

# Osteoporosis International

## Determinants of vitamin D supplementation prescription in nursing homes: a survey among general practitioners --Manuscript Draft--

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<b>Full Title:</b>	Determinants of vitamin D supplementation prescription in nursing homes: a survey among general practitioners
<b>Article Type:</b>	Original Article
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<b>Abstract:</b>	<p>Purpose: To assess the profile and determinants of vitamin D supplementation prescription in nursing homes.</p> <p>Methods: General practitioners (GPs) having at least one patient in a nursing home in Liège, Belgium, were asked to complete the survey.</p> <p>Results: A total of 119 GPs participated in the survey. Among the respondent GPs, 65 (54.6%) systematically prescribe vitamin D to their institutionalized patients and the 54 (45.4%) others prescribe only sometimes. The main reasons for prescribing vitamin D cited by GPs who do so systematically are as follows: because they believe nursing home residents are mostly deficient in vitamin D status (92.1%), because they believe vitamin D supplementation prevents osteoporotic fractures (77.8%), and because vitamin D supplementation is recommended by various scientific societies (38.1%). GPs who only prescribe vitamin D supplementation in some patients mainly do so following a diagnosis of osteoporosis (82.4%), on the basis the 25(OH)D level (78.4%), in case of history of fracture (54.9%) or after a recent fracture (43.4%). Surprisingly, 16 physicians (31.4%) only prescribe vitamin D when they think of it. Interestingly, while 40.7% of GPs always prescribe the same dose of vitamin D, the remaining 59.3%, prescribe a dose that will mainly depend on the results of the 25(OH)D level (94.0%), the patient's bone health (49.3%) or history of fracture (43.3%).</p> <p>Conclusions: More than half of GPs systematically prescribe vitamin D to their patients living in nursing homes. The other GPs usually prescribe vitamin D following the result of the vitamin D status or after a diagnosis of osteoporosis.</p>
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<b>Response to Reviewers:</b>	<p>Title : Determinants of vitamin D supplementation prescription in nursing homes: a survey among general practitioners</p> <p>Comments for the Author:</p> <p>Reviewer #1: Summary: This interesting and well written original investigation reports that more than half of general practitioners systematically prescribed vitamin D to their patients living in nursing homes, and that the remaining general practitioners prescribed vitamin D following measurement of vitamin D levels or after diagnosis of osteoporosis. The authors surveyed 119 general practitioners in Liege, Belgium, who had at least one patient in a nursing home, with a self-administered questionnaire. Of these, 54.6% systematically prescribed vitamin D to their nursing home patients, whereas 45.4% prescribed vitamin D after measuring this or after diagnosis of osteoporosis. Physicians systematically prescribing vitamin D did so in the belief that nursing home residents are mostly deficient in vitamin D, because they believed that vitamin D prevents fractures, and because scientific societies recommended this. The physicians who prescribed vitamin D for some patients only did this after a diagnosis of osteoporosis, on the basis of the vitamin D level, after previous fracture, or after recent fracture. Sixteen physicians prescribed vitamin D only when they thought of it. 40.7% of physicians always prescribed the same dose of vitamin D, while the other 59.3% based the dose on the blood level obtained, bone health of the patient, or history of fracture. The study concluded that more than half of general practitioners systematically prescribed vitamin D to their patients living in nursing homes, and that the remaining general practitioners prescribed vitamin D following measurement of vitamin D levels or after diagnosis of osteoporosis.</p> <p>Major points:</p> <p>1)Page 5, paragraph 2, line 1-5, methods: How many general practitioners are in the city of Liege? What percentage of these has at least one patient in a nursing home? How representative of the general practitioners in the city of Liege is this cohort?</p> <p>Author's response : There are more than 800 GPs in the Province of Liège, Belgium. Only volunteer GPs were included in this study and, as indicated in the discussion section of the article, it is a limitation of the study: "The first one is that we have no information about the GPs' characteristics. We don't know whether respondents are representative of the population of GPs in nursing home or if they represent a homogeneous group." Indeed, we may think that GPs who feel most affected by vitamin D supplementation responded to the survey and not the others.</p> <p>2)Page 10, paragraph 1, lines 3-4, discussion: Were the physicians in the city or province of Liege? Is the city the same as the province?</p> <p>Author's response : The GPs came from the province of Liège, which includes the city of Liège. We chose to perform our study in the province of Liège, which is a larger area, to obtain more answers and therefore increase the statistical power of our study. The characteristics of the GPs are probably very similar between the city and the province of Liège.</p> <p>Minor points:</p> <p>1)Page 8, paragraph 1, line 6, results: What does "blood test blood biology" mean? This should be clarified. Author's response : « blood test blood biology » was replaced by « blood biology », directly in the text.</p> <p>Reviewer #2:</p> <p>It would have been nice to know more about the GPs who answered these questions. It is difficult to believe they are a homogeneous group.</p> <p>Author's response : The authors fully agree with this comment. Therefore, this has been discussed as the first limitation of the study:</p>

« This study has some limitations. The first one is that we have no information about the GPs' characteristics. We don't know whether respondents are representative of the population of GPs in nursing home or if they represent a homogeneous group».

Comments:

1. Was it at all possible to have elicited responses from those who never did prescribe vitamin D? Was there bias in how the questionnaire was presented?

Author's response : As suggest by the reviewers, the responses obtained in this study may be affected by 2 types of potential biases: a bias of volunteering and a bias of social desirability. This point was added to the discussion section of the manuscript : « In this study, no physicians stated they never prescribe vitamin D to their patients living in nursing home. This can be explained by a possible bias of volunteering. Indeed, maybe that the GPs who never prescribe vitamin D did not want to answer the questionnaire. Another possible explication is the presence of a bias of social desirability. In surveys, subjects sometimes tend to answer what they think is expected by the investigator, which does not always reflect the reality. Because of these two possible biases, the prescription of vitamin D could be overestimated in this study. ».

2. How are decisions for prescribing supplements made in long-term care in Belgium?  
Author's response : as stated in the manuscript, numerous scientific societies recommend to supplement the elderly population with vitamin D, especially those living in nursing homes. Nevertheless, in Belgium, vitamin D supplementation is not mandatory and depends on GP's judgment.

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3 **Determinants of vitamin D supplementation prescription in nursing homes: a**  
4 **survey among general practitioners**  
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## **Summary**

A total of 119 GPs participated to a survey aimed to assess the profile and determinants of vitamin D supplementation prescription in nursing homes. Among the respondent GPs, 65 (54.6%) systematically prescribe vitamin D to their institutionalized patients and the 54 (45.4%) others prescribe only sometimes.

## **Abstract**

**Purpose:** To assess the profile and determinants of vitamin D supplementation prescription in nursing homes.

**Methods:** General practitioners (GPs) having at least one patient in a nursing home in Liège, Belgium, were asked to complete the survey.

**Results:** A total of 119 GPs participated in the survey. Among the respondent GPs, 65 (54.6%) systematically prescribe vitamin D to their institutionalized patients and the 54 (45.4%) others prescribe only sometimes. The main reasons for prescribing vitamin D cited by GPs who do so systematically are as follows: because they believe nursing home residents are mostly deficient in vitamin D status (92.1%), because they believe vitamin D supplementation prevents osteoporotic fractures (77.8%), and because vitamin D supplementation is recommended by various scientific societies (38.1%). GPs who only prescribe vitamin D supplementation in some patients mainly do so following a diagnosis of osteoporosis (82.4%), on the basis the 25(OH)D level (78.4%), in case of history of fracture (54.9%) or after a recent fracture (43.4%). Surprisingly, 16 physicians (31.4%) only prescribe vitamin D when they think of it. Interestingly, while 40.7% of GPs always prescribe the same dose of vitamin D, the remaining 59.3%, prescribe a dose that will mainly depend on the results of the 25(OH)D level (94.0%), the patient's bone health (49.3%) or history of fracture (43.3%).

**Conclusions:** More than half of GPs systematically prescribe vitamin D to their patients living in nursing homes. The other GPs usually prescribe vitamin D following the result of the vitamin D status or after a diagnosis of osteoporosis.

**Key words:** vitamin D, survey, nursing homes, general practitioners

## **Introduction**

Vitamin D deficiency is recognized as a major public health problem [1, 2]. The associations between vitamin D levels and various health conditions and diseases have been assessed in a large and rapidly expanding literature. It is well-known, for a long time, that vitamin D deficiency is a risk factor for osteoporosis [3] and fractures [4]. Furthermore, in the 2000s, several studies have also shown an association between low level of vitamin D and muscle weakness [5], falls [6], cardiovascular disease [7] as well as poor immune, endocrine and central nervous system [2, 8-10]. A meta-analysis published in 2007 even showed a significant relationship between vitamin D status and risk of death [11].

There is currently no consensus on an optimal level of vitamin D assessed by serum 25 hydroxyvitamin D (25[OH] D) level. There is also a debate on the cut-off value to define vitamin D deficiency. Indeed, some authors consider that vitamin D deficiency is defined by a 25(OH)D level  $\leq 20$  ng/mL (50 nmol/L) [12] but other authors consider a level  $\leq 30$  ng/mL as a deficiency [13]. However, whatever the threshold selected, vitamin D deficiency is often associated with suboptimal health [14, 15].

Vitamin D deficiency is becoming endemic in many parts of the world [16]. Recent studies have found high prevalence of vitamin D deficiency and insufficiency in different populations, including elder adults [2] and nursing home residents [17-19]. The prevalence of 25(OH)D deficiency affects more than 25% of community-dwelling elderly and the prevalence is almost doubled among nursing home residents [20] It is admitted that prevalence of vitamin D insufficiency increases with age due to reduction in exposure to sunlight, poor nutrition, and a decrease in the capacity to produce vitamin D<sub>3</sub> in the skin [21].

Since the prevalence of vitamin D inadequacy is high, supplementation with vitamin D has been recommended, especially in high risk and elderly populations [15]. Indeed, several studies have suggested some positive effects of vitamin D supplementation on muscle strength, bone health and fall among elderly adults [22-24].

Albeit vitamin D supplementation is recommended in the frail and elderly populations [15, 25, 26] such as in nursing homes, the number of subjects receiving vitamin D is still not optimal. The determinants of vitamin D prescription have been poorly investigated, especially in nursing homes setting. Therefore, the aim of this study was to assess the profile and determinants of vitamin D prescription in nursing homes.

## **Methods**

### **Type of study**

This study consisted in a self-administrated questionnaire survey conducted between April and May 2015.

### **Participants**

General practitioners (GPs) having at least one patient in a nursing home in Liège, Belgium, were eligible to participate in this study. There were no exclusion criteria: all GPs agreeing to complete the questionnaire were included in the study. We contacted the GPs via associations of GPs and via the nursing homes who agreed to participate in the study.

### **Data collection**

Data were collected using a self-administered questionnaire. This short questionnaire, requiring maximum 5 minutes to complete, consists of 3 sets of questions:

- The first set concerned vitamin D prescription habits of the GPs. Participants were asked if they systematically, sometimes or never prescribe vitamin D to their institutionalized patients. According to their responses, respectively 7, 17 and 8 other questions were asked (multiple responses allowed) in order to grasp the reasons why they systematically, sometimes or never prescribe vitamin D.
- The second set of questions enquired on the dosage that GPs usually prescribe. First, doctors were asked whether they systematically prescribe the same dose of vitamin D to their patients in nursing home. GPs who responded “yes” were asked to specify, using an open question, the dose and the frequency of vitamin D supplements that they prescribe to their patients. GPs who responded “no” had to provide precisions about the choice of the prescribed regimen by means of 10 closed questions.
- Finally, the third set of questions consisted of 3 items appraising the prescription of calcium in association with vitamin D.

Two possibilities were given to complete the survey: GPs could either directly complete the survey online or complete a paper version of the questionnaire made available at the nurses office of the nursing homes involved in this study. The survey web link was sent via e-mail to GPs, through the associations of doctors.

### **Statistical analysis**

All variables were reported as absolute and relative frequencies (%). Data were directly encoded online either by the respondent or by the investigator (for paper versions). Then,



data were processed by the website (online survey). Analyzes were performed using Statistica 10 software.

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## Results

Out of the 398 GPs who have at least one patient in a nursing home in Liège, Belgium and who were contacted, 119 GPs (29.9%) have responded to the survey. Among the 138 GPs who were asked to complete the paper version, 34 responded to the survey. The online version of the questionnaire was sent to 260 GPs and 85 of them (32.7%) responded.

Among the 119 GPs who responded to the survey, 65 (54.6%) systematically prescribe vitamin D to their institutionalized patients and the 54 (45.4%) others prescribe only sometimes. The main reasons for prescribing vitamin D given by GPs who do so systematically are shown in table 1. Please note that multiple choices were allowed.

**Table 1: reasons given by GPs for prescribing systematically vitamin D**

	<i>Number (%)</i>
Nursing home residents are mostly deficient in vitamin D	58 (92.1)
Vitamin D prevents osteoporotic fractures	49 (77.8)
It is recommended to prescribe vitamin D for the elderly	24 (38.1)
Vitamin D is good for the health of the elderly	23 (36.5)
Vitamin D has a low toxicity and very few side effects	16 (25.4)
Vitamin D is cheap	6 (9.5)
Other	7 (11.1)

As shown in table 1, GPs systematically prescribe vitamin D mainly because they believe nursing home residents are mostly deficient in vitamin D (92.1%), because they believe vitamin D supplementation prevents osteoporotic fractures (77.8%), and because vitamin D supplementation is recommended by various scientific societies (38.1%). Other reasons were cited by 7 GPs: vitamin D could have a placebo effect, could reduce the risk of falling, could improve muscle tonicity, could improve the immune response, and because there are recommendations and evidence on the benefits of vitamin D. Let us specify that the answers “vitamin D could reduce the risk of falling” and “vitamin D could improve muscle tonicity” have been cited by 2 different GPs.

Table 2 shows the reasons given by GPs for prescribing vitamin D supplementation only in some patients and not in others.

**Table 2: reasons given by GPs for prescribing sometimes vitamin D**

	<b>Number</b>
	<b>(%)</b>
The patient is osteoporotic	42 (77.8)
The patient is deficient in vitamin D (based on the 25(OH)D level)	40 (74.1)
The patient has an history of fractures	28 (51.9)
The patient has had a recent fracture	22 (40.7)
When I think of it	16 (29.6)
The patient is at high risk of falls	15 (27.8)
The patient is frail	13 (24.1)
The patient is going little outside	12 (22.2)
The patient is a women	12 (22.2)
The patient has muscle weakness	10 (18.5)
The patient has low vitamin D dietary intakes	7 (12.9)
The patient is very old (>80 years)	6 (11.1)
The patient is suffering from a specific disease (depression, dementia, autoimmune disease, cardiovascular disease,...)	5 (9.3)
The patient has a low BMI (<21kg/m <sup>2</sup> )	6 (11.1)
The patient is a men	4 (7.4)
The patient has a very high BMI (>25kg/m <sup>2</sup> )	1 (1.9)
Others	3 (5.6)

Our results highlight that the choice to supplement some patients with vitamin D is principally based, on a diagnosis of osteoporosis (82.4%), on the results of a the 25(OH)D level (78.4%) in case of history of fracture (54.9%) or after a recent fracture (43.4%). Surprisingly, 16 physicians (31.4%) only prescribe vitamin D when they think of it. Other reasons reported for prescribing vitamin D were: depending on life expectancy, based on the patient's drug therapy and according to the results of a blood biology among osteoporotic or osteopenic patients.

Out of the 119 survey participants, 113 responded to the questions regarding the prescribed dose of vitamin D. Among them, 46 (40.7%) reported always prescribing the same dose of vitamin D to patients living in nursing home whereas 67 (59.3%) GPs do not always prescribe the same dose of vitamin D. For these 67 GPs, the prescribed dose depends on several reasons, as shown in table 3.

**Table 3: Factors influencing vitamin D dose prescribed by GPs (n= 67)**

	<i>Number (%)</i>
Degree of deficiency of 25(OH)D	63 (94.0)
Bone health	33 (49.3)
Previous fractures	29 (43.3)
Risk of falling	17 (25.4)
Muscle health	11 (16.4)
Concomitant diseases	11 (16.4)
Gender	11 (16.4)
Age of the patient	8 (11.9)
BMI	6 (9.0)
Others	7 (10.4)

Our survey showed that the prescribed dose of vitamin D mainly depends on the results of a blood test (94.0%), on the patient's bone health (49.3%) or whether the patient has a history of fracture (43.3%). Other reasons influencing the dose of vitamin D prescribed were raised by doctors: patient's preference regarding the form of the supplement, patient's digestive tolerance, patient's calcium supplementation intake, presence of chronic renal failure and frequency of outings. The most frequently systematically prescribed dose is 50.000 UI per month (44.1%).

A total of 98 doctors answered the questions about calcium association with vitamin D supplementation. Among them, 50.0% always prescribe calcium in combination with vitamin D, 44.6% sometimes prescribe calcium with vitamin D and 5.4% never prescribe this supplementation.

## Discussion

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4 The aim of the current study was to assess the profile and determinants of vitamin D  
5 supplementation prescription in nursing homes. To achieve this objective, a survey was  
6 conducted among GPs having, at least, one patient living in a nursing home in the Province  
7 of Liège. A total of 119 GPs answered to the survey.  
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11 The main results of this study show that 50% of GPs systematically prescribe vitamin D to  
12 their patients living in nursing homes whereas guidelines on vitamin D supplementation  
13 suggest a systematic supplementation in elderly patients [25]. The establishment of  
14 guidelines have increased the awareness in the medical community regarding the need for  
15 vitamin D status assessment and possible supplementation to support an overall healthy  
16 condition [27]. As a consequence, the last 10 years, the total number of vitamin D  
17 prescriptions has increased exponentially [27] but is still suboptimal. The number of elderly  
18 subjects, to whom vitamin D (any compounds) was prescribed, significantly increased from  
19 9.9% in 2006 to 22.8% in 2013 [27]. In 2009, a study showed that only 13% of  
20 institutionalized women received vitamin D supplements and that this figure is increasing  
21 [28]. Nevertheless, there is a significant variability in the prescriptions for vitamin D  
22 supplementation from physicians, as shown by Caillet in a French population [29].  
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32 The GPs that do not systematically usually prescribe vitamin D following a diagnosis of  
33 osteoporosis or blood test results revealing a low 25(OH)D level. This is consistent with the  
34 recommendations of many scientific societies recommending an oral supplementation in  
35 individuals presenting a serum 25(OH)D concentration below the threshold of 50 nmol/l [15].  
36 Following these guidelines, a recent study showed an increase in vitamin D prescription in  
37 Italy [27]. However, our survey did not assess the 25(OH)D threshold value below which  
38 doctors prescribe vitamin D to their institutionalized patients. Although doctors often  
39 prescribe vitamin D based on a blood test, the trend of paying agencies and the HAS (“Haute  
40 Autorité de Santé”) is rather to reduce the prescription of this test. The main determinants of  
41 vitamin D prescription, mentioned in the present study, are similar to those cited in other  
42 studies performed in different setting such as in primary care or patients with rheumatoid  
43 arthritis (i.e.: older age, diagnosis of osteoporosis, fractures, female gender) [30-32]. Despite  
44 the growing scientific interest in the benefits of vitamin D in the literature [27] a surprising  
45 determinant, highlighted in our study, was that 16 physicians (31.4%) only prescribe vitamin  
46 D when they think of it. Another surprising fact is that only few physicians prescribe vitamin D  
47 to prevent muscle wasting, contrary to what is recommended by scientific societies [33].  
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In this study, no physicians stated they never prescribe vitamin D to their patients living in nursing home. This can be explained by a possible bias of volunteering. Indeed, maybe that the GPs who never prescribe vitamin D did not want to answer the questionnaire. Another possible explication is the presence of a bias of social desirability. In surveys, subjects sometimes tend to answer what they think is expected by the investigator, which does not always reflect the reality. Because of these two possible biases, the prescription of vitamin D could be overestimated in this study.

A little less than half of the GPs in this study systematically prescribe the same dose of vitamin D to their patients. The most commonly dose prescribed by these doctors is 50.000UI per month (dose prescribed by 44.1% of these GPs). Specify that in Belgium, the most commonly prescribed form is D-cure (i.e. ampoule of 25.000UI). This is higher than the current recommendations advocating the intake of 800-1000 IU / day of vitamin D in the elderly population, or the equivalent of this dose taken following another regimen [34]. This could be explained because the institutionalized elderly are frailer and more deficient in vitamin D compared to healthy elderly [17, 18]. Currently, it is unknown whether this advice, initially designed for healthy adults/elderly, will lead to vitamin D sufficiency in the large majority of nursing home residents, taking into account the frailty of this population with multiple comorbidities, polypharmacy, and dependency on basic activities of daily living [35]. This could also be explained by the fact that an ampoule of D-cure is insufficient to reach a sufficient 25(OH) D. The vitamin D status is also related to the response to treatment, sun exposure or intake of vitamin D. Some authors believe considerably higher doses would be needed to ensure that almost all older adults reached a sufficient level of 25(OH)D [36].

The others GPs prescribe doses of vitamin D based on the degree of deficiency, as it is recommended by several societies to rapidly increase the rate of 25 (OH)D in the elderly [34, 37]. Indeed, the repletion dose will vary among individuals according to their starting level of 25(OH)D. Therefore, the dose may need to be adjusted based on the blood test [35]. Each 2.5 µg (100 IU) of added vitamin D will increase the serum 25(OH)D level by about 2.5 nmol/L (range 1.75– 2.75 nmol/L) or 1.0 ng/ml (range 0.7 to 1.1 ng/ml) [38]. However, scientific societies also considered the upper limit for safety to be 10,000 IU/day vitamin D, though agreed that the level for intoxication is likely to be higher than this [33]. All physicians who completed the survey reported prescribing vitamin D in the D3 form. This is not surprising given that this is the only form available in Belgium. This is the most commonly prescribed supplementation form, as shown in other studies [29].

Regarding calcium supplement, among GPs prescribing vitamin D supplement, 52.0% of them always prescribe calcium in combination with vitamin D, 44.9% sometimes prescribe

1 calcium with vitamin D and 3.1% never prescribe this supplementation. These results can be  
2 explained by the lack of a consensus on this subject. Scientific societies recommend vitamin  
3 D supplementation, ideally in combination with calcium, to improve efficacy [33].  
4 Nevertheless, in Belgium, vitamin D supplementation is not mandatory and depends on GP's  
5 judgment. This is in line with the results of 2 different meta-analyses which suggest that oral  
6 vitamin D appears to reduce the risk fractures only when calcium is added [12, 39]. However,  
7 this is controversial and a study has highlighted a change in prescription profile, within the  
8 last ten years, with a shift from the prescription of the combination of calcium and vitamin D  
9 to the prescription of vitamin D alone [27]. This could partly be explained by the increasing  
10 concerns about the cardiovascular effects of calcium supplementation [40].

11 This study has some limitations. The first one is that the first limit is that we have no  
12 information about the GPs' characteristics. We don't know whether respondents are  
13 representative of the population of GPs in nursing home or if they represent a homogeneous  
14 group. Indeed, we don't know the number of GP shaving at least one patient in a nursing  
15 home, in Liège. We hypothesize that GPs who feel most affected by vitamin D  
16 supplementation responded to the survey and not the others. The second limitation is that  
17 the survey was carried out in the province of Liège only. Nevertheless, to be as  
18 representative as possible, the survey was distributed to doctors working in various nursing  
19 homes (from different town, with different socio-economic level, from public or private  
20 sectors). The third limitation is the response rate which is about 30%, which does not  
21 guarantee the representativeness of the responses of all the GPs. To achieve this  
22 number/response, we opted to combine an online version and paper questionnaires made  
23 available in the involved nursing homes, since it is cheaper than post [41]. The majority of  
24 questionnaires were distributed online because the response rate would be better for online  
25 studies [41]. The fourth limitation is the lack of information about the doctors who responded  
26 (demographic characteristics, number of patients, town of practice,...) and the non-  
27 respondents. One last limitation is that the survey does not take into account any self-  
28 medication with vitamin D.

29 In conclusion, the number of vitamin D prescriptions has increased in recent years. This study  
30 points out that more than half of GPs systematically prescribe vitamin D to their patients  
31 living in nursing homes. If this figure is increasing, it is not yet optimal. The others GPs  
32 usually prescribe vitamin D following a blood test or a diagnosis of osteoporosis. The results  
33 of the present survey offer future perspectives for public health actions, in order to increase  
34 the rate of vitamin D prescription and to reduce the prevalence of vitamin D inadequacy.

## Conflict of interest

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3 FB, CR, JP and CD have no competing interest. OB has received grants or fees for research  
4 from GlaxoSmithKline, IBSA, Merck Sharp & Dohme, Theramex, Novartis, Pfizer,  
5 Rottapharm, Servier and SMB. EC is consultant for DiaSorin and IDS and has received  
6 lecture fees from IDS, DiaSorin, Roche, Abbott, Pfizer and Amgen. JYR has received  
7 consulting fees, paid advisory boards, lecture fees, and/or grant support from Servier,  
8 Novartis, Negma, Lilly, Wyeth, Amgen, GlaxoSmithKline, Roche, Merckle, Nycomed, NPS,  
9 Theramex, UCB, Merck Sharp and Dohme, Rottapharm, IBSA, Genevrier, Teijin, Teva,  
10 Ebewee Pharma, Zodiac, Analis, Novo-Nordisk, and Bristol Myers Squibb.  
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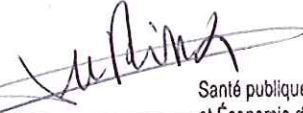
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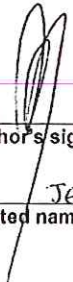
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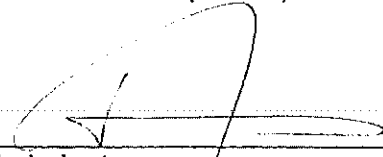
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