



Finding the Optimum Scenario in Risk-benefit Assessment: An Example on Vitamin D

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Author's contribution

This work was carried out in collaboration between all authors. Author FLB designed the study, did literature research, developed the model, performed the statistical analysis and wrote the first draft of the manuscript. Authors JH, HV, MP, RA, MN contributed by adding expertise from various research disciplines and in finalizing the paper. In addition, authors JH and MN assisted in the model development and statistical analysis. All authors have read and approved the final manuscript.

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ABSTRACT

Background: In risk-benefit assessment of food and nutrients, several studies so far have focused on comparison of two scenarios to weigh the health effect against each other. One obvious next step is finding the optimum scenario that provides maximum net health gains.

Aim: This paper aims to show a method for finding the optimum scenario that provides maximum net health gains.

Methods: A multiple scenario simulation. The method is presented using vitamin D intake

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in Denmark as an example. In addition to the reference scenario, several alternative scenarios are simulated to detect the scenario that provides maximum net health gains. As a common health metric, Disability Adjusted Life Years (DALY) has been used to project the net health effect by using the QALIBRA (Quality of Life for Benefit Risk Assessment) software.

Results: The method used in the vitamin D example shows that it is feasible to find an optimum scenario that provides maximum net health gain in health risk-benefit assessment of dietary exposure as expressed by serum vitamin D level. With regard to the vitamin D assessment, a considerable health gain is observed due to the reduction of risk of other cause mortality, fall and hip fractures when changing from the reference to the optimum scenario.

Conclusion: The method allowed us to find the optimum serum level in the vitamin D example. Additional case studies are needed to further validate the applicability of the approach to other nutrients or foods, especially with regards to the uncertainty that is usually attending the data.

Keywords: Optimum scenario; vitamin D; risk-benefit assessment; DALY; QALIBRA.

1. INTRODUCTION

Risk-benefit assessments of food and nutrients focus on interventions and policies in connection with food consumption and health outcomes [1]. Until recently, the risk and benefit assessments of food have been separate processes with different methods. Due to the increasing interest of estimation of the net health impact of food consumption, development of methods that integrate both the health benefits and risks of food (ingredient) in one go have gained interest.

Currently, there are some methods and approaches on how to perform risk-benefit assessment of food [2,3,4,5,6,7]. These methods focus on comparison of two or more scenarios and determine which one of the scenarios prevails over the other from the perspective of public health. When applying these methods, the assessment may stop at an early stage, i.e. before the health effects are integrated in a common health metric. Several case studies have been performed; low calorie sweeteners [8], farmed salmon, soy protein [9], benzo[a]pyrene and heat treatment of milk [10] to validate the applicability of the BRAFO tiered approach [5].

Whereas those studies typically compared two scenarios, one obvious next step is to investigate more than two scenarios and find the optimum scenario to improve public health. This approach was suggested by [11,12]. This paper aims to show how this can be done by comparing the net health gains of different scenarios, expressed in a common health metric (DALY, disability adjusted life years). The method is presented in a case study on vitamin D intake in Denmark. So far, the health risk and benefit associated with vitamin D have not been integrated using common health metric. Our objective is to illustrate how an optimum scenario can be found. Therefore, several simplifying assumptions are made and the result is a crude estimate of the optimal vitamin D serum level needed to be achieved for the maximum net health gain in Danish population.

The method focusses on estimating each health effect expressed in DALYs in the reference scenario, followed by the estimation of the health effect of alternative scenarios with changing serum 25(OH)D concentration. The DALY difference between the alternative

scenarios and reference scenario expresses the net health gain. It is computed with the QALIBRA (Quality of Life for Benefit Risk Assessment) tool [4]. Subsequently, the scenario that results in the maximum net health gain is considered the optimum scenario.

2. VITAMIN D

Vitamin D plays an important role in reducing the risk of several diseases [13]. However, the current dietary intake in the population is lower than the recommended intake [14,15]. Due to the high latitudes, indoor activities and low vitamin D intake, the serum 25(OH)D level is relatively low in most populations in Northern Europe [16]. Hence, it has been suggested to increase the recommended intake [15,17,18]. Recently, the Nordic Nutrition Recommendations (NNR) increased the recommended dietary intake from 7.5 to 10 ug/day [15].

Studies suggest that higher 25(OH)D serum levels are associated with beneficial effects, i.e. for reducing the risk of several diseases [13,19,20,21,22,23]. On the other hand, some studies report that vitamin D may lead to an adverse effects at both higher and lower levels [24] and when taken excessively [25]. This implies that there will be an intermediate optimal serum 25(OH)D level and finding this level would be imperative to attain the maximum health benefits.

Several studies suggest various optimum serum 25(OH)D levels, needed to reduce the risk of some diseases. Based on the existing data, the suggested optimal serum level needed to reduce the risk of osteoporosis, cardiovascular diseases and colorectal cancer is 75-110 nmol/l [20]. For fracture 75 nmol/l [26] and to lower the risk of mortality 50-60 nmol/l [24] have been suggested.

In this paper, we aimed to establish the optimum serum 25(OH)D level for the Danish population and therefore several alternative scenarios are simulated from which an optimum serum level can be identified using DALY.

2.1 Health Effect Identification

To identify the endpoints that are associated with vitamin D, we reviewed national and international authoritative reports such as WHO/IARC [27], EFSA [17] and IOM [18] which are up-to-date scientific opinions based on a collection of nutritional and observational studies.

According to WCRF/AIRC and WHO/FAO [28,29] criteria for the strength of evidences, the most convincing evidence is substantiated by multiple randomized controlled intervention trials of sufficient size, duration and quality in a population representative for the target population showing consistent effects. So far, there is strong scientific evidence for the effect of vitamin D on bone related diseases [18,19,21,22,30], while the evidence for other endpoints such as cardiovascular diseases and diabetes is conflicting [17,18,27].

In this paper, we have considered endpoints that have convincing evidence. These are: hip fracture, other nonvertebral fracture and fall. In addition, we have included an endpoint where the evidence is relatively weak, but the reported quantitative data on the dose-response relationship are particularly suitable for the purpose of our study (total mortality). As the endpoint "total mortality" includes mortality from the other endpoints considered in this

assessment, we use the term “other cause mortality” to distinguish this effect from “total mortality”.

2.2 Description of Dose-response and Selection of Population

Various studies on the association between vitamin D and health effects describe the vitamin D dose differently in the dose-response relation. Usually, the dose is represented as 25(OH)D level in nmol/l serum [24] or ng/ml serum [31] and sometimes the dose is represented as intake in IU or µg per day [22]. The serum level of vitamin D gives information about the recent exposure to vitamin D [32] and since we wanted to establish the optimal serum 25(OH)D level, we related the dose to serum level in nmol/l throughout this study. The relation between intake and serum level (nmol/l) is presented in section 2.5.

For fall and fractures, the selected populations are elderly of both sexes because the Randomized Control Trial (RCT) studies included in the dose-response considers elderly of general population [19,21,22]. The sub-populations associated to the selected endpoints and the types of study are given in Table 1.

Table 1. The selected endpoints and population of interest related to vitamin D intake

Endpoints	Type of study and population characteristics	References
Fractures (hip and other nonvertebral)	Meta-analysis of RCT*, ≥65 years old, both sexes.	[22]
Fall	Meta-analysis of RCT*, ≥65 years old, both sexes	[19]
Other cause mortality	Cohort study, survey, ≥30 years old, both sexes	[24,33,34,35]

*RCT: Randomized controlled trial

For other cause mortality, various studies conducted the relation between vitamin D and mortality in different subpopulation [24,33,34,35,36]. In our study, the target population is both sexes of age ≥30 years old for this endpoint.

2.3 Intake of Vitamin D and Serum 25(OH)D Level

In Denmark, fish is the primary dietary source of vitamin D [14], followed by eggs, milk and meat products. The relative contribution of the various foods for the daily dietary intake of vitamin D in Denmark is shown in Table 2 [14].

Table 2. Food type contributing to the daily vitamin D intake of the Danish population

Food type	% of contribution
Fish	43
Meat	29.5
Milk and cheese	13
Eggs	9.5
Butter and margarine	5

The average dietary vitamin D intake is obtained from [14]: 3.8 µg/d for men and 3.1 µg/d for women. These values are transformed to serum levels in nmol/l as explained in section 2.5. As alternative scenarios, we have simulated a series of serum 25(OH)D level: 35, 50, 65, 72, 80, 90, 100, 120 and 166 nmol/l for both sexes and ages. These values were chosen in a process of trial and error, using interpolation to find the optimum.

2.4 Health Impact Estimation

To estimate the net health effect, the QALIBRA (Quality of Life for Benefit Risk Assessment) software is used [4]. This software run the simulation based on the following DALY equation for each disease [5]. For the net effect, DALYs are summed over every disease.

$$DALY_{a,s} = P_{eff(a,s)} * [P_{rec} * YLD_{rec} * w + P_{die} * (YLD_{die} * w + LE_{a,s} - CA - YLD_{die}) + (1 - P_{die} - P_{rec}) * (LE_{a,s} - CA) * w] \quad (1)$$

Where:

$DALY_{a,s}$	disability adjusted life years at age group a and sex s
$P_{eff(a,s)}$	probability of onset of the disease at age and sex, per year
P_{rec}	probability of recovery from the disease
P_{die}	probability that the disease causes death
YLD_{rec}	mean duration of disease for those who recover
YLD_{die}	mean duration of disease for those who die
CA	current age of individual in year of disease onset (years)
$LE_{a,s}$	normal life expectancy (i.e. expected age at death) at age a and for sex s
w	disability weight for disease.

Since we are interested in the health effect of the difference of the scenarios, estimating the change in DALY between scenarios is imperative [5].

The $\Delta DALY$ between scenarios is calculated using:

$$\Delta DALY = \Sigma DALY_{alt} - \Sigma DALY_{ref} \quad (2)$$

Where, $\Delta DALY$ is change in DALY; $\Sigma DALY_{alt}$, summation of DALYs caused by every endpoint of all individuals in the population at the alternative scenario and $\Sigma DALY_{ref}$, summation DALYs caused by every endpoint of all individuals in the population at the reference scenario.

The DALY is summed for the ages and sexes considered for each endpoint, with $N_{a,s}$ the populations size for age and sex in Denmark.

$$\Sigma DALY = \Sigma_{endpoints, \Sigma_{a,s}} N_{a,s} * DALY_{a,s} \quad (3)$$

DALYs represent health loss; therefore, if the estimation of $\Delta DALY$ results in a positive value then the change in consumption has an adverse health effect (health loss). If the $\Delta DALY$ is negative, then the change in consumption has a beneficial effect [4,5].

2.5 Conversion of Vitamin D Intake in 25(OH)D Serum Level and Dose-Response

Vitamin D intake has to be related to 25(OH)D serum concentration because our aim is to find an optimum serum level. It also allows a comparison of all endpoints, because some studies report an association between serum level and disease instead of intake and disease. For the conversion of intake to serum concentration, we used two studies by Cashman et al. [37,38], that relate the dietary vitamin D intake ($\mu\text{g}/\text{d}$) with serum level (nmol/l) in two age groups. We have chosen the 50 percentile data points from both studies as point estimates of the vitamin D intake level that is needed to achieve the serum level in the study subjects. So, for fall, hip and other nonvertebral fracture the 50 percentile data points for both sexes as reported by Cashman et al. [37] are used, because the target populations for these endpoints are elderly of both sexes. Since the target population for other cause mortality is ≥ 30 years old of both sexes, the intake in $\mu\text{g}/\text{d}$ is related to serum level in nmol/l using the 50 percentile data points of both studies of Cashman et al. [37,38]. For all conversion from dietary intake in $\mu\text{g}/\text{d}$ to serum (S) level in nmol/l serum, the following linear model (eqn. 4) is used.

$$(S, \text{ nmol/l}) = a * (\text{vitamin D intake, } \mu\text{g/d}) + b \quad (4)$$

The fitted values for a and b are $a=2.08$ and $b=35.2$ when both sexes data points are used, i.e. for hip fracture, other nonvertebral fracture and fall [37]; $a=1.95$ and $b=35$ when both sexes data points from [37,38] studies are used, i.e. for other cause mortality.

For different endpoints, this approach may assign different reference scenario intakes in terms of serum levels to men and women. These reference scenario serum levels are derived from different average intakes for men and women (see section 2.3) and eqn. 4. They are 43 nmol/l (fractures and fall) and 42 nmol/l (other cause mortality) for men and 42 nmol/l (fractures and fall); 41 nmol/l (other cause mortality) for women. As a side effect of our approach, this may result in small differences in the assumed reference level as a function of the same intake for different endpoints.

Using this method, intakes are converted to serum concentrations expressed as nmol/l. Subsequently, to determine the relative risk (RR) based on our intake scenarios, the serum level-RR relations are derived from studies that describe vitamin D intake in IU/d for most of the selected endpoints (Table 3). When the doses are given in a range, we have used the mean value. The intake values in the dose-response for fall were reported in ranges and qualitatively as less or greater than 60nmol/l [19]. When given in range, the mean value was used and when given qualitatively, we assumed 55 nmol/l and 87 nmol/l. To relate IU/d to $\mu\text{g}/\text{d}$, we used the standard conversion formula [39]: 1 IU = 0.025 μg .

The values printed in *italics* in the table are calculated using equation 4.

In the studies used for fall, hip and other nonvertebral fracture [19,21,22] the relative risks were determined compared to placebo, so presumably $RR=1$ at an intake of 0 IU/d (serum level ≈ 35 nmol/l). This is not included in our analysis because it is not explicitly stated in the papers, and it is indicated that in general vitamin D doses ≤ 400 IU/d are not sufficient for the prevention of fractures [21,22]. Also, the fit of the dose response model to the data would not benefit from including values corresponding to this $RR=1$ in the analysis.

Table 3. Data (Intake, serum level and mean Relative Risks) of the endpoints hip fracture, other nonvertebral fracture and fall, used to derive the dose response relations

Endpoints	IU/d	µg/d	nmol/l	Mean RR	95% CI	References
Hip fracture	400*	-	-	1.15	0.88, 1.5	[21,22]
	500	12.5	61	0.91	0.78, 1.05	
	600	15	66	0.82	0.69, 0.97	
	750	18.75	74	0.74	0.61, 0.88	
Other nonvertebral fracture	400*	-	-	1.03	0.86, 1.24	
	500	12.5	61	0.86	0.77, 0.96	
	600	15	66	0.8	0.72, 0.89	
	750	18.75	74	0.77	0.68, 0.87	
Fall			55	1.35	0.98, 1.84	[19]
			80	0.81	0.71, 0.92	
	850	21.25	87	0.77	0.65, 0.9	

*Vitamin D dose of ≤400 IU/d is not sufficient for the prevention of fractures [21,22]. Therefore, data points of ≤400 IU/d were not used for fractures

The dose response relations expressing RR as a function of serum level are modeled using a log-linear function for each endpoint separately, except for other cause mortality.

$$\ln(RR) = (S, \text{nmol/l}) *c + d \tag{5}$$

The fitted values (c and d) are given in Table 4.

The parameters c, d and the estimated RR for the reference scenario using eqn. 5, are shown in Table 3. Equation 5 is applied to calculate the RR for the alternative scenarios.

Table 4. The fitted values and estimated RR's for the reference scenario serum levels per endpoint and sex

Endpoint	Fitted values		RR-men	RR-women
	c	d		
Hip fracture	-0.016	0.85	1.19	1.22
Other nonvertebral fracture	-0.009	0.44	1.04	1.06
Fall	-0.018	1.3	1.67	1.73
*Total mortality			0.85	0.85

*The model for total mortality is given in eqn. 10

Fig. 1 illustrates the serum level (nmol/l)-RR data points that are used to estimate the fitted values shown in Table 4, and the fitted dose-response models, including the model for other cause mortality (see below). The fitted models have RR=1 at different serum levels values above the zero intake and reference intake scenarios, which means that RRs cannot be compared between endpoints.

The serum level-RR relations for hip fracture, other nonvertebral fracture and fall show the same trend (decreasing risk with increasing serum level). For other cause mortality, the serum level-RR relation shows increasing risk at low and high serum level.

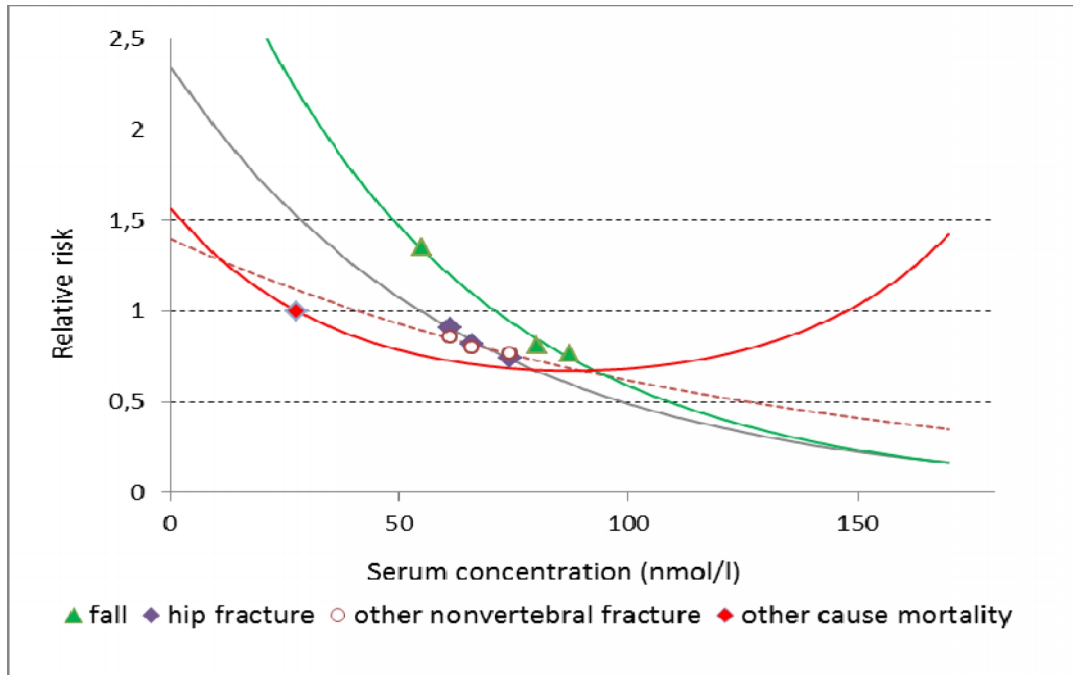


Fig. 1. The serum level-RR data points (Table 3) and the fitted lines describing the relation between serum level and relative risk (eqn. 5)

The estimated RR has to be converted to absolute risk for the reference scenario $P_{eff}(S_{ref})$. To this end we have assumed that the current incidence Inc is related to the current intake. Thus,

$$\int_0^{\infty} P_{eff}(S)p(S)dS = Inc/N \quad (6)$$

However, by assuming that everyone's serum level is the average of the population, we simplified the above equation to:

$$P_{eff(a,s)}(S_{ref}) = Inc_{a,s} / N_{a,s} \quad (7)$$

Where $Inc_{a,s}$ is the incidence of the diseases in the relevant sex and age group, which is obtained from epidemiological studies as described in section 2.6. The variation in incidence per age group and (when relevant) sex is considered for hip fracture and fall. Due to lack of data, only sex variation is considered for other nonvertebral fracture.

To estimate the absolute risk at an alternative scenario $P_{eff}(S_{alt})$, we use the fact that by definition the ratio of absolute risk to relative risk at the reference scenario is similar to the ratio of absolute risk to relative risk at an alternative scenario [40].

$$P_{eff}(S_{ref}) / RR(S_{ref}) = P_{eff}(S_{alt}) / RR(S_{alt}) \quad (8)$$

Then, by rewriting eqn. 8, $P_{eff}(S_{alt})$ becomes:

$$P_{eff}(S_{alt}) = RR(S_{alt}) * P_{eff}(S_{ref}) / RR(S_{ref}) \quad (9)$$

To calculate the RR of other cause mortality, results from [35] are used. Zitterman et al., [35] describe the RR of changes from reference category serum level ΔS (nmol/l) as:

$$\ln(RR) = -0.0132 * \Delta S + 0.00011 * (\Delta S)^2 \quad (10)$$

This model (eqn. 10) is applied here, using reference category serum level 27.5 nmol/l with RR=1, as given by [35], so the serum level (nmol/l) is given by $S = \Delta S + 27.5$.

To estimate the probability of effect for mortality at the reference scenario ($P_{eff,M}(S_{ref})$), the mortality rate is used. This mortality rate is calculated for the different age groups and sexes separately, data is obtained from [41].

$$P_{eff,M(a,s)}(S_{ref}) = \text{Mortality}_{a,s} / N_{a,s} \quad (11)$$

To estimate $P_{eff,M}(S_{alt})$ we use the same definition as eqn. 8. Thus,

$$P_{eff,M}(S_{alt}) = RR(S_{alt}) * P_{eff,M}(S_{ref}) / RR(S_{ref}) \quad (12)$$

The above equation gives us total mortality. However, total mortality also includes the mortality from the other endpoints included in our study (fall, hip fracture and other nonvertebral fracture). Hence, taking into account the other endpoints from total mortality, the probability effect for other cause mortality ($P_{eff(\text{other cause mortality})}$) becomes:

$$P_{eff(\text{other cause mortality}) a,s}(S) = P_{eff,M(a,s)}(S) - \sum_j P_{eff(j)a,s}(S) * P_{die(j)a,s}(S) \quad (13)$$

Where $P_{die(j)}$ and $P_{eff(j)}$ are the probability of death due to disease j and the probability of onset of disease j .

2.6 Parameters for DALY Calculation

To estimate the input parameters in QALIBRA, a similar approach as in [38] is used. Mainly Danish national epidemiological data are used and to some extent, international and analogous country epidemiological data were used in case of scarcity of Danish data. Furthermore, in case of data unavailability, assumptions have been made, as explained below. The model population is 1000 individuals with age and sex representative of the Danish population [41].

$P_{eff(a,s)}$ is estimated for all endpoints as explained in section 2.5. The incidences, Inc are obtained from different studies; for hip fracture [42], nonvertebral fracture [43] and fall [44]. P_{eff} for other cause mortality is described in eqn. 13, mortality rate is obtained from Denmark Statistics [41].

When an individual develops a disease, either the individual recovers from the disease (P_{rec}), dies due to the disease (P_{die}) or survives with the disease (P_{sur}) until the normal life expectancy [4,5]. P_{die} is estimated for hip fracture [45], nonvertebral fracture [46] and fall [47]. P_{die} for other cause mortality by definition is 1. P_{sur} is estimated for hip fracture from [48], nonvertebral fracture [44], fall [49] and for other cause mortality is set to 0.

P_{rec} is calculated for all endpoints using

$$P_{rec} = 1 - (P_{sur} + P_{die}) \tag{14}$$

YLD_{die} for hip fracture is assumed to be 2 years, the highest mortality period since onset of hip fracture [45] and YLD_{rec} is assumed as the follow up period, 5 years [50]. For the other bone related diseases, it is assumed that YLD_{rec} and YLD_{die} are equal to the values used for hip fracture. For other cause mortality, by definition both parameters are set to 0.

Severity weight w, is obtained from the WHO burden of disease estimation [51]. The summary input parameters are presented in Table 5.

Table 5. The summary of input parameters for DALY calculation

Endpoints	Estimated parameters					
	P _{sur}	P _{rec}	YLD _{rec}	P _{die}	YLD _{die}	w
Hip fracture	0.57	0.135	5	0.295	2	0.372
Nonvertebral fracture	0.65	0.23	5	0.122	2	0.18
Fall	0.11	0.78	5	0.11	2	0.2
Other cause mortality	0	0	0	1	0	1

* The P_{sur} is not a typical input parameter required to estimate DALYs in QALIBRA, but it is used to estimate P_{rec}

3. RESULTS

Table 6 contains the DALYs simulated with the QALIBRA tool for each endpoint. Our aim was to determine the optimum scenario that provides maximum net health gains in comparison with the reference scenario. The results presented in Table 6 are the differences in DALYs between the alternative scenarios and the reference scenario, for each endpoint. That can be interpreted as the health, expressed in DALYs, one can gain if the serum concentration changes from the reference to the alternative.

It appears that for hip fracture, nonvertebral fracture and fall, the healthy life years increase with increasing serum 25(OH)D level. Among these endpoints, a considerable gain of DALYs is observed primarily from fall prevention when the serum level increases. For other nonvertebral fracture only a slight benefit is observed with increasing serum level.

Apparently, a substantial gain in healthy life years is achieved with increasing serum 25(OH)D level up to 90 nmol/l from the reduction of the risk of other cause mortality, reaching a maximum benefit of -92 DALY/1000 individuals. However, the benefit gradually decreases when the achieved serum 25(OH)D level reaches 100 nmol/l and up. Combined with the other endpoints, the health benefits gained by the reduction of the risk of other cause mortality is dominant up to the serum level of 90 nmol/l.

Even though the net healthy life year's is gradually reducing after 90 nmol/l, there seems to be a benefit compared with the reference serum level up to 120 nmol/l. At a serum level of 166 nmol/l, the net benefit shifted to net risk, 156 DALY/1000. Since the DALY was not calculated for the serum level between 120-166nmol/l, the precise turning point from net benefit to net risk cannot be defined in our assessment. However, it is in the range of the serum level of 120-166 nmol/l.

Table 6. The estimated median DALYs/1000 individuals for each endpoint

Scenarios (nmol/l)	Hip fracture	Other nonvertebral fracture	Fall	Other cause mortality	Net
Ref. Vs. 35	12	0.85	9.7	34	56
Ref. Vs. 50	-2.6	-1.0	-9.5	-1.4	-15
Ref. Vs. 65	-7	-2.8	-23	-19	-52
Ref. Vs. 72	-8.6	-3.4	-28	-23	-63
Ref. Vs. 80	-9.6	-4.2	-32	-26	-72
Ref. Vs. 90	-12.4	-5.2	-37	-37	-92
Ref. Vs. 100	-13.7	-6.0	-41	-14	-75
Ref. Vs. 120	-16.4	-7.3	-46.4	18	-52
Ref. Vs. 166	-20	-10	-53	239	156

The DALY of the optimum scenario is printed in **Bold and italics** in Table 6

Fig. 2 shows the results presented in Table 6 in a graph. The maximum net health gains is achieved when serum 25(OH)D level reaches the optimum serum level of 90 nmol/l (rectangular green mark on the red line). Note however, that many uncertainties have not been incorporated and that the curves showing the DALYs versus serum level is rather flat.

It is noted that the shape of the curve for the total DALY (red line) in Fig. 2 is highly influenced by the DALY of “other cause mortality” (blue line). As it turns out the optimum for just other cause mortality is also the optimum for the combined effect. That is no real surprise, mortality is the most severe health effect (w=1) and affects a wide range of subpopulation groups compared to the other endpoints. Compared with mortality, fall and fractures are relatively small health effects with less severity weigh and affect small subpopulation groups.

Table 7 shows the incidences at the reference and the optimum serum levels computed with the QALIBRA tool. The percent of reduction of incidences of fall and hip fracture is relatively higher; accounting for 66% and 54% respectively, when changing from the reference to the optimum scenario.

Table 7. The incidence/1000 person per year at reference optimum scenario and % change of incidences between the scenarios

Scenarios (nmol/l)	Hip fracture	Other nonvertebral fracture	Fall	Other cause mortality
*Reference	8.7	5.4	36	55
Optimum	4	3.4	12.4	44
% of Change	54	37	66	20

*The serum level for the reference scenario varies between 41- 43 nmol/l (see section 2.3)

Fig. 3 shows a scatter plot of the variation in DALYs gained/lost when changing from the reference scenario to the optimum scenario, produced by the QALIBRA tool. Each dot in the graph shows the DALY change for an individual characterized by age (left side plot) and by sex (right side plot).

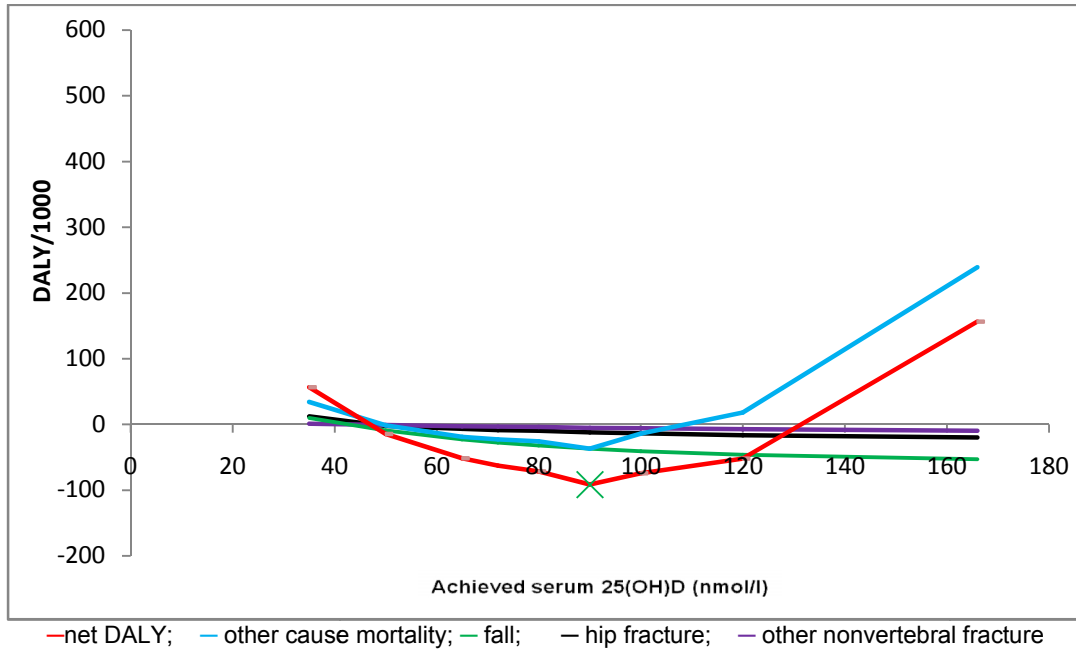


Fig. 2. The DALY of each health effect and total DALY

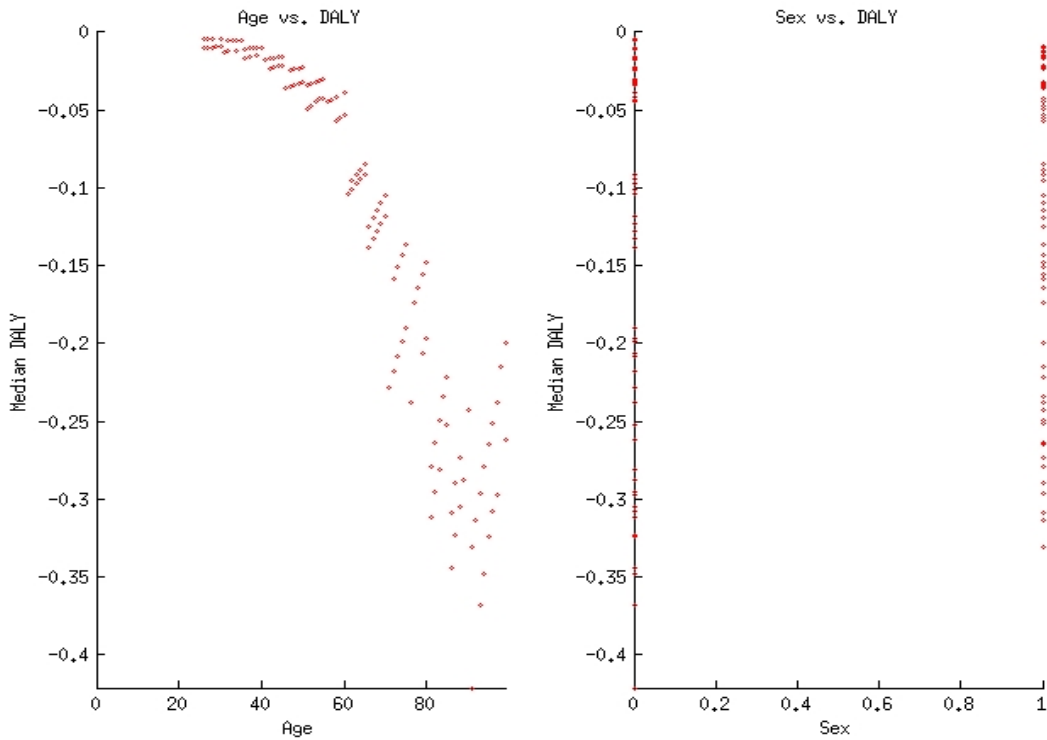


Fig. 3. Scatter plot of the DALY change per age and per sex (0 in the x-axis represent women, 1 in the x-axis represent men) at optimum scenario

The left plot shows the variability of DALYs gain/lost with age. Ages from 0 to 30 years are not included as this age group is not affected by any of the endpoints considered in this study. The increase in healthy life years gain is observed with increasing age, because elderly people benefit primarily from the prevention of fractures, falls and other cause mortality when the serum 25(OH)D level changes from the reference to the optimum scenario. Adults of age 30-64 gain less DALYs compared to the elderly since this age group benefits only from the reduction of other cause mortality as for this age class the other endpoints are not included in the analysis. Also in the young age groups the probability of (other cause) mortality is very low and therefore a reduction in mortality risk has a small effect.

The second scatter plot (right plot) shows the variation of DALY in sex, it is noted that age contributes more to the total variation in DALY than sex, this is primarily because the variation of mortality rate (for other cause mortality) and incidence rate are larger per age class than per sex.

4. DISCUSSION AND CONCLUSION

The case study of vitamin D illustrates a method for finding the optimum scenario that provides maximum net health gains. To show how to find the optimum scenario, the net health impact of the different endpoints for several scenarios were calculated with the QALIBRA software (www.qalibra.eu). The QALIBRA software explicitly uses two scenarios (reference and alternative scenario) and shows the DALY difference of those scenarios. Since our aim was to determine the scenario that provides maximum health gains in comparison with the reference scenario, several alternative scenarios have been simulated in QALIBRA. Then, the difference of the DALY between the alternative and reference scenario that gives the maximum net health gain is considered the optimum scenario. In the vitamin D example, nine alternative scenarios were compared to the reference scenario to determine the scenario that provides maximum net health gains.

The study is the first to show a comprehensive quantitative assessment of vitamin D on aggregate health effects by expressing them in common health metrics (DALY). In addition to the well-known effect of vitamin D on bone, other effects are reported to be associated with vitamin D. However, so far only strong scientific evidence for a preventive effect of vitamin D on fall and fractures exists [19,21,22]. The higher dose required for the prevention of fractures may be overestimated [21,22], recent study indicates that vitamin D supplementation alone does not significantly reduce the risk of fractures [52]. In this assessment, we have considered these endpoints that have strong scientific evidences and another endpoint (total mortality) with less convincing scientific evidences, in order to analyze their contribution to the net health effects. The preferred way to combine convincing and less convincing effects is to incorporate uncertainty. Although the QALIBRA tool allows for the introduction of uncertainty by making a probabilistic assessment, this was not done here. The focus of this paper was to show a method to find the optimum scenario (serum level). For this reason other simplifications have been introduced as well.

The most important finding of this study is showing that it is possible to determine the scenario that provides the optimum public health effect from the cumulative effect of all the endpoints considered. Because the function that describes the relation between serum concentration and net health gain is rather smooth a simple series of increasing serum concentrations readily shows the optimum. If the net health effect appears to change quickly with increasing serum levels, then the bisection method or even more sophisticated

mathematical methods can be used. Consequently, according to our assessment the simulated scenario that provides the maximum benefit is when serum 25(OH)D level reaches 90 nmol/l. Note that the assessment considers the reference category serum level (27.5 nmol/l) in the calculation as given by [35]. Using another value for this reference would change the optimum in the same direction. Because the net health effect for the serum level values of 81-89 nmol/l and 91-99 nmol/l are not estimated in this assessment, the precise optimum would be somewhere between 81 and 99 nmol/l. The result is in accordance with other studies conducted for various endpoints [53,54]. Ideally, men and women would have different optimal serum levels, because of the minor difference in response to intake of vitamin D and/or serum level. However, in this assessment the intake and the dose-response difference in men and women are not substantially different (see section 2.3 and 2.5).

It is essential to point out the limitations of the assessment to better interpret the quantitative result. For the reference serum level, we have derived the serum level that results from the mean Danish intake stratified by sex. For the conversion of intake in $\mu\text{g/d}$ to nmol/l, we have used only two studies [37,38] and ignored the variation between individuals by using the 50 percentile intake-serum relationship only. Note that serum levels do not only depend on intake but that UV exposure contributes a large part of the serum level. However, when we used another study [55] to relate the intake in $\mu\text{g/d}$ to serum 25(OH)D level in nmol/l the results are fairly similar. Also, we have included an endpoint (total mortality) that has relatively weak scientific evidences but dominates the outcome. Moreover, very few data points were available to estimate the relation between the RRs and serum concentration, and extrapolation beyond the range of the available data (see Fig. 1) was needed to analyze all the different scenarios. The choice of the log-linear model (eqn 5.) and the decision not to include low intake relative risk values when fitting the model have an impact on the quantitative result. Furthermore, YLD_{die} and YLD_{rec} are assumed to have a fixed value but these values may depend on age, sex and/or vitamin D serum level. Because of all these assumptions and uncertainties, the quantitative result obtained in this assessment should be interpreted with care. When more data will become available in the future, the same methodology can be applied to obtain more precise estimates of the health impact of different intake scenarios.

The change of serum 25(OH)D level from the reference scenario (see section 2.5) to the optimum scenario (90 nmol/l) provides a gain of -92 DALY/1000 Danish individuals. For this -92 DALY net health gain, other cause mortality contributes 40%. The target population for other cause mortality includes a larger fraction of the population compared to the other endpoints. Combined with the maximum severity of the effect (death), this explains why the DALY gain by this endpoint alone accounts for 40% of the net gain. Similarly, fall contributes about 40% for the net gain. The DALY gain from hip and other nonvertebral fracture seem relatively trivial. On the other hand, when the serum level reaches to 120 nmol/l and up, the healthy life years gain (due to other cause mortality) shifts to healthy life years loss. The dose-response studies included in this study show a reduction of risk of bone diseases (fractures and fall) with increasing circulating serum level [19,21,22]. However, other studies (not included in this study) on the effect of vitamin D on bone health indicate that a higher circulating serum level (> 130 nmol/l) may adversely affect bone health [56,57]. If these studies would be included in the assessment, the DALY of the bone diseases and the net DALY might change, mainly for the higher scenario (166 nmol/l). But, the inclusion of these studies will probably not have a large impact on the DALY of the optimum scenario.

The net DALY in Fig. 2 is highly influenced by the DALY of the other cause mortality. Studies show a U and reverse J- shape for the association of vitamin D with mortality [24,33]. Likewise, the dose-response study used for other cause mortality [35] shows a similar pattern between the serum level and RR of mortality. This implies that there is an increasing risk of mortality at high and low serum level, with the optimum in between. As the minimum of the quadric function given by equation (10) lies at $\Delta S = 60$, the dose-response study we used in our assessment for the other cause mortality shows that $60 + 27.5 = 87.5$ nmol/l gives the lowest risk of mortality. Because of the differences in the method used to determine the optimum serum level required to protect from disease, several studies suggests different levels. Some studies and IOM consider a serum level of >50 nmol/l to be adequate [58,59,60]. Others have suggested that the most advantageous serum level begin at 75 nmol/l and that the best are between 90 and 100 nmol 25(OH)D/L [52,53], which is in accordance with the result obtained in this study interpreted in DALY.

Concerning the variation in sex and age, the variation of the DALY in Fig. 2 is mostly due to the variation in the incidences and mortality rate variation per age class. For most of the selected endpoints, the difference in incidences and mortality rate (other cause mortality) is larger between age classes than between sexes, (see Fig. 2, right plot).

In this study we have used vitamin D to show a method to find the best scenario, which achieves the maximum net health gain. A similar approach can be used for other foods or food components and biomarkers. As part of determining the best scenario, food processing parameter optimization (e.g. time-temperature, storage time) may also be integrated into the risk-benefit assessment to optimize the health [40].

The vitamin D concentration is the result of food and supplement intake but is also the result of UV-exposure as we consider the baseline serum level in our assessment. UV exposure is linked with skin cancer risk. That risk is not directly included in our assessment. A more complete assessment would separate the intake and UV-exposure effects. Furthermore, the development of methods to include aspects of a disease such as disease recurrence, complete and partial disease remission is needed. Future research may also focus on method development for output validation in relation to the QALIBRA tool.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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