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Preventing Vitamin D Deficiency (VDD): A Systematic review of Economic Evaluations

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Abstract

Background: Vitamin D Deficiency (VDD) is a public health concern worldwide. If untreated, it can lead to reduced quality of life and escalated costs brought about by ill-health. Preventive programmes to improve population vitamin D status exist but little is known about their the cost-effectiveness. This information is vital so that decision-makers adopt efficient strategies and optimise use of public resources.

Aims: Systematically review and critically appraise economic evaluations of population strategies to prevent VDD.

Methods: The databases reviewed were MEDLINE, EMBASE, Econlit, NHS EED, CEA and RepEc. All full economic evaluations of VDD prevention strategies were included. Interventions considered were food fortification, supplementation and public health campaigns. Data extracted included type of evaluation, population and setting, the measure of benefits and main results.

Results: Of the 2492 records screened, 14 studies were included. The majority of studies focused on supplementation within at-risk groups with the primary objective of either preventing fractures or falls in older adults. There was insufficient economic evidence to draw conclusions about the cost-effectiveness of population strategies. No study was identified that offered a direct comparison of the two main alternative population strategies: food fortification versus supplementation.

Conclusion: Whilst there is a growing body of evidence on the cost-effectiveness of micro-nutrient programmes, there is a paucity of data on vitamin D fortification and how fortification programmes compare to population supplementation programmes. We highlight research gaps, and offer suggestions of what is required to undertake population-based cost-effective analysis.

Keywords: systematic review; vitamin D deficiency; public health; cost-effectiveness

Introduction

Vitamin D deficiency (VDD) is associated with reduced intestinal absorption of calcium, leading to low bone mineralisation (rickets and osteomalacia), skeletal deformities, hypocalcaemic seizures, tetany and heart disease (1, 2). VDD can also manifest as musculoskeletal pain and weakness that may ultimately result in falls in the elderly population (3). A recent post-mortem study conducted in Germany found that the prevalence of undiagnosed osteomalacia was as high as 25% in the adult population (4). VDD affects populations worldwide and its prevention and improvement in nutritional status is a global public health priority, thereby ensuring optimal bone health in both children and adults (1, 5).

The main source of Vitamin D is ultraviolet radiation (UV-B) containing sunlight, which prompts vitamin D production in the skin. VDD is therefore endemic in high latitude settings (>35°N) such as the UK (5), Canada (6), Belgium (7) and Scandinavia (5) where less UV-B sunlight is obtained throughout the year. Despite this geographical fact, VDD has predominantly been reported in low and mid latitudes (0°-35°), namely African and Asian countries, where cultural and dietary factors limit sunlight exposure and calcium intake (8). Vitamin D from sunlight or food sources is biologically inactive and needs to be converted in the human body, via two hydroxylation steps, into the hormone calcitriol (also called active vitamin D) whose function is to maintain healthy levels of calcium and phosphorus by increasing the intestinal absorption of those bone minerals (1). Therefore, Vitamin D is an indirect determinant of bone mineralization during childhood and adulthood. The best measure of vitamin D status is the also biologically inert 25 hydroxyvitamin D (25OHD), present in the blood serum. The main risk factors for VDD include older age, dark skin pigmentation, and any barrier to UV-B light reaching the skin such as full body clothing, spending most time indoors, and air pollution (8). Because vitamin D is fundamental for healthy bone development and growth, optimal vitamin D intake is crucial in infants and young children, as well as

pregnant and breastfeeding women, and these populations are a common public health target, with the aim of avoiding irreversible consequences of severe VDD (9).

Most countries have adopted public health policies to prevent VDD in at-risk groups of the population (10), opting for either 1) mandatory fortification of staple foods such as milk (Sweden and Finland) or voluntary fortification of breakfast cereals (UK) (10), or 2) supplementation programmes for pregnant and breastfeeding women, and infants (10). Despite these initiatives, VDD still persists as a serious public health concern (5). 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 (5). 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 (2, 5, 11). There has been continued research effort to determine a population strategy that is both clinically- and cost-effective. In November 2014, the UK's National Institute for Health and Care Excellence (NICE) identified a lack of economic evidence to support vitamin D supplementation for certain groups of the population (12). In addition, in 2016 the global consensus recommendations on the prevention and management of rickets highlighted the paucity of economic evaluation of rickets prevention strategies (8).

This study aims to systematically review economic evaluations of VDD prevention and identify the evidence gaps to inform future research and public health policy.

In addition, it aims to:

- Determine the cost-effectiveness of population strategies;
- Identify whether cost-effectiveness varies by population subgroup and country setting;
- 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 (for example, death, quality-of-life, fractures, falls).

Methods

Search Strategy

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology (13) where applicable. Literature searches were conducted in January 2015 and updated in April 2016. The search strategy included terms relating to VDD and health economics (full search strategy provided in the supplementary material). The following bibliographic databases were searched: MEDLINE, EMBASE, Econlit, NHS EED, CEA and RepEC. Additionally, the reference lists of the included articles were searched. The screening was conducted by the main reviewer (MA) and the second reviewer (EF) screened 10% of the titles and abstracts.

Inclusion/exclusion criteria

All full economic evaluations, defined as a consideration of both costs and outcomes together, 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. There were no language restrictions. Studies where VDD occurred as secondary to other health conditions, such as liver disease or malabsorption, were excluded.

Data extraction

The relevant characteristics of each study in relation to the methods used and main results 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 (14) 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. Second, the studies were grouped by type of intervention analysed. High heterogeneity was expected across studies due to the great 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.

Results

Our search strategy generated 2492 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. A total of 2466 were excluded and the primary reason for exclusion was not being a full economic evaluation. The remaining 26 full-text studies were examined and 14 studies were selected for data extraction, 9 from the main search and 5 from the updated searches. A flowchart illustrating the study selection process is shown in Figure 1.

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. Studies were carried out in the UK (15-19), the USA (20, 21), Australia (22, 23), France (24), Finland (25), Sweden (26) and Germany (27). Additionally, there was one multi-country study that carried out cost-effectiveness analyses in seven European countries (28). The majority of studies (n=7) evaluated supplementation strategies of vitamin D alone in the adult population (16, 17, 20, 21, 23-25). Other studies investigated calcium and vitamin D interventions either through oral supplements (n=4) (15, 22, 26, 28) or food fortification (n=1) (27). One study evaluated interventions of supplementation with multi-vitamins that included vitamin D (19).

Supplementation with vitamin D alone

Eight studies evaluated interventions using supplements with vitamin D alone (16-18, 20-22, 24, 25) (Table 1) and all except one (18) focused on the elderly population. Five were cost-utility analyses using quality-adjusted life-years (QALYs) to measure benefits (16, 20, 21, 23, 24), two were cost-effectiveness analyses (17, 25) and one was a cost-consequence analysis (18). Three studies compared universal supplementation against screening for VDD followed by supplementation (18,

21, 24), three studies evaluated vitamin supplements against interventions to prevent falls (20, 23, 25) and two evaluated supplements against current care to prevent fractures (17) and falls (16) . Markov models were the preferred analytical method to simulate falls and fractures pathways (n=4) (16, 17, 21, 23). Screening and subsequent treatment was found to be more cost-effective than universal supplementation in the elderly population (21, 24), while universal supplementation was cost-saving when comparing to the screening alternative in the whole population (18). Interventions with vitamin D supplements in the elderly population were cost-effective when compared to current practice for the prevention of falls (16) and fractures (17), and when compared with multiple interventions for the prevention of falls (20, 23).

Supplementation with vitamin D and calcium

Four economic evaluations focused on the prevention of VDD using supplements with a combination of vitamin D and calcium (Table 1) (15, 22, 26, 28). Two of them were cost-utility analyses using QALYs as a measure of benefit (22, 26) and two were cost-effectiveness analyses measuring the cost per 'avoided fracture' (15, 28). Three studies (15, 26, 28) sourced the effectiveness data from a large French trial (29, 30) involving women in nursing homes. Two of these performed a trial-based analysis (15, 28) while another modelled the outcomes beyond the trial follow-up period through a Markov model (26). When compared with placebo, vitamin D and calcium were cost-effective in women aged 50 and 60 years (26) and cost-saving for at-risk women aged over 70-years-old in Sweden (26) and several other European countries (28). When compared with annual supplementation of high-dose vitamin D only (300 000 IU), the latter was found to be more cost-effective (15).

A different approach was used by Church and colleagues (22), 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 (22).

Supplementation with multi-vitamin preparation containing vitamin D

One study evaluated an intervention using multi-vitamin supplements containing vitamin D (Table 2) (19). 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. (19). 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

One study evaluated food fortification with vitamin D and calcium to prevent fractures in elderly women in Germany (Table 3) (27). It was a cost-effectiveness analysis comparing no fortification, which is the current German policy, with voluntary bread fortification. The analysis used a fortification model based on the German population's bread consumption (31). Effectiveness data on the fracture risk reduction was based on a Cochrane review of the effectiveness of vitamin D and calcium supplements (32). The authors found the intervention was cost-saving (27).

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 supplementary material). There was a general lack of rigour in 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.

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 5 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 favour interventions using it, particularly to prevent heavy-burden clinical outcomes, such as fracture in the elderly. The effectiveness of vitamin D and the incidence of falls were important driver of results.

We highlight below the main strengths and limitations of the currently available evidence and provide recommendations for future research.

Population

The majority of the economic evaluations focused on the elderly population living in Western countries, highlighting a dearth of studies in all other at-risk groups: infants and children, pregnant women, lactating women and ethnic minorities, as well as populations living in other geographical areas, in particular those with high prevalence of rickets.

Severe symptomatic VDD has been reported in dark skinned infants, namely rickets, cardiomyopathy and seizures (2, 9). This review found only one study which attempted an economic sub-group analysis focusing on dark skinned adult populations but results were limited by the paucity of

evidence to support the analysis (18). Despite this, the study showed that, when the incidence of VDD increased, so did the probability of supplementation being cost-effective for that population (18). 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, six studies presented decision models, all Markov models, simulating the prevention of fractures (17, 26) or falls (16, 21-23). Markov models are appropriate as they enable long-term programmes to be modelled and account for recurrence. VDD and its complications are dynamic health states, 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) (15-23, 25, 26, 28) while one analysed high-dose parenteral supplementation (24). The comparators varied and included exercise (25), screening followed by

treatment (18, 21, 24), multi-interventions to prevent falls (20, 22, 23), parenteral vitamin D supplementation (15) and no intervention (16, 17, 26, 28). Only one study evaluated food fortification (27).

Most of the interventions compared targeted a specific group of the population and aimed to prevent one clinical outcome related to VDD. The results are likely to not 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 aged over 70 years and those at high-risk of fractures (21, 24). 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 population level (18).

There is a lack of studies evaluating population-based programmes. The only two studies that undertook broader analyses in several at-risks groups in the UK's population (18, 19) highlight serious limitations due to the evidence gaps to support such analyses.

Evaluation of combined strategies to prevent VDD has not yet been undertaken. Similarly to what the literature reports for other micronutrients (33, 34), 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 cover the whole population, specifically those who do not regularly consume the fortified food (33). Combined strategies are more likely to meet cost-effectiveness and coverage targets (33).

Considering the low uptake of vitamin D supplements and the heterogeneity in food consumption among different population group, and similarly to what the literature reports for other micronutrients (33, 34), 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

policies. Nonetheless, economic evaluations of combined interventions to prevent VDD have not yet been undertaken. We reiterate that stand-alone interventions may not be the most efficient strategy and highlight the importance of producing new economic evidence evaluating multi- interventions.

Clinical outcomes

The most used clinical outcomes were fractures (n=8) (15, 17, 18, 20, 24, 26-28) and falls (n=5) (16, 21-23, 25), although the evidence supporting such associations is controversial. The latest Cochrane reviews suggested that supplementation with vitamin D alone has no impact on risk of fractures (32) but may reduce the risk of falls in individuals with low vitamin D status at baseline, if a minimum of 800 International Units (IU) per day is provided (35). The association of Vitamin D and calcium is likely to prevent a small number of hip and non-vertebral fractures in the elderly population (32).

The choice of clinical outcome and the source of effectiveness data must be carefully considered and estimates tested in sensitivity analysis. For example, hip fractures have a great impact on morbidity, quality of life and mortality. They are also one of the costliest health outcomes in the elderly population. Therefore, risk reduction of hip fractures is likely to drive cost-effectiveness results (27).

VDD has severe clinical consequences in children, namely rickets, which is associated with pain, deformities, muscle weakness, poor growth, hypocalcaemic seizures, tetany and heart disease and their sequelae, including death (8). Despite their high prevalence in risk groups (11), these outcomes have not yet been picked up by 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 chronic conditions is approximately 50% (36). 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 (37). Therefore, economic evaluations assuming 100% uptake rate will overestimate the benefits of supplementation programmes. Further, we 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 (16, 17), makes 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 only study evaluating fortification programmes sourced effectiveness data of vitamin D and calcium from a Cochrane review using supplements (27). 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 food vehicle needs to be accessible, ideally a staple food with a well-established consumption pattern within the targeted population (33). 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 used in eight of the fourteen included studies (16, 19-24, 26). Utility measures were sourced from osteoporosis studies and used in economic evaluations of preventing falls (16, 21-23) and fractures (20, 24, 26). 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 fractures (38).

Although attempts have been made to include QALY estimates for pregnant women and children (12), 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 costs and resources used are reported. The studies focused on the healthcare sector, with great 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 several 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 in supplementation and the nutrient's cost in food fortification programmes (33). Moreover, it highlighted the importance of accounting for information campaigns and staff training, without whom the effectiveness of the programmes is compromised.

Quality of the studies

In general, studies adequately describe interventions compared, the outcome measures and satisfactory drew conclusions from the results reported. Nonetheless, the quality assessment highlighted poor reporting practices namely the lack of justification of the type of economic evaluation used, the choice of perspective and alternatives compared. Full results are presented in supplementary material and summarised in Table 3. It is possible that, because studies have been published in clinical journals, the authors have chosen to emphasise clinical aspects in detriment of analytical methods.

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 (39, 40).

Micronutrient deficiencies are effectively prevented through supplementation and food fortification programmes and most countries have adopted a combination of both (33). None of the studies included in this review presented a direct comparison of the two strategies, neither 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 for its wide population coverage and low maintenance costs (33).

Further research is needed to evaluate if the same applies to vitamin D interventions.

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Conflict of interests

None declared

Key points

- Current economic evaluations are set in high-income countries and focus on the prevention of VDD in the elderly population, using fractures and falls as clinical outcomes;
- Data is lacking regarding the cost-effectiveness of population strategies to prevent VDD;
- Economic evaluations focusing on population-based interventions are needed, as well as subgroup analysis for vulnerable groups such as infants, children, breastfeeding and pregnant women and individuals with darker skin.

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Table 1 Characteristics of the studies evaluating supplementation with vitamin D

Study	Population and setting	Interventions	Type of EE and method	Perspective	Time horizon	Clinical outcome	Measure of benefit	Results
Supplementation with vitamin D alone								
Frick et al. 2010 (20)	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 (21)	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 benefit 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.
Poole et al. 2014 (17)	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 (24)	Individuals over 65 years. France	Universal supplementation with high-dose Vitamin D; Universal supplementation followed by 25OHD test (after 3 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 (18)	Pregnant and breastfeeding women, children aged less than 5 years, adults over 65 years,	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

	dark skinned population. UK							£10 million, £21 million, £25 million and £160 million, respectively.
Poole et al. 2015 (16)	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 (23)	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 (25)	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.

Supplementation with vitamin D in association with calcium or other nutrients								
Study	Population and setting	Interventions	Type of EE and method	Perspective	Time horizon	Clinical outcome	Measure of benefit	Results
Togerson et al. 1995 (15)	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 (26)	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 (28)	Elderly women in nursing homes Belgium, France, Germany, Netherlands, Spain,	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.

	Sweden, and the UK.							
Church et al. 2011 (22)	Individuals over 65 years living in the community and in residential care. Australia	<u>Community dwelling</u> : Tai-chi; Home hazard assessment; Exercise, multiple interventions; Cataract surgery; Psychotropic medication withdrawal; Cardiac pacing. <u>Residential care</u> : 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	<u>Community dwelling</u> : Most cost-effective were Tai chi, home hazard assessment and group exercise. <u>Residential care</u> : The most cost-effective intervention was medication review, followed by supplementation with vitamin D and calcium.
Filby et al. 2015 (19)	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 Health Care Service) and societal	Lifetime	Pregnancy affected by a neural tube defects, symptomatic vitamin D deficiency or LRNI for vitamin A and C in each subgroup	Cost per QALY	<u>Scenario 1</u> : universal offering scheme was not cost-effective, ICER of £620,898. Universal scheme in <u>scenario 2</u> was likely to be cost-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;

Table 2 Characteristics of the studies evaluating supplementation with multi-vitamin supplements

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 (27)	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

Table 3 Summary of the results

Study ID	Intervention	Population	Result	Quality/comments
Sandmann et al. 2015 (27)	Bread fortification with vitamin D (800IU) + calcium (200mg)	Elderly (+65 years)	Bread fortification was cost-saving	Adequate
Zarca et al 2014 (24)	Population screening vs. Universal supplementation with vitamin D	Elderly (+65 years)	Screening was the most cost-effective	Adequate
Filby et al. 2014 (18)	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
Lee et al. 2013 (21)	Population screening vs. Universal supplementation with vitamin D	Elderly (+65 years)	Screening was the most cost-effective alternative	Inadequate
Patil et al. 2016 (25)	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 (17)	Supplementation with vitamin D (800IU) vs. Current practice	Elderly (65-80 years)	Supplementation (800IU) was cost-saving	Adequate
Church et al. 2015 (23)	Supplementation with vitamin D (800IU)	Elderly (+84 years; nursing homes)	Supplementation (800IU) was cost-saving	Adequate
Togerson et al. 1995 (15)	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 et al. 2002 (26)	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

Lilliu et al. 2003 (28)	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
Church et al. 2011 (22)	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
Frick et al. 2010 (20)	Supplementation with vitamin D (800IU) vs. No intervention	Elderly (+65 years)	Supplementation (800IU) was cost-effective	Adequate
Poole et al. 2015 (16)	Supplementation with vitamin D (800IU) vs. No intervention	Elderly (+65 years)	Supplementation (800IU) was cost-effective (cost-saving for the older cohorts)	Adequate
Filby et al. 2015 (19)	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