seo economisch onderzoek
amsterdam economics

Cost Effectiveness Vitamin D Supplements: Literature review

Datum	January 27, 2022
Authors	Lucy Kok & William Luiten
Clients	Goodlife Pharma bv & Galephar Netherlands bv
Feature	2022-02

Introduction

Cause

As of January 1, 2019, the low dose of Vitamin D (less than 5,600 IU) has been removed from the basic health insurance package. Vektis (2019) and Nivel (2020) conclude that substitution has subsequently taken place to use a higher dose. The number of users has decreased, while costs have increased. Insurers have subsequently urged the Minister of Health, Welfare and Sport for a new review of the compensation. On March 10, 2021, the Minister of Health, Welfare and Sport asked the National Health Care Institute for advice on the reimbursement of high doses of vitamin D and combination preparations with calcium. These are doses that are only available on prescription and are prescribed by a general practitioner or specialist to patients who suffer from, among other things, a vitamin D deficiency, osteoporosis, arthrosis and high blood pressure.

On September 24, 2021, the Advisory Package Package (ACP) of the Zorginstituut discussed the proposal to further limit the reimbursement for vitamin D. In this meeting it was concluded that this is a fundamental and broader discussion about accessibility and adherence and "for a general line of reasoning that can be for its own account." Ultimately, this should result in an advice about "for own account in general and vitamin D in particular." Because this fundamental discussion requires more preparation, the Zorginstituut decided in December to issue an advisory report on vitamin D separately in the first quarter of 2022.

Research questions

It is important for the discussion to know what the social consequences will be if the higher dose of vitamin D also disappears from the basic package. The client has the following three to ask:

- What are the consequences of vitamin D deficiency for the patient and society as a whole (burden of disease)?
- What is the cost-effectiveness of prescribing vitamin D?
- What are the economic consequences for vulnerable groups if the compensation were to disappear fall?

Delineation and research approach

To answer the research questions, the literature on vitamin D deficiency and the effect of vitamin D supplements was first mapped out. Based on the literature study, the client determines whether we calculate the burden of disease and cost-effectiveness for the Netherlands, calculate one of the two or neither. The results of the literature study are set out in this memorandum.

Below is the literature on vitamin D deficiency in the Netherlands. We then describe the literature on the burden of disease of vitamin D deficiency. We do the same for you

the cost-effectiveness and the effect of the personal contribution on healthcare use. We formulate a conclusion based on the results of the literature study.

Prevalence of vitamin D deficiency in the Netherlands

In the literature, vitamin D deficiency is defined as the blood level contains less than 50 nmol/l vitamin D (Bischoff-Ferrari, 2012; Holick et al., 2011). About 50 nmol/l is needed to prevent muscle and bone weakening. It is also important for normalization of PTH levels1 . Risk factors for vitamin D deficiency are insufficient exposure to sunlight or reduced production of vitamin D, in conjunction with an insufficient supply through food (Wielders et al., 2010).

A study by Boonman-de-Winter at al. (2015) shows that in the winter months 59 percent of the Dutch population has a vitamin D deficiency. Men under 50 and women over 70 in particular are relatively often confronted with a vitamin D deficiency. In the summer months

the proportion of people with vitamin D deficiency drops to 35 percent. This mainly concerns women over 70 (Boonman-de Winter et al, 2015). In the Netherlands, approximately 50 percent of elderly people living at home and 85 to 90 percent of residents of a care or nursing home have a vitamin D level that is too low. Among adults, 19 to 51 percent of people of non-Western descent (Turkish, Moroccan and Surinamese descent) have a vitamin D deficiency. 2

Use of Vitamin D Supplements

To combat vitamin D deficiency, people use vitamin D supplements. Research by Info2action (2021) shows that in 2020 3.5 million people in the Netherlands will take vitamin D supplements at a low dose (less than 5,600 IU). In 2021 this has increased to five million people due to corona. In addition, by 2020, nearly 900,000 people will be prescribed vitamin D (5,600 IU or more).
3 And in 2020, 540,000 people will use vitamin D in combination with calcium.

In 2019, people with a low income are overrepresented in the group that uses of prescription vitamin D supplements: 52 percent of users belong to the 40 percent

1 Parathyroid hormone (PTH) is a hormone produced in the four parathyroid glands. It plays an important role in keeping the blood calcium level constant.
2 NHG guideline laboratory diagnostics vitamin D deficiency
3 GIP data 2020. https://www.gipdatabank.nl/servicepagina/open-data

households with the lowest income (Nivel, 2020). The proportion with a non-Western migration background is also striking: 26 percent of users have a non-Western migration background, while only 14 percent of people in the Netherlands have a non-Western migration background.4
In other words, people with a non-Western migration background are more likely to use vitamin D supplements. In addition, especially women and the elderly take prescription vitamin D supplements. 75 percent of users are women and 78 percent are older than 45 years (Nivel, 2020). The background characteristics of people prescribed vitamin D supplements thus correspond to the background characteristics of people with vitamin D deficiency.

People who take prescription vitamin D supplements usually have several health problems. 73 percent of users use more than five medications. And 88 percent of users have to deal with one or more chronic conditions (Nivel, 2020).

The background characteristics of patients taking the combined calcium and vitamin D preparations correspond to the background characteristics of patients taking vitamin D alone.
This mainly concerns women, the elderly and people with low incomes. 95 percent of the people who use combination preparations are older than 45 and almost 50 percent belong to the 40 percent of households with the lowest income.

Burden of disease vitamin D deficient

This chapter shows what is known in the literature about the consequences of vitamin D deficiency. What are the consequences for the burden of disease and what are the economic consequences for society in terms of loss of production due to extra absenteeism, more unemployment, higher incapacity for work and higher healthcare costs? The Zorginstituut defines the burden of disease as the (relative) amount of health that a patient loses (on average) during his normal expected lifespan as a result of the condition.5

Consequences of vitamin D deficiency for the patient
Figure 1 shows that vitamin D deficiency affects almost all parts of the body.
It starts at birth. If the mother has vitamin D deficiency, it can have harmful effects on the child. It can lead to acute respiratory disease in the baby (Camargo et al., 2007). In addition, a deficiency of vitamin D in pregnant women leads to an increased risk of preeclampsia (Bodnar et al., 2007; Kamudoni et al., 2016) and a caesarean section.
(Merewood et al., 2009).

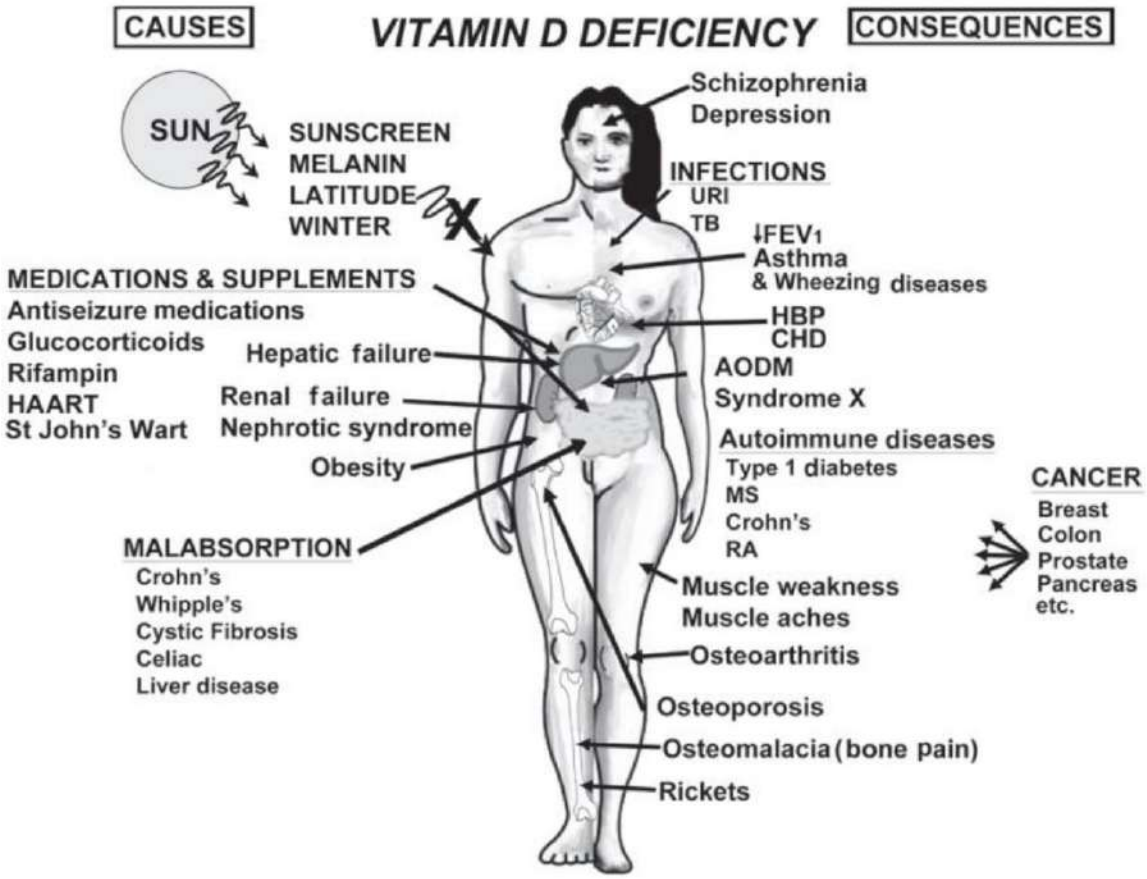
Vitamin D has an effect on the strength of bones and muscles. In children, vitamin D deficiency increases the risk of rickets, in which there is insufficient bone formation and deformity of the bones (Holick et al., 2009). In adults, vitamin D deficiency leads to brittle bones and a higher risk of bone fractures (Lips et al. 2019; Thanapluetiwong et al., 2020; Yao et al., 2019).
In addition, it is associated with various cancers (Holick, 2006; Yamaji et al., 2012

[4] CBS-statline

[5] Healthcare Institute Netherlands (2018). Disease burden in practice. The theory and practice of calculating burden of disease in package assessments

and Lappe et al., 2007; Keum et al., 2019; Bjelakovic et al., 2014). It concerns breast, colon, prostate and pancreatic cancer. Vitamin D deficiency is also associated with a higher risk of cardiovascular disease (Wang et al., 2008; Melamed et al., 2008) and acute respiratory infections. (Martineau et al., 2017). The study by Deleskog et al. (2012) shows that children and adults with a vitamin D deficiency have a higher risk of type 2 diabetes.

Figure 1 The diseases associated with vitamin D deficiency



Bron: Holick (2012).

There are no studies on the disease burden of vitamin D deficiency. There are also no figures available on the quality of life or mortality of people with and without vitamin D deficiency. There are studies into the disease burden of the individual diseases that are the result of vitamin D deficiency (eg. Lorentzon, 2021 and Ruiz-Adame and Correa, 2020). Using such studies, it is possible to calculate the share of vitamin D deficiency in the disease burden of individual diseases, in accordance with the method of Grant et al. 2009 (see the next section).

Economic consequences of vitamin D deficiency

Grant et al. (2009)6 have attempted to estimate the burden of disease of vitamin D deficiency in Western Europe (Table 1). First they have the costs associated with the diseases

[6] Grant works as a researcher for Sunarc. Sunarc receives funding from the vitamin D supplement industry, among others.

calculated as a percentage of total healthcare costs in Western Europe. They then use figures from the literature to calculate the production loss. The loss of production and the extra healthcare costs is the total burden of disease of the disease. They then calculate the proportion of patients who are ill due to vitamin D deficiency. They calculate this fraction by, among other things, using studies that look at the effect of vitamin D supplements on the risk of the disease. With the supplements, they increase the vitamin D level in the intervention group and then compare the outcome measures with the group that does not take supplements. They also use studies that compare people with low vitamin D levels to those with high levels of vitamin D. They then multiply the fraction of the disease caused by vitamin D deficiency by the total cost of the disease. This gives the 'burden of disease' of vitamin D. Grant et al. (2009) conclude that the 'burden of disease' of vitamin D deficiency amounts to 17.7 percent of healthcare costs. Of this, 11.4 percent would consist of health care expenditure and 6.3 percent of productivity loss. For the Netherlands this would be about 12 billion euros per year. These costs would disappear if everyone in Europe had a vitamin D level of 100 nmol/l.

Table 1 Burden of disease amounts to 17.7% of healthcare costs, according to Grant et al. (2009)

illnesses	Share in health care expenditure (%)	indirect cost ten (% of health care expenditure)	Total (% of health care expenditure)	Vitamin D fraction of the cost	Burden of disease vitamin D as % of health care expenditure
	1	2	3=1+2	4	=4*3
Osteoporosis, hip osteoarthritis and fractures	1,5	0,5	2	0,25	0,5
Cancer	6,4	9,6	16	0,3	4,8
Cardiovascular disease	12	6	20	0,2	4,0
Type 2 diabetes 7 1,5		2,4	9,4	0,2	1,9
Heart failure		0,5	2	0,25	0,5
Infectious Diseases					
Influenza	2,5	5	7,5	0,3	2,3
Pneumonia 2.5		1	3,5	0,3	1,1
Other respiratory infections	2	0,5	2,5	0,2	0,5
Autoimmune diseases					
Multiple sclero sis	1	0,2	1,2	0,5	0,6

Bron: Grant et al. (2009).

Note: Indirect costs consist of informal care and loss of productivity due to death and disease.

The method Grant uses is interesting. However, there is much to be said for the effect:

- Grant et al. (2009) are based on a selection of studies, not on meta-analyses in which the results of all published studies are summarized. The studies they select need not be representative of the average results across all studies.
- Grant et al. (2009) extrapolate the effects of vitamin D supplementation in specific groups to the entire population. For example, they use a randomized trial

with control group (RCT) from Lappe et al. (2007) on the effect of vitamin D supplements on cancer. Lappe et al. only look at women over 55 years of age. Grant et al. extrapolated the results of Lappe et al. (2007) to society as a whole. If supplements have a greater effect on women over the age of 55, this is unjustified.

- It is unclear how Grant et al. translate the results of the studies used into the fractions used.

- Grant et al. assume that the effect of vitamin D on the risk of disease is linear. In other words, if the vitamin D level goes from 25 nmol/l to 50 nmol/l, it has the same effect on getting the disease as if the vitamin D level goes from 50 nmol/l to 75 nmol/l.
- The results of the study by Grant et al. (2007) are therefore based on strong assumptions, and possibly distorted by the choice of the studies on which they are based.

It is therefore difficult to calculate the burden of disease of vitamin D deficiency, because the disease burden of the individual diseases is not entirely caused by vitamin D deficiency. To calculate the share of vitamin D in the disease burden, we believe that too many assumptions are required to be able to make a true estimate of the disease burden of vitamin D deficiency.

Cost Effectiveness Vitamin D Supplements

This chapter reviews the literature on the cost-effectiveness of vitamin D supplements. Benefits are the health gain and sometimes also economic benefits, such as reduced absenteeism due to illness. Health gain is expressed in the number of life years gained.[7] Cost-effectiveness is often expressed in the net costs per life year gained. Based on this number, the Zorginstituut assesses whether an intervention is included in the package. The lower the costs per life year gained, the greater the benefits of the treatment are in relation to the costs. If the costs per life year gained are less than 20 thousand euros (with a low burden of disease) to 80 thousand euros per life year gained (with a high burden of disease), the health care institute considers the treatment cost-effective. The idea behind this is that society is more willing to pay for treatment of a disease with a high burden of disease.

The literature always finds a positive result when it comes to cost-effectiveness of vitamin D supplements. The cost-effectiveness of vitamin D supplements is usually calculated per vitamin D deficiency related disease. Most of the literature concerns the cost-effectiveness in the prevention of osteoporosis and cancer.

Cost-effectiveness of vitamin D supplements in cancer The use of vitamin D supplements lowers the risk of dying from cancer. Bjelakovic et al. (2014) and Keum et al. (2019) both come to this conclusion based on their meta-analysis. The chance of dying from cancer is 13 percent lower for people taking vitamin D

[7] It concerns life years in full health: QALYs (Quality Adjusted Life Year). People's health is scored on a scale from 0 (death) to 1 (perfect health). One QALY equals one year in perfect health. One QALY also corresponds to two years in a health condition with a score of 0.5. The number of QALYs is thus the health score (range 0 to 1) multiplied by the number of life years.

taking supplements. Keum et al. (2019) also conclude that only daily intake of supplements has an effect on the risk of dying from cancer, as opposed to monthly intake.

In Germany, 30,000 fewer people per year would die from cancer if vitamin D supplements were used (Niedermaier, 2021). They use the study by Keum et al. (2019) discussed above to estimate the effect of vitamin D supplements (1,000 IU/day, 25mg) on cancer deaths. They also calculate the number of life years lost due to premature death from cancer of people over 50 in Germany. They then calculate the cost-effectiveness by comparing the annual costs of vitamin D supplements to the health care costs of cancer. They conclude that the costs per life year gained amount to 2,798 euros.

Cost-effectiveness of vitamin D supplements in osteoporosis

Osteoporosis leads to health damage and healthcare costs because patients fall earlier and also break something more often than people without osteoporosis. In 2019, according to Kanis et al. (2021), there were almost one million people in the Netherlands with osteoporosis. Kanis et al. conclude that in 2019 almost 100 thousand fractures in the Netherlands were the result of osteoporosis. Kanis et al. expects the number of fractures to increase to 137 thousand by 2034. the economist

The economic costs of osteoporosis in the Netherlands are estimated by Kanis et al. (2021) at 1.9 billion euros (1.8 percent of healthcare expenditure in 2019 in the Netherlands).

Vitamin D supplements combined with calcium lower the risk of falling by 12 percent and the risk of fracture by between 6 and 16 percent. Those are the results of meta-analyses performed by Thanapluetiwong et al. (2020), Yao et al. (2019) and Bolland et al. (2018). Vitamin D supplements without calcium had on average no effect on the number of falls and the number of fractures. Thanapluetiwong et al. (2020) recommend taking a daily vitamin D3 supplement in combination with calcium with at least 800 IU (20 mg). The literature is not unequivocal about the effect of a high dose compared to a low dose.

Hiligsmann, et al. (2015)8 conclude that the cost-effectiveness of osteoporosis treatment – including vitamin D/calcium supplements – of over-60s in Belgium is 40,578 euros amounts for women and 23,477 euros for men. Torgerson (1995), Weaver et al. (2019)9 and Lilliu et al. (2003) also conclude that the use of vitamin D supplements in combination with calcium has more benefits than costs. However, they do not calculate costs per life year gained.

Effect of personal contribution on healthcare use

Studies in the United States into increasing the co-payment have shown that especially people with a low income avoid necessary care due to higher co-payments (Newhouse, 1993, Ghosh, et al., 2019). Ghosh et al. examine the effect of introducing Medicaid on the

8 This research was funded by SMB Belgium, a vitamin D supplement producer.
9 Weaver works for Pfizer.

use of prescription medications. Medicaid provides health insurance for individuals and families with low incomes and wealth. Ghosh et al. found that low-income people are more likely to use prescription drugs in states that introduced Medicaid than in states that did not. They also came to the conclusion that it
usage grew less in states that only reimbursed a portion of the cost. This shows that people with a low income are sensitive to the use of medicines if they have to pay the costs themselves.

Newhouse's (1993) study is still regarded as the leading research into the effect of co-payments for care because it is based on an experiment. In the experiment, participants were split into five groups. The first group did not pay a personal contribution, the other groups had to pay a personal contribution (25, 50 and 95 percent). In one group it was a mix, 50 percent for the dentist and mental health care and 25 percent for other care.
People who were reimbursed for all costs made more frequent use of care than people who were not reimbursed for all costs. This involves visiting the general practitioner, visiting the hospital, using prescribed medicines and the dentist. In addition, it turned out that the higher the deductible, the less use was made of care. The effect was greater for people with a lower income or a chronic illness. These two groups are more likely to avoid healthcare if they have to pay part of the costs themselves.

Due to the reduced use of care, the health of people with a low income or people with a chronic illness had deteriorated. If people with a low income did not pay a personal contribution, they scored better on 4 out of 30 outcomes than people who did have to pay a personal contribution.

Extra costs due to loss of reimbursement
If the reimbursement of vitamin D supplements disappears, the costs for the users will rise. The previous section shows that patients avoid healthcare if the costs they have to pay rise. It is therefore important to know to what extent costs are increasing.

The extra costs for the patient consist firstly of the price of the vitamin D supplement.10
In addition, the pharmacy charges costs for the provision of care, also known as dispensing.11
And nine percent VAT is paid on both costs. For patients with organizing problems
who use multiple medicines, different pharmacy costs apply. The pharmacy has to add the medicine weekly in a so-called medicine roll or baxter roll, the weekly manual setting.12
Adding the medicines in a medicine roll can also be done every two or three weeks.

10 The prices of the supplements come from the Z-index from 2022. The Z-index is a database with information about healthcare products. The file offers support to doctors, pharmacists, the business community, the government and health insurers in prescribing, delivering, ordering, claiming and reimbursement of health care products.

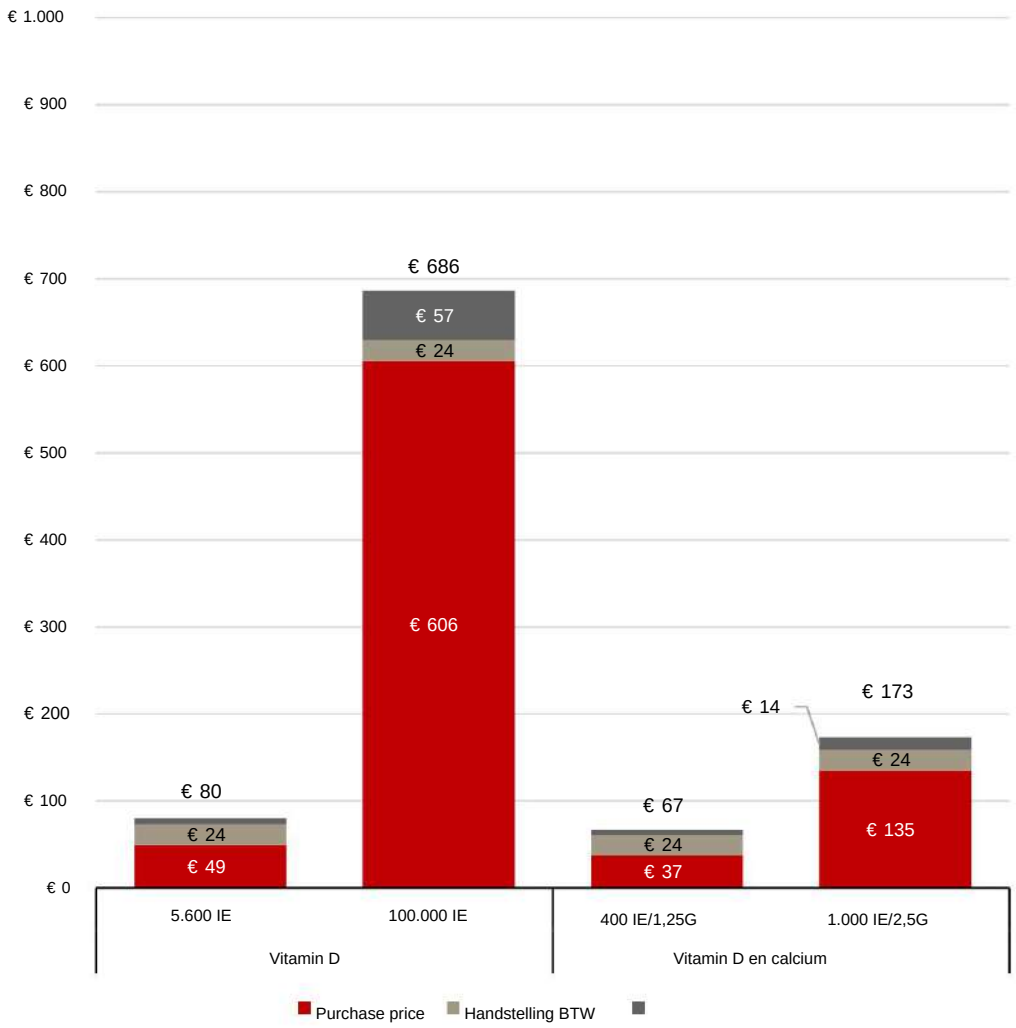
11 The costs for the handover were 6.50 euros (including VAT) in 2021. https://www.medicijnkos ten.nl/toelichting

12 The costs for the weekly delivery were 4.30 euros per medicine in 2020 and come from the SFK. https://www.sfk.nl/publicaties/PW/2021/prijs-vervolguitgifte-stijgt-naar-medium-20ac-6-45.
The NZA has announced that it will fund the weekly handing differently from 1 January 2023.
Its impact is still unclear.

happen, but in the case of vitamin D, this only happens once. That is why this study is based on the weekly hand setting.

Figure 2 shows the annual costs of the lowest dose and the highest dose of vitamin D supplements that are reimbursed. The annual cost of prescription vitamin D supplements is between 80 euros (5,600 IU) and 686 euros (100,000 IU). The annual cost of the capsules 100,000 IU applies if the person takes 100,000 IU supplements throughout the year. 100,000 IU is prescribed throughout the year for specific conditions such as multiple sclerosis (MS), but is also prescribed for shorter periods. If the patient does not use the capsules throughout the year, the costs are logically lower. The user of combination preparations loses between 67 and 173 euros per year. In the case of 400 IU in combination with 1.25G calcium, this leads to an average cost item of 97 euros per year. At the highest dose, in the form of 1,000 IU in combination with 2.5G calcium, the costs rise to approximately 170 euros per year.

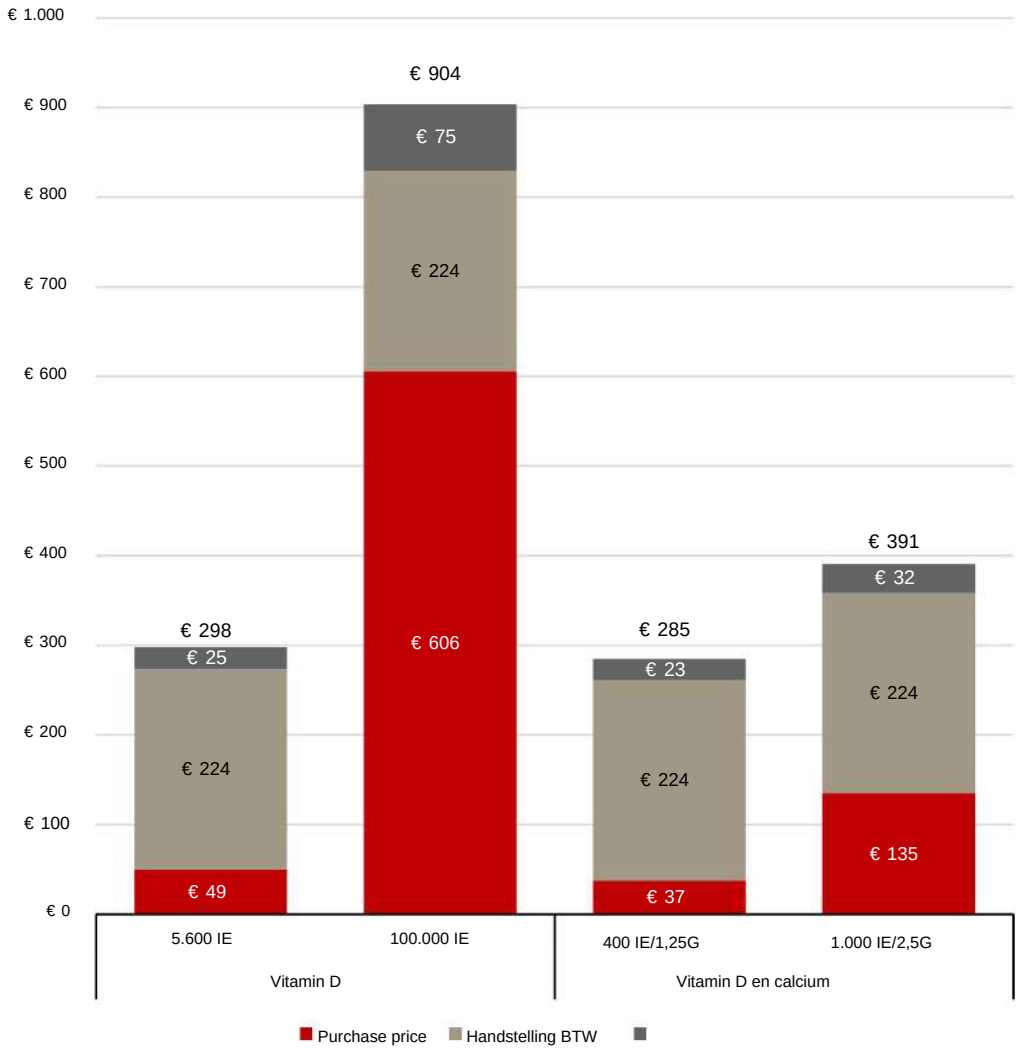
Figure 2 The annual costs for patients who take 5,600 IU vitamin D supplements increase by 80 euros if the reimbursement is no longer available



Explanation: This concerns the average price per product class. The figures are based on the AIP. The handover costs 5.96 euros and must be paid four times a year. Nine percent VAT is paid on both amounts.

If the patient receives supplements in a medicine roll, the annual costs are higher because of the weekly handling. The patient spends 224 euros per year on the weekly manual delivery (excluding VAT). Patients who only take vitamin D supplements then lose between 300 and 900 euros per year (Figure 3). Persons who use combination preparations lose 285 euros per year if they use 400 IU/1.25G and almost 390 euros if they use 1,000 IU/2.5G supplements.

Figure 3 Patients who receive their medicines in a medicine roll lose between 285 and 904 euros annually if vitamin D supplements are no longer reimbursed



Explanation: This concerns the average price per product class. The figures are based on the AIP 5,600 IE costs an average of 50 euros and 605 euros for 100,000 IE. For the combination preparations, the costs are 37 for 400 IU/1.25G and 135 euros for 1,000 IU/2.5G. The weekly handing costs 4.30 euros each time and must be paid weekly. In total this is about 224 euros per year. Nine percent VAT is paid on both amounts.

In 2021, 46 percent of the patients taking 5,600 IU of vitamin D supplements received the supplements in a medicine roll.13 Their costs therefore increase by 298 euros annually if vitamin D supplements are removed from the basic package.

Conclusions

- In the Netherlands, 60 percent of people have less than 50 nmol/l vitamin D in their blood level during the winter months. Vitamin D deficiency is most common in the elderly, women, people with a migrant background and people with low incomes. In 2021
  Five million people in the Netherlands take low-dose vitamin D supplements. In 2020, 886 thousand people in the Netherlands received prescription vitamin D supplements and 540 thousand people received prescription vitamin D supplements in combination with calcium.
- Vitamin D deficiency affects a wide range of diseases. The diseases occur in childhood, but also later in life. Vitamin D deficiency is associated with various types of cancer, cardiovascular disease, respiratory disease and brittle bones.
- Users of prescription vitamin D supplements are mainly over the age of 45, women and people with low incomes (Nivel, 2020). 52 percent of the users belong to the 40 percent of households with the lowest income in the Netherlands.
- Users of prescription vitamin D supplements in combination with calcium are almost always over the age of 45 (Nivel, 2020). In addition, they usually have a relatively low income and they are women.
- There is no qualitatively good research into the burden of disease. According to the study by Grant et al. (2009), the cost of vitamin D deficiency is largely due to cardiovascular disease and cancer. However, the results are not well substantiated.
- It is difficult to estimate the burden of disease of vitamin D deficiency, because no figures are available on the quality of life or mortality of people with and without vitamin D deficiency. This is because the disease burden of vitamin D deficiency is caused
  due to individual diseases resulting from a vitamin D deficiency.
- According to Kanis et al. (2021), nearly one million people in the Netherlands have osteoporosis. Osteoporosis leads to health damage and healthcare costs because patients fall earlier and also break something more often than people without osteoporosis. The use of vitamin D in combination with calcium lowers the risk of a fracture. Hiligsmann, et al. (2015) conclude that the cost-effectiveness of osteoporosis treatment – including vitamin D/calcium supplements – of people over 60 in Belgium is 40,578 euros for women and 23,477 euros for men.
- The cost-effectiveness of vitamin D supplements in cancer appears to have the most positive effect. According to Niedermaier (2021), the costs per life year gained were 2,798 euros. •

The study by Ghosh et al. (2019) shows that people with a low income use more medicines if they are reimbursed for the costs. Newhouse (1993) came to the conclusion that the higher the co-payment, the lower the chance of health care use. The effect was greater for people with a lower income or a chronic illness. Due to the reduced use of care, the

13 fiROM-data Farminform 2022

health of people with a low income or people with a chronic illness deteriorated.

- If vitamin D supplements are not included in the basic package, a patient will lose between 80 and 690 euros. If combination preparations are used, the costs increase. The costs are then between 67 euros in the case of 400 IU/1.25G and 391 euros in the case of 1,000 IU vitamin D supplements and 2.5G calcium.
- The costs are higher for patients who receive the supplements in a medicine roll. If the reimbursement disappears, these patients will spend 298 euros per year on 5,600 IU of vitamin D supplements. If the patient takes 100,000 IU supplements throughout the year, the patient will lose 900 euros per year. Persons who use combination preparations lose 285 euros per year if they use 400 IU/1.25G and approximately 390 euros if they use 1,000 IU/2.5G supplements.
- 46 percent of people who use vitamin D supplements with 5,600 IU receive these supplements in a drug role.

Next steps

The above report shows that vitamin D deficiency affects a wide range of diseases. In addition, several studies show that vitamin D supplements are a cost-effective means. The studies found do not yet paint a picture of the effects for the Netherlands.
This information is important for the broader discussion.

Based on the collected information, we can also calculate the cost-effectiveness of vitamin D in combination with calcium specifically for the Netherlands. The most feasible is the cost-effectiveness of vitamin D and calcium supplements in osteoporosis. The result of the calculation is a table showing the costs and benefits in euros for various parties of supplements compared to no supplements. We value the increase in quality of life at the value of a year of life as prescribed by the National Health Care Institute.
We also calculate the cost-effectiveness ratio as prescribed by the Zorginstituut. Based on this number, the Zorginstituut normally assesses whether an intervention is admitted to the package.

The costs and benefits of removing a higher dose of vitamin D from the basic package then depend on the proportion of people who no longer use the prescribed medicines as a result of the personal contribution. It is unknown how many people will stop taking vitamin D supplements when the fee disappears. Therefore, we calculate the break-even point.
The break-even point is the point at which costs equal revenues. In this case, the costs are the additional burden of disease because patients no longer use the supplements. And the revenues are the reduced health care expenses because the supplements are no longer in the package.
If the cost-effectiveness is high, then stopping a small proportion of patients is already negative for society. The break-even analysis therefore provides an estimate of the probability that the benefits of not reimbursed for vitamin D supplements will not outweigh the costs.

We do not consider it feasible to eliminate the burden of disease of vitamin D deficiency in the Netherlands to calculate.

Bibliography

Bischoff-Ferrari, H. A. (2012). “Vitamin D–why does it matter?”–defining vitamin D deficiency and its prevalence. Scandinavian Journal of Clinical and Laboratory Investigation, 72(sup243), 3-6.

Bjelakovic, G., Gluud, L. L., Nikolova, D., Whitfield, K., Wetterslev, J., Simonetti, R. G., ... & Gluud, C. (2014). Vitamin D supplementation for prevention of mortality in adults. Cochrane database of systematic reviews, (1).

Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM (2007). Maternal vitamin D deficiency increases the risk of preeclampsia. J Clin Endocrinol Metab 92:3517-3522, 2007

Bolland, M. J., Grey, A., & Avenell, A. (2018). Effects of vitamin D supplementation on musculo skeletal health: a systematic review, meta-analysis, and trial sequential analysis. The lancet Diabetes & endocrinology, 6(11), 847-858.

Boonman-de Winter, LJM, Albersen, A., Mohrmann, K., Bakx-van Baal, CMAC, Thijssen, D. WMT and

Bressers, JPHM (2015). High prevalence of vitamin D deficiency in the southwestern Netherlands. Ned Tijdschr Geneeskd, 159(A8167), A8167.

Brecht, J. G., & Schädlich, P. K. (2000). Burden of illness imposed by osteoporosis in Germany. HEPAC Health Economics in Prevention and Care, 1(1), 26-32.

Camargo, C.A. Jr, Rifas-Shiman, S.L., Litonjua, A.A., Rich-Edwards, J.W., Weiss, S.T., Gold, D.R., Kleinman, K., Gillman, M.W. (2007). Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. Am J Clin Nutr 85:788-795, 2007

Deleskog, A., Hilding, A., Brismar, K., Hamsten, A., Efendic, S., Östenson, C.G. (2012). Low se rum 25-hydroxyvitamin D level predicts progression to type 2 diabetes in individuals with prediabetes but not with normal glucose tolerance. Diabetologia 55:1668-1678, 2012

Health Council (2021). Vitamin D and the prevention of COVID-19 and acute respiratory infections. No. 2021/09, The Hague, 3 March 2021.

Ghosh, A., Simon, K., & Sommers, B. D. (2019). The effect of health insurance on prescription drug use among low-income adults: evidence from recent Medicaid expansions. Journal of health economics, 63, 64-80.

Grant, W. B., Cross, H. S., Garland, C. F., Gorham, E. D., Moan, J., Peterlik, M., ... & Zittermann, A. (2009). Estimated benefit of increased vitamin D status in reducing the economic bur den of disease in western Europe. Progress in biophysics and molecular biology, 99(2-3), 104-113.

Hiligsmann, M., Ben Sedrine, W., Bruyere, O., Evers, SM, Rabenda, V., & Reginster, JY (2015). Cost-effectiveness of vitamin D and calcium supplementation in the treatment of elderly women and men with osteoporosis. The European Journal of Public Health, 25(1), 20-25.

Holick, M.F. (2006). Calcium plus vitamin D and the risk of colorectal cancer. N Engl J Med 354:2287-2288, 2006

Holick, M.F., Lim, R., Dighe, A.S. (2009). Case records of the Massachusetts General Hospital. Case 3-2009. A 9-month-old boy with seizures. N Engl J Med 360:398-407, 2009

Holick, M.F., Binkley, N.C., Bischoff-Ferrari, H.A., Gordon, C.M., Hanley, D.A., Heaney, R.P., Murad, M.H., Weaver, C.M. (2011). Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96: 1911–30.

Holick, M. F. (2012). Vitamin D: a D-lightful vitamin for health. Endocrinology and Metabolism, 27(4), 255-267.

Info2Action (2021). Special Vitamine D. Basis scanningdata: P1-2017 P10-2020.

Kamudoni, P., Poole, C., & Davies, S. J. (2016). An estimate of the economic burden of vitamin D deficiency in pregnant women in the United Kingdom. Gynecological Endocrinology, 32(8), 592-597.

Kanis, J. A., Norton, N., Harvey, N. C., Jacobson, T., Johansson, H., Lorentzon, M., ... & Borgström, F. (2021). SCOPE 2021 a new scorecard for osteoporosis in Europe. Archives of Osteoporosis, 16(1), 1-82.

Keum, N., Lee, D. H., Greenwood, D. C., Manson, J. E., & Giovannucci, E. (2019). Vitamin D supplementation and total cancer incidence and mortality: a meta-analysis of randomized controlled trials. Annals of Oncology, 30(5), 733-743.

Khaw, KT, Stewart, AW, Waayer, D., Lawes, CM, Toop, L., Camargo Jr, CA, & Scragg, R. (2017). Effect of monthly high-dose vitamin D supplementation on falls and non-verte bral fractures: secondary and post-hoc outcomes from the randomised, double-blind, pla cebo-controlled ViDA trial. The lancet Diabetes & endocrinology, 5(6), 438-447.

Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP: Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr 85:1586-1591, 2007

Lilliu, H., Pamphile, R., Chapuy, M. C., Schulten, J., Arlot, M., & Meunier, P. J. (2003). Calcium–vitamin D3 supplementation is cost-effective in hip fractures prevention. Maturitas, 44(4), 299-305.

Lips, P., Cashman, K. D., Lamberg-Allardt, C., Bischoff-Ferrari, H. A., Obermayer-Pietsch, B., Bianchi, M. L., ... & Bouillon, R. (2019). Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society. European journal of endocrinology, 180(4), P23-P54.

Lorentzon, M., Johansson, H., Harvey, N. C., Liu, E., Vandenput, L., McCloskey, E. V., & Kanis, J. A. (2021). Osteoporosis and fractures in women: the burden of disease. Climacteric, 1-7.

Martineau, A. R., Jolliffe, D. A., Hooper, R. L., Greenberg, L., Aloia, J. F., Bergman, P., ... & Ca margo, C. A. (2017). Vitamin D supplementation to prevent acute respiratory tract infec tions: systematic review and meta-analysis of individual participant data. bmj, 356.

Melamed ML, Muntner P, Michos ED, Uribarri J, Weber C, Sharma J, Raggi P: Serum 25-hy droxyvitamin D levels and the prevalence of peripheral arterial disease: results from NHANES 2001 to 2004. Arterioscler Thromb Vasc Biol 28:1179-1185, 2008

Merewood A, Mehta SD, Chen TC, Bauchner H, Holick MF: Association between vitamin D de ficiency and primary cesarean section. J Clin Endocrinol Metab 94:940-945, 2009

Newhouse, J. (1993) Free for all: Lessons from the RAND Health Insurance Experiment. Cam bridge, Mass.: Harvard University Press.

Niedermaier, T., Gredner, T., Kuznia, S., Schöttker, B., Mons, U., & Brenner, H. (2021). Vitamin D supplementation to the older adult population in Germany has the costÿsaving potential of preventing almost 30 000 cancer deaths per year. Molecular oncology.

Nivel (2020) Monitor vitamins, minerals and paracetamol from the pack. June 2020. PO Box 1568, 3500 BN, Utrecht.

Ruiz-Adame, M., & Correa, M. (2020). A systematic review of the indirect and social costs studies in fragility fractures. Osteoporosis International, 31(7), 1205-1216.

Thanapluetiwong, S., Chewcharat, A., Takkavatakarn, K., Praditpornsilpa, K., Eiam-Ong, S., & Susantitaphong, P. (2020). Vitamin D supplement on prevention of fall and fracture: A Meta-analysis of Randomized Controlled Trials. Medicine, 99(34).

Torgerson, D. J., & Kanis, J. A. (1995). Cost-effectiveness of preventing hip fractures in the elderly population using vitamin D and calcium. QJM: An International Journal of Medicine, 88(2), 135-139.

Vektis (2019). Costs of vitamin D preparations will increase by 5 million in 2019. 25/09/2019.

Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, Benjamin EJ, D'Agostino RB, Wolf M, Vasan RS (2008). Vitamin D deficiency and risk of cardiovascular disease. Circulation 117:503-511, 2008

Weaver, C. M., Bischoff–Ferrari, H. A., & Shanahan, C. J. (2019). Cost-benefit analysis of calcium and vitamin D supplements. Archives of osteoporosis, 14(1), 1-12.

Wielders, JP, Muskiet, FA, & van de Wiel, A. (2010). New light on vitamin D: re-evaluation of an essential prohormone. Dutch journal of medicine, 154(49), 2271-2276.

Yao, P., Bennett, D., Mafham, M., Lin, X., Chen, Z., Armitage, J., & Clarke, R. (2019). Vitamin D and calcium for the prevention of fracture: a systematic review and meta-analysis. JAMA network open, 2(12), e1917789-e1917789.

Yamaji, T., Iwasaki, M., Sasazuki, S., Sakamoto, H., Yoshida, T., Tsugane, S. (2012). Association between plasma 25-hydroxyvitamin D and colorectal adenoma according to dietary cal cium intake and vitamin D receptor polymorphism. Am J Epidemiol 175:236-244, 2012