. Osteoporosis International. 2011;22(4):1009-21.

54. Ford L, Graham V, Wall A, Berg J. Vitamin D concentrations in an UK inner-city multicultural outpatient population. Annals of clinical biochemistry. 2006;43(6):468-73.

55. Ashwell M, Stone EM, Stolte H, Cashman KD, Macdonald H, Lanham-New S, et al. UK Food Standards Agency Workshop Report: an investigation of the relative contributions of diet and sunlight to vitamin D status. Br J Nutr. 2010;104(4):603-11.

56. Lerch C, Meissner T. Interventions for the prevention of nutritional rickets in term born children. The Cochrane Library. 2007.

57. Bhan A, Rao AD, Rao DS. Osteomalacia as a result of vitamin D deficiency. Endocrinology and metabolism clinics of North America. 2010;39(2):321-31.

58. Cooper MS, Gittoes NJL. Diagnosis and management of hypocalcaemia. BMJ : British Medical Journal. 2008;336(7656):1298-302.

59. Sanyal D, Raychaudhuri M. Infants with dilated cardiomyopathy and hypocalcemia. Indian journal of endocrinology and metabolism. 2013;17(Suppl1):S221.

60. Elidrissy ATH, Munawarah M, Alharbi KM. Hypocalcemic rachitic cardiomyopathy in infants. Journal of the Saudi Heart Association. 2013;25(1):25-33.

61. Yilmaz O, Olgun H, Ciftel M, Kilic O, Kartal I, Iskenderoglu NY, et al. Dilated cardiomyopathy secondary to rickets-related hypocalcaemia: eight case reports and a review of the literature. Cardiology in the young. 2015;25(02):261-6.

62. Tomar M, Radhakrishnan S, Shrivastava S. Myocardial dysfunction due to hypocalcemia. Indian pediatrics. 2010;47(9):781-3.

63. Balasubramanian S, Shivbalan S, Kumar PS. Hypocalcemia due to vitamin D deficiency in exclusively breastfed infants. Indian pediatrics. 2006;43(3):247.

64. Maiya S, Sullivan I, Allgrove J, Yates R, Malone M, Brain C, et al. Hypocalcaemia and vitamin D deficiency: an important, but preventable, cause of life-threatening infant heart failure. Heart. 2008;94(5):581-4.

65. Brown J, Nunez S, Russell M, Spurney C. Hypocalcemic rickets and dilated cardiomyopathy: case reports and review of literature. Pediatric cardiology. 2009;30(6):818-23.

66. Bublik N, Alvarez JA, Lipshultz SE. Pediatric cardiomyopathy as a chronic disease: a perspective on comprehensive care programs. Progress in Pediatric cardiology. 2008;25(1):103-11.

67. Cesur Y, Yuca S, Kaya A, Yilmaz C, Bay A. Vitamin D deficiency rickets in infants presenting with hypocalcaemic convulsions. The West Indian medical journal. 2013;62(3):201-4.

68. Salama MM, El-Sakka AS. Hypocalcemic seizures in breastfed infants with rickets secondary to severe maternal vitamin D deficiency. Pakistan Journal of Biological Sciences. 2010;13(9):437.

69. Mehrotra P, Marwaha R, Aneja S, Seth A, Singla B, Ashraf G, et al. Hypovitaminosis D and hypocalcemic seizures in infancy. Indian pediatrics. 2010;47(7):581-6.

70. Basatemur E, Sutcliffe A. Incidence of Hypocalcemic Seizures Due to Vitamin D Deficiency in Children in the United Kingdom and Ireland. Journal of Clinical Endocrinology and Metabolism. 2014;100(1):E91-E5.

71. Hatun S, Ozkan B, Orbak Z, Doneray H, Cizmecioglu F, Toprak D, et al. Vitamin D deficiency in early infancy. The Journal of nutrition. 2005;135(2):279-82.

72. Schnadower D, Agarwal C, Oberfield SE, Fennoy I, Pusic M. Hypocalcemic seizures and secondary bilateral femoral fractures in an adolescent with primary vitamin D deficiency. Pediatrics. 2006;118(5):2226-30.

73. Julies P, Jacobs B. Hypocalcaemic convulsions due to vitamin D deficiency may masquerade as simple febrile convulsions. Archives of Disease in Childhood. 2011;96(Suppl 1):A68-A.

74. Robinson PD, Högler W, Craig ME, Verge CF, Walker JL, Piper AC, et al. The re-emerging burden of rickets: a decade of experience from Sydney. Archives of Disease in Childhood. 2006;91(7):564-8.

75. Chesney RW. Vitamin D deficiency and rickets. Reviews in endocrine & metabolic disorders. 2001;2(2):145-51.

76. Ward LM, Gaboury I, Ladhani M, Zlotkin S. Vitamin D-deficiency rickets among children in Canada. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2007;177(2):161-6.

77. Munns CF, Simm PJ, Rodda CP, Garnett SP, Zacharin MR, Ward LM, et al. Incidence of vitamin D deficiency rickets among Australian children: an Australian Paediatric Surveillance Unit study. Med J Aust. 2012;196(7):466-8.

78. Ashraf S, Mughal M. The prevalence of rickets among non-Caucasian children. Archives of disease in childhood. 2002;87(3):263-4.

79. Goldacre M, Hall N, Yeates DG. Hospitalisation for children with rickets in England: a historical perspective. The Lancet. 2014;383(9917):597-8.

80. Sahay M, Sahay R. Rickets–vitamin D deficiency and dependency. Indian journal of endocrinology and metabolism. 2012;16(2):164.

81. Annweiler C, Beauchet O. Questioning vitamin D status of elderly fallers and nonfallers: a meta-analysis to address a ‘forgotten step’. Journal of internal medicine. 2015;277(1):16-44.

82. Gillespie LD, Robertson MC, Gillespie WJ, Lamb SE, Gates S, Cumming RG, et al. Interventions for preventing falls in older people living in the community. Cochrane Database of Systematic Reviews. 2009;(4)(CD007146).

83. Cameron ID, Gillespie LD, Robertson MC, Murray GR, Hill KD, Cumming RG, et al. Interventions for preventing falls in older people in care facilities and hospitals. Cochrane Database Syst Rev. 2012;12.

84. Ageing WHO, Unit LC. WHO global report on falls prevention in older age: World Health Organization; 2008.

85. Scuffham P, Chaplin S, Legood R. Incidence and costs of unintentional falls in older people in the United Kingdom. Journal of epidemiology and community health. 2003;57(9):740-4.

86. Gannon B, O’Shea E, Hudson E. The economic costs of falls and fractures in people aged 65 and over in Ireland. Irish Centre for Social Gerontology, Galway. 2007.

87. Lucas PJ, Jessiman T, Cameron A, Wiggins M, Hollingworth K, Austerberry C. Healthy Start vouchers study: The views and experiences of parents, professionals and small retailers in England. Accessed on. 2013;17.

88. Acheson SD. Public health in England: the report of the Committee of Inquiry into the Future Development of the Public Health Function: HM Stationery Office; 1988.

89. National Institute for Health and Care Excellence (NICE). Developing NICE guidelines: the manual. Process and methods [PMG20]. 3 ed 2014.

90. Sassi F, Hurst J. The prevention of lifestyle-related chronic diseases: an economic framework. OECD Health Working Papers. 2008(32):1.

91. Morris S, Devlin N, Parkin D. Economic analysis in health care: John Wiley & Sons; 2007.

92. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes: Oxford university press; 2015.

93. Brouwer WB, Culyer AJ, van Exel NJA, Rutten FF. Welfarism vs. extra-welfarism. Journal of health economics. 2008;27(2):325-38.

94. Hurley J. Welfarism, extra-welfarism and evaluative economic analysis in the health sector. Chichester: John Wiley and Sons; 1998. p. 373-96.

95. Johansson P-O. An introduction to modern welfare economics: Cambridge University Press; 1991.

96. Tsuchiya A, Williams A. Welfare economics and economic evaluation. In: Drummond M, McGuire A, editors. Economic evaluation in health care: merging theory with practice. New York: Oxford University Press; 2001. p. 27-8.

97. Kaldor N. Welfare propositions of economics and interpersonal comparisons of utility. The Economic Journal. 1939:549-52.

98. Hicks JR. The foundations of welfare economics. The Economic Journal. 1939;49(196):696-712.

99. McGuire A. **Theoretical concepts in the economic evalution of health care**. In: Drummond M, McGuire A, editors. Economic evaluation in health care : merging theory with practice. New York: Oxford University Press; 2001. p. 1-21.

100. Boadway RW. Integrating equity and efficiency in applied welfare economics1974.

101. Sen A. Commodities and capabilities. Amsterdam: North-Holland1985.

102. Sen A. Social choice theory: A re-examination. Econometrica: Journal of the Econometric Society. 1977:53-89.

103. Hall J, Gafni A, Birch S. Health economics critiques of welfarism and their compatibility with Sen's capabilities approach. CHERE Working Paper, 16 (September); 2006.

104. Culyer AJ. The normative economics of health care finance and provision. Oxford review of economic policy. 1989;5(1):34-58.

105. Torrance GW, Siegel J, Luce B, Gold M, Russell L, Weinstein M. Framing and designing the cost-effectiveness analysis. Cost-effectiveness in Health and Medicine. 1996:54-81.

106. Coast J. Maximisation in extra-welfarism: A critique of the current position in health economics. Social science & medicine. 2009;69(5):786-92.

107. Pearce D, Atkinson G, Mourato S. Cost-benefit analysis and the environment: recent developments: Organisation for Economic Co-operation and development; 2006.

108. Layard PRG. Cost-benefit analysis: Cambridge University Press; 1994.

109. Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. British medical bulletin. 2010;96(1):5-21.

110. Briggs AH, Claxton K, Sculpher MJ. Decision modelling for health economic evaluation: Oxford University Press, USA; 2006.

111. Black WC. The CE plane: a graphic representation of cost-effectiveness. Medical decision making. 1990;10(3):212-4.

112. Gray AM, Clarke PM, Wolstenholme JL, Wordsworth S. Applied methods of cost-effectiveness analysis in healthcare: Oxford University Press; 2010.

113. Canadian Agency for DrugsTechnologies in Health C. Guidelines for the economic evaluation of health technologies: Canada. 2006.

114. Andronis L, Barton P, Bryan S. Sensitivity analysis in economic evaluation: an audit of NICE current practice and a review of its use and value in decision-making: Prepress Projects; 2009.

115. Briggs AH. Handling uncertainty in economic evaluation. In: Drummond MF, McGuire A, editors. Economic evaluation in health care: merging theory with practice: OUP Oxford; 2001.

116. Brennan A, Akehurst R. Modelling in health economic evaluation. What is its place? What is its value? Pharmacoeconomics. 2000;17(5):445-59.

117. Claxton K, Eggington S, Ginnelly L, Griffin S, McCabe C, Philips Z, et al., editors. A pilot study of value of information analysis to support research recommendations for the National Institute for Clinical Excellence. 26th Annual Conference of the Society for Medical Decision Making; 2004.

118. Yokota F, Thompson KM. Value of information literature analysis: a review of applications in health risk management. Medical Decision Making. 2004;24(3):287-98.

119. Edwards RT, Charles JM, Lloyd-Williams H. Public health economics: a systematic review of guidance for the economic evaluation of public health

interventions and discussion of key methodological issues. BMC public health. 2013;13(1):1001.

120. Messonnier M. Economics and public health at CDC. MMWR supplements. 2006;55(2):17-9.

121. National Institute for Health and Care Excellence (NICE). Judging whether public health interventions offer value for money. Local government briefing (LGB10)2013.

122. Raulio S, Erlund I, Männistö S, Sarlio-Lähteenkorva S, Sundvall J, Tapanainen H, et al. Successful nutrition policy: improvement of vitamin D intake and status in Finnish adults over the last decade. European journal of public health. 2017;27(2):268-73.

123. Thacher TD, Pludowski P, Shaw NJ, Mughal MZ, Munns CF, Högler W. Nutritional rickets in immigrant and refugee children. Public Health Reviews. 2016;37(1):3.

124. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons; 2011.

125. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine. 2009;151(4):264-9.

126. Drummond M, Jefferson T. Guidelines for authors and peer reviewers of economic submissions to the BMJ. Bmj. 1996;313(7052):275-83.

127. Torgerson DJ, Kanis JA. Cost-effectiveness of preventing hip fractures in the elderly population using vitamin D and calcium. Quarterly Journal of Medicine. 1995;88(2):135-9.

128. Poole C, Smith J, Davies J. Cost-effectiveness and budget impact of Empirical vitamin D therapy on unintentional falls in older adults in the UK. BMJ open. 2015;5(9):e007910.

129. Poole CD, Smith JC, Davies JS. The short-term impact of vitamin D-based hip fracture prevention in older adults in the United Kingdom. Journal of Endocrinological Investigation. 2014;37(9):811-7.

130. Filby A, Lewis L, M. T. An Economic Evaluationn of Interventions to Improve the Uptake of Vitamin D Supplements in England and Wales. . National Institute for Health and Care Excellence; 2014.

131. Filby A, Taylor A, Jenks M, Burley V. Examining the Cost-Effectiveness of Moving the Healthy Start Vitamin Programme from a Targeted to a Universal Offering: Final Report. National Institute for Health and Care Excellence

2015.

132. Frick KD, Kung JY, Parrish JM, Narrett MJ. Evaluating the cost-effectiveness of fall prevention programs that reduce fall-related hip fractures in older adults. Journal of the American Geriatrics Society. 2010;58(1):136-41.

133. Lee RH, Weber T, Colon-Emeric C. Comparison of cost-effectiveness of vitamin D screening with that of universal supplementation in preventing falls in community-dwelling older adults. Journal of the American Geriatrics Society. 2013;61(5):707-14.

134. Church J, Goodall S, Norman R, Haas M. An economic evaluation of community and residential aged care falls prevention strategies in NSW. New South Wales public health bulletin. 2011;22(3-4):60-8.

135. Church JL, Haas MR, Goodall S. Cost Effectiveness of Falls and Injury Prevention Strategies for Older Adults Living in Residential Aged Care Facilities. Pharmacoeconomics. 2015;33(12):1301-10.

136. Zarca K, Durand-Zaleski I, Roux C, Souberbielle JC, Schott AM, Thomas T, et al. Cost-effectiveness analysis of hip fracture prevention with vitamin D supplementation: A Markov micro-simulation model applied to the French population over 65 years old without previous hip fracture. Osteoporosis International. 2014;25(6):1797-806.

137. Hiligsmann M, Burlet N, Fardellone P, Al-Daghri N, Reginster J-Y. Public health impact and economic evaluation of vitamin D-fortified dairy products for fracture prevention in France. Osteoporosis International. 2017;28(3):833-40.

138. Patil R, Kolu P, Raitanen J, Valvanne J, Kannus P, Karinkanta S, et al. Cost-effectiveness of vitamin D supplementation and exercise in preventing injurious falls among older home-dwelling women: findings from an RCT. Osteoporosis International. 2016;27(1):193-201.

139. Willis MS. The health economics of calcium and vitamin D3 for the prevention of osteoporotic hip fractures in Sweden. International Journal of Technology Assessment in Health Care. 2002;18(4):791-807.

140. Sandmann A, Amling M, Barvencik F, Konig HH, Bleibler F. Economic evaluation of vitamin D and calcium food fortification for fracture prevention in Germany. Public Health Nutr. 2015:1-10.

141. Lilliu H, Pamphile R, Chapuy MC, Schulten J, Arlot M, Meunier PJ. Calcium-vitamin D3 supplementation is cost-effective in hip fractures prevention. Maturitas. 2003;44(4):299-305.

142. Ethgen O, Hiligsmann M, Burlet N, Reginster J-Y. Public health impact and cost-effectiveness of dairy products supplemented with vitamin D in prevention of osteoporotic fractures. Archives of Public Health. 2015;73(1):48.

143. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. Vitamin D3 and calcium to prevent hip fractures in elderly women. New England journal of medicine. 1992;327(23):1637-42.

144. Chapuy MC, Arlot ME, Delmas PD, Meunier PJ. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. BMJ: British Medical Journal. 1994;308(6936):1081.

145. Avenell A, Mak J, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. The Cochrane Library. 2014.

146. Fiedler JL, Sanghvi TG, Saunders MK. A review of the micronutrient intervention cost literature: program design and policy lessons. Int J Health Plann Manage. 2008;23(4):373-97.

147. Tulchinsky T, Kaluski DN, Berry E. Food fortification and risk group supplementation are vital parts of a comprehensive nutrition policy for prevention of chronic diseases. European journal of public health. 2004;14(3):226-7.

148. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. Interventions for preventing falls in older people living in the community. Cochrane Database of Systematic Reviews. 2012(9).

149. Sabaté E. Adherence to long-term therapies: evidence for action: World Health Organization; 2003.

150. Moy RJ, McGee E, Debelle GD, Mather I, Shaw NJ. Successful public health action to reduce the incidence of symptomatic vitamin D deficiency. Archives of Disease in Childhood. 2012;97(11):952-4.

151. Davis JC, Robertson MC, Comans T, Scuffham PA. Guidelines for conducting and reporting economic evaluation of fall prevention strategies. Osteoporos Int. 2011;22(9):2449-59.

152. Lo YT, Chang YH, Lee MS, Wahlqvist ML. Health and nutrition economics: diet costs are associated with diet quality. Asia Pac J Clin Nutr. 2009;18(4):598-604.

153. Lenoir-Wijnkoop I, Dapoigny M, Dubois D, van Ganse E, Gutierrez-Ibarluzea I, Hutton J, et al. Nutrition economics - characterising the economic and health impact of nutrition. Br J Nutr. 2011;105(1):157-66.

154. Sanghvi T, Dary O, Houston R. How can vitamin and mineral deficiencies be reduced? Food and Nutrition Bulletin. 2007;28(1).

155. Bentley TG, Weinstein MC, Willett WC, Kuntz KM. A cost-effectiveness analysis of folic acid fortification policy in the United States. Public health nutrition. 2009;12(04):455-67.

156. Rabovskaja V, Parkinson B, Goodall S. The cost-effectiveness of mandatory folic acid fortification in Australia. The Journal of nutrition. 2013;143(1):59-66.

157. Monahan M, Boelaert K, Jolly K, Chan S, Barton P, Roberts TE. Costs and benefits of iodine supplementation for pregnant women in a mildly to moderately iodine-deficient population: a modelling analysis. The Lancet Diabetes & Endocrinology. 2015;3(9):715-22.

158. Postma M, Londeman J, Veenstra M, De Jong-van den Berg L, De Walle H. Cost-effectiveness of periconceptional supplementation of folic acid. Pharmacy world & science. 2002;24(1):8-11.

159. Phillips M, Sanghvi T, Suarez R, McKigney J, Fiedler J. The costs and effectiveness of three vitamin A interventions in Guatemala. Soc Sci Med. 1996;42(12):1661-8.

160. Moore D, Poynton M. Review of the benefits and costs of water fluoridation in New Zealand: Sapere Research Group; 2015.

161. Baltussen R, Knai C, Sharan M. Iron fortification and iron supplementation are cost-effective interventions to reduce iron deficiency in four subregions of the world. J Nutr. 2004;134(10):2678-84.

162. Goodall S, Norman R, Gallego G. Cost-effectiveness Analysis of Iodine Fortification in Australia and New Zealand. 2007.

163. Dalziel K, Segal L, Katz R. Cost-effectiveness of mandatory folate fortification v. other options for the prevention of neural tube defects: results from Australia and New Zealand. Public Health Nutr. 2010;13(4):566-78.

164. Jentink J, van de Vrie-Hoekstra NW, de Jong-van den Berg LT, Postma MJ. Economic evaluation of folic acid food fortification in The Netherlands. Eur J Public Health. 2008;18(3):270-4.

165. Food Standards Australia and New Zealand (FSANZ). Cost benefit analysis of fortifying the food supply with folic acid. 2006.

166. Food Standards Australia and New Zealand (FSANZ). Cost benefit analysis of fortifying the food supply with iodine. 2006.

167. Fiedler JL, Afidra R. Vitamin A fortification in Uganda: comparing the feasibility, coverage, costs, and cost-effectiveness of fortifying vegetable oil and sugar. Food & Nutrition Bulletin. 2010;31(2):193-205.

168. Popkin BM, Solon FS, Fernandez T, Lantham MC. Benefit-cost analysis in the nutrition area: a project in the Philippines. Social Science & Medicine Part C: Medical Economics. 1980;14(3):207-16.

169. Meenakshi J, Johnson NL, Manyong VM, DeGroote H, Javelosa J, Yanggen DR, et al. How cost-effective is biofortification in combating micronutrient malnutrition? An ex ante assessment. World Development. 2010;38(1):64-75.

170. Segal L, Dalziel K, Katz R. Informing a strategy for increasing folate levels to prevent neural tube defects: a cost-effectiveness analysis of options: a report for Food Standards Australia and New Zealand, Monash University and University of South Australia, ed. Food Standards Australia and New Zealand. 2007.

171. Fiedler JL, Dado DR, Maglalang H, Juban N, Capistrano M, Magpantay MV. Cost analysis as a vitamin A program design and evaluation tool: a case study of the Philippines. Social Science & Medicine. 2000;51(2):223-42.

172. Fiedler JL, Macdonald B. A strategic approach to the unfinished fortification agenda: feasibility, costs, and cost-effectiveness analysis of fortification programs in 48 countries. Food & Nutrition Bulletin. 2009;30(4):283-316.

173. Gyles CL, Lenoir-Wijnkoop I, Carlberg JG, Senanayake V, Gutierrez-Ibarluzea I, Poley MJ, et al. Health economics and nutrition: a review of published evidence. Nutrition reviews. 2012;70(12):693-708.

174. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal. Process and methods (PMG9)2013.

175. Brazier J, Deverill M, Green C, Harper R, Booth A. A review of the use of health status measures in economic evaluation. Health Technol Assess. 1999;3(9):i-iv, 1-164.

176. von Von Neumann J, Morgenstern O. Theory of games and economic behavior: Princeton University Press; 1955.

177. Karimi M, Brazier J. Health, health-related quality of life, and quality of life: what is the difference? Pharmacoeconomics. 2016;34(7):645-9.

178. Boyd NF, Sutherland HJ, Heasman KZ, Tritchler DL, Cummings BJ. Whose utilities for decision analysis? Medical Decision Making. 1990;10(1):58-67.

179. Marlow R, Finn A, Trotter C. Quality of life impacts from rotavirus gastroenteritis on children and their families in the UK. Vaccine. 2015;33(39):5212-6.

180. McPhail S, Beller E, Haines T. Two perspectives of proxy reporting of health-related quality of life using the Euroqol-5D, an investigation of agreement. Medical care. 2008;46(11):1140-8.

181. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med. 1993;118(8):622-9.

182. Sneeuw KC, Sprangers MA, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease. Journal of Clinical Epidemiology. 2002;55(11):1130-43.

183. Morrow AM, Hayen A, Quine S, Scheinberg A, Craig JC. A comparison of doctors', parents' and children's reports of health states and health-related quality of life in children with chronic conditions. Child: care, health and development. 2012;38(2):186-95.

184. Rothman ML, Hedrick SC, Bulcroft KA, Hickam DH, Rubenstein LZ. The validity of proxy-generated scores as measures of patient health status. Medical care. 1991:115-24.

185. Pickard AS, Knight SJ. Proxy Evaluation of Health-Related Quality of Life: A Conceptual Framework for Understanding Multiple Proxy Perspectives. Medical Care. 2005;43(5):493-9.

186. Higashi T, Hays RD, Brown JA, Kamberg CJ, Pham C, Reuben DB, et al. Do proxies reflect patients' health concerns about urinary incontinence and gait problems? Health Qual Life Outcomes. 2005;3(1):75.

187. Menzel P, Dolan P, Richardson J, Olsen JA. The role of adaptation to disability and disease in health state valuation: a preliminary normative analysis. Social science & medicine. 2002;55(12):2149-58.

188. Chao Y, Ekwaru J, Ohinmaa A, Griener G, Veugelers P. Vitamin D and health-related quality of life in a community sample of older Canadians. Quality of Life Research. 2014;23(9):2569-75.

189. Rafiq R, Swart K, van Schoor N, Deeg D, Lips P, de Jongh R. Associations of serum 25-hydroxyvitamin D concentrations with quality of life and self-rated health in an older population. The Journal of Clinical Endocrinology & Metabolism. 2014;99(9):3136-43.

190. Tolentino-Wilson O, Narvacan-Montano C. Association of 25 (OH) D Serum Concentrations on Health-Related Quality of Life among Patients with Low Vitamin D. Journal of the ASEAN Federation of Endocrine Societies. 2014;29(1):54.

191. Iglesias CP, Manca A, Torgerson DJ. The health-related quality of life and cost implications of falls in elderly women. Osteoporos Int. 2009;20(6):869-78.

192. Chang N-T, Chi L-Y, Yang N-P, Chou P. The impact of falls and fear of falling on health-related quality of life in Taiwanese elderly. Journal of community health nursing. 2010;27(2):84-95.

193. Thiem U, Klaaßen-Mielke R, Trampisch U, Moschny A, Pientka L, Hinrichs T. Falls and EQ-5D rated quality of life in community-dwelling seniors with concurrent chronic diseases: a cross-sectional study. Health Qual Life Outcomes. 2014;12(1):1.

194. Brazier JE, Green C, Kanis JA. A systematic review of health state utility values for osteoporosis-related conditions. Osteoporos Int. 2002;13(10):768-76.

195. Peasgood T, Herrmann K, Kanis JA, Brazier JE. An updated systematic review of Health State Utility Values for osteoporosis related conditions. Osteoporos Int. 2009;20.

196. Stenhagen M, Ekström H, Nordell E, Elmståhl S. Accidental falls, health-related quality of life and life satisfaction: A prospective study of the general elderly population. Archives of gerontology and geriatrics. 2014;58(1):95-100.

197. Salkeld G, Cameron ID, Cumming RG, Easter S, Seymour J, Kurrle SE. Quality of life related to fear of falling and hip fracture in older women: a time trade off study. BMJ. 2000;320.

198. Sadler GR, Lee H-C, Seung-Hwan Lim R, Fullerton J. Recruiting hard-to-reach United States population sub-groups via adaptations of snowball sampling strategy. Nursing & health sciences. 2010;12(3):369-74.

199. Solans M, Pane S, Estrada MD, Serra-Sutton V, Berra S, Herdman M, et al. Health-Related Quality of Life Measurement in Children and Adolescents: A Systematic Review of Generic and Disease-Specific Instruments. Value in health. 2008;11(4):742-64.

200. Stevens KJ. Working with children to develop dimensions for a preference-based, generic, pediatric, health-related quality-of-life measure. Qualitative Health Research. 2010;20(3):340-51.

201. Chen G, Flynn T, Stevens K, Brazier J, Huynh E, Sawyer M, et al. Assessing the health-related quality of life of Australian adolescents: an empirical comparison of the child health utility 9D and EQ-5D-Y instruments. Value in Health. 2015;18(4):432-8.

202. Frew EJ, Pallan M, Lancashire E, Hemming K, Adab P. Is utility-based quality of life associated with overweight in children? Evidence from the UK WAVES randomised controlled study. BMC pediatrics. 2015;15(1):211.

203. Stevens K. Assessing the performance of a new generic measure of health-related quality of life for children and refining it for use in health state valuation. Applied Health Economics and Health Policy. 2011;9(3):157-69.

204. Stevens K. Valuation of the child health utility 9D index. Pharmacoeconomics. 2012;30(8):729-47.

205. Canaway AG, Frew EJ. Measuring preference-based quality of life in children aged 6–7 years: a comparison of the performance of the CHU-9D and EQ-5D-Y—the WAVES Pilot Study. Quality of Life Research. 2013;22(1):173-83.

206. Van Hout B, Janssen M, Feng Y-S, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health. 2012;15(5):708-15.

207. McCabe C, Brazier J, Gilks P, Tsuchiya A, Roberts J, O'Hagan A, et al. Estimating population cardinal health state valuation models from individual ordinal (rank) health state preference data. 2004.

208. Brazier J, Roberts J, Tsuchiya A, Busschbach J. A comparison of the EQ-5D and SF-6D across seven patient groups. Health economics. 2004;13(9):873-84.

209. Conner-Spady B, Suarez-Almazor ME. Variation in the Estimation of Quality-adjusted Life-years by Different Preference-based Instruments. Medical care. 2003;41(7):791-801.

210. Martin AJ, Glasziou P, Simes R, Lumley T. A comparison of standard gamble, time trade-off, and adjusted time trade-off scores. International Journal of Technology Assessment in Health Care. 2000;16(1):137-47.

211. Asch S, Connor SE, Hamilton EG, Fox SA. Problems in recruiting community-based physicians for health services research. Journal of General Internal Medicine. 2000;15(8):591-9.

212. Barton P, Bryan S, Robinson S. Modelling in the economic evaluation of health care: selecting the appropriate approach. Journal of health services research & policy. 2004;9(2):110-8.

213. Davis S, Stevenson M, Tappenden P, Wailoo A. NICE DSU Technical Support Document 15: Cost-effectiveness modelling using patient-level simulation. School of Health and Related Research, University of Sheffield. 2014.

214. Allen RE, Dangour AD, Tedstone AE, Chalabi Z. Does fortification of staple foods improve vitamin D intakes and status of groups at risk of deficiency? A United Kingdom modeling study. Am J Clin Nutr. 2015;102(2):338-44.

215. Allen RE. Would fortification of more foods with vitamin D improve vitamin D intakes and status of groups at risk of deficiency in the UK? : London School of Hygiene & Tropical Medicine; 2013.

216. Office for National Statistics. Census. UK Data Service Census Support. 2011.

217. Mytton J, Frater AP, Oakley G, Murphy E, Barber MJ, Jahfar S. Vitamin D deficiency in multicultural primary care: a case series of 299 patients. Br J Gen Pract. 2007;57(540):577-9.

218. Janssen HC, Samson MM, Verhaar HJ. Vitamin D deficiency, muscle function, and falls in elderly people. The American journal of clinical nutrition. 2002;75(4):611-5.

219. O'Neill CM, Kazantzidis A, Kiely M, Cox L, Meadows S, Goldberg G, et al. A predictive model of serum 25-hydroxyvitamin D in UK white as well as black and Asian minority ethnic population groups for application in food fortification strategy development towards vitamin D deficiency prevention. The Journal of Steroid Biochemistry and Molecular Biology. 2016.

220. Hayden K, Sandle L, Berry J. Ethnicity and social deprivation contribute to vitamin D deficiency in an urban UK population. The Journal of steroid biochemistry and molecular biology. 2015;148:253-5.

221. Lawson M, Thomas M. Vitamin D concentrations in Asian children aged 2years living in England: population survey. Bmj. 1999;318(7175):28.

222. Therapyaudit Limited. FreeD: Vitamin D supplementation in Lewisham. 2014.

223. Priemel M, von Domarus C, Klatte TO, Kessler S, Schlie J, Meier S, et al. Bone mineralization defects and vitamin D deficiency: Histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. Journal of Bone and Mineral Research. 2010;25(2):305-12.

224. Rabenberg M, Scheidt-Nave C, Busch MA, Rieckmann N, Hintzpeter B, Mensink GBM. Vitamin D status among adults in Germany – results from the German

Health Interview and Examination Survey for Adults (DEGS1). BMC Public Health. 2015;15:641.

225. Suzuki T, Kwon J, Kim H, Shimada H, Yoshida Y, Iwasa H, et al. Low Serum 25-Hydroxyvitamin D Levels Associated With Falls Among Japanese Community-Dwelling Elderly. Journal of Bone and Mineral Research. 2008;23(8):1309-17.

226. Beauchet O, Annweiler C, Verghese J, Fantino B, Herrmann F, Allali G. Biology of gait control Vitamin D involvement. Neurology. 2011;76(19):1617-22.

227. Annweiler C, Schott AM, Rolland Y, Beauchet O. Vitamin D deficiency is associated with orthostatic hypotension in oldest-old women. J Intern Med. 2014;276(3):285-95.

228. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35(11):1095-108.

229. Kind P, Hardman G, Macran S. UK population norms for EQ-5D: Centre for Health Economics, University of York York; 1999.

230. Curtis L, Burns A. Unit Costs of Health and Social Care 2016. Canterbury; 2016.

231. Food Standards Agency (FSA). Improving folate intakes of women of reproductive age and preventing neural tube defects: practical issues. 2007. Contract No.: .

232. NABIM. Statistics 2014 [Available from: http://www.nabim.org.uk/statistics.

233. Affairs DfEFaR. The Food Labelling Regulations 1996. Statutory Instruments 1996.

234. Food Standards Agency (FSA). Food Information Regulations 2014: Summary guidance for food business operators and enforcement officers in Scotland, Wales and Northern Ireland. 2014.

235. Food Standard Agency (FSA). Consultation on front of pack nutrition labelling Department oh Health (online); 2012.

236. Brown J, Kotz D, Michie S, Stapleton J, Walmsley M, West R. How effective and cost-effective was the national mass media smoking cessation campaign 'Stoptober'?(). Drug and Alcohol Dependence. 2014;135(100):52-8.

237. Committee JF. British National Formulary (online) London [Available from: http://www.medicinescomplete.com.

238. Zipitis CS, Markides GA, Swann IL. Vitamin D deficiency: Prevention or treatment? Archives of Disease in Childhood. 2006;91(12):1011-4.

239. McGee E. Prevention of rickets and vitamin D deficiency in Birmingham: The case for universal supplementation. 2014.

240. Szpakowicz D. The Healthy Start Scheme: An Evidence Review. In: Research SGS, editor. 2016.

241. Davies J, Saunders K. Healthy Start in the West Midlands. Department of Health; 2012.

242. Ara R, Wailoo A. Using health state utility values in models exploring the cost-effectiveness of health technologies. Value in Health. 2012;15(6):971-4.

243. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value in Health. 2010;13(5):509-18.

244. McFadden A, Green JM, McLeish J, McCormick F, Williams V, Renfrew MJ. Healthy Start vitamins—a missed opportunity: findings of a multimethod study. BMJ open. 2015;5(1):e006917.

245. Shaw N, Pal B. Vitamin D deficiency in UK Asian families: activating a new concern. Archives of Disease in Childhood. 2002;86(3):147-9.

246. Anglin RE, Samaan Z, Walter SD, McDonald SD. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. The British journal of psychiatry. 2013;202(2):100-7.

247. Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JP. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. Bmj. 2014;348:g2035.

248. Tarride J-E, Burke N, Leslie WD, Morin SN, Adachi JD, Papaioannou A, et al. Loss of health related quality of life following low-trauma fractures in the elderly. BMC Geriatrics. 2016;16(1):84.

249. Dolan P, Kahneman D. Interpretations of utility and their implications for the valuation of health. The Economic Journal. 2008;118(525):215-34.

250. Brock D, Wikler D. Ethical issues in resource allocation, research, and new product development. Disease control priorities in developing countries. 2006;2:259-60.

251. Seal JA, Doyle Z, Burgess JR, Taylor R, Cameron AR. Iodine status of Tasmanians following voluntary fortification of bread with iodine. The Medical Journal of Australia. 2007;186(2):69-71.

252. Food Standards Australia and New Zealand (FSANZ). Consideration of mandatory fortification with iodine for Australia and New Zealand. 2008.

253. Filby A, Wood H, Jenks M, Taylor M, Burley V, Barbier M, et al. Examining the Cost-Effectiveness of Moving the Healthy Start Vitamin Programme from a Targeted to a Universal Offering: Cost-effectiveness Systematic Review. 2015.

254. Åkeson PK, Lind T, Hernell O, Silfverdal S-A, Öhlund I. Serum vitamin d depends less on latitude than on skin color and dietary intake during early winter in northern europe. Journal of pediatric gastroenterology and nutrition. 2016;62(4):643-9.

255. Adams J, Mytton O, White M, Monsivais P. Why are some population interventions for diet and obesity more equitable and effective than others? The role of individual agency. PLoS medicine. 2016;13(4):e1001990.

256. Parkinson B, Goodall S, Norman R. Measuring the loss of consumer choice in mandatory health programmes using discrete choice experiments. Appl Health Econ Health Policy. 2013;11(2):139-50.

257. Griffin M, Shickle D, Moran N. European citizens' opinions on water fluoridation. Community dentistry and oral epidemiology. 2008;36(2):95-102.

258. Wirth JP, Nichols E, Mas'd H, Barham R, Johnson QW, Serdula M. External mill monitoring of wheat flour fortification programs: an approach for program managers using experiences from Jordan. Nutrients. 2013;5(11):4741-59.

259. Serdula M, Nichols E, Aburto N, Masa'd H, Obaid B, Wirth J, et al. Micronutrient status in Jordan: 2002 and 2010. European journal of clinical nutrition. 2014;68(10):1124.

260. Peckham S, Lowery D, Spencer S. Are fluoride levels in drinking water associated with hypothyroidism prevalence in England? A large observational study of GP practice data and fluoride levels in drinking water. J Epidemiol Community Health. 2015:jech-2014-204971.

261. Cheng K, Chalmers I, Sheldon TA. Controversy: adding fluoride to water supplies. BMJ: British Medical Journal. 2007;335(7622):699.

262. Morris J, Rankin J, Draper ES, Kurinczuk J, Springett A, Tucker D, et al. Prevention of neural tube defects in the UK: a missed opportunity. Archives of disease in childhood. 2015:archdischild-2015-309226.

263. Jentink J, van de Vrie-Hoekstra NW, Postma MJ. Economic evaluation of folic acid food fortification in the Netherlands. The European Journal of Public Health. 2008;18(3):270-4.