Efficacy of food fortification on serum 25-hydroxyvitamin D concentrations: systematic review

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ABSTRACT

Background: Many residents of the United States and Canada depend on dietary sources of vitamin D to help maintain vitamin D status. Because few natural food sources contain vitamin D, fortified foods may be required.

Objective: We aimed to determine the effects of vitamin D–fortified foods on serum 25-hydroxyvitamin D [25(OH)D] concentrations.

Design: We searched MEDLINE (1966 to June Week 3 2006), Embase, CINAHL, AMED, Biological Abstracts, and the Cochrane Central Register of Controlled Trials for randomized controlled trials (RCTs) comparing vitamin D–fortified foods with a control and reporting serum 25(OH)D concentrations. Two reviewers independently determined study eligibility, assessed trial quality, and extracted relevant data. Disagreements were resolved by consensus. Meta-analyses of absolute mean change in 25(OH)D were conducted by using a random-effects model, with evaluation of heterogeneity.

Results: Nine RCTs (n = 889 subjects) were included, of which 8 consistently showed a significant beneficial effect of food fortification on 25(OH)D concentrations. Although 7 RCTs (n = 585 subjects) potentially were meta-analyzable, we were unable to combine the overall results because of significant heterogeneity. The individual treatment effects ranged from 14.5 (95% CIs: 10.6, 18.4) nmol/L to 34.5 (17.64, 51.36) nmol/L (3.4–25 µg vitamin D/d). Subgroup analyses showed a reduction in heterogeneity and significant treatment effect when 4 trials that used milk as the fortified food source were combined.

Conclusion: Most trials were small in size and inadequately reported allocation concealment, but results showed that vitamin D–fortified foods improved vitamin D status in adults. Am J Clin Nutr 2008;88:1528–34.

INTRODUCTION

Vitamin D deficiency is common, especially among persons living in northern latitudes(1,2). Evidence of low vitamin D status in residents of Canada and the United States and of the association of that status with a greater risk of osteoporosis, autoimmune disorders, type 1 diabetes, and cancer is growing (3). As a result, much attention is being paid to safe and effective ways to increase vitamin D intake in the general population.

Vitamin D in the human body is mainly obtained via cutaneous synthesis of previtamin D₃ from 7-dehydrocholesterol through exposure to ultraviolet B light, at wavelengths of 290 to 320 nm (4). However, in winter months, at northern latitudes (above the 35th parallel), ultraviolet energy is insufficient for the photoconversion of 7-dehydrocholesterol to previtamin D₃ (5). Public acceptance of the association between sun exposure and greater risk of skin cancer has resulted in an avoidance of sun exposure and an increase in sunscreen use, which may further contribute to lower vitamin D status. In addition to environmental factors such as ultraviolet B light exposure, vitamin D status depends on individual characteristics such as age, body mass index (BMI), and skin color (3).

In the absence of ongoing synthesis, maintenance of vitamin D adequacy depends on body stores of vitamin D and intake from dietary sources or supplements. However, few foods (eg, fatty fish, egg yolks, and fish liver oils) contain vitamin D naturally, and these foods often are not consumed on a regular basis (6). Estimates of the mean daily intake of vitamin D in the United States from food-consumption data collected for persons participating in the 1999–2000 Nutritional Health and Nutrition Examination Survey (NHANES) showed that total vitamin D intake from food sources across all age groups is small (3.8–6.9 µg/d) and that few older adults achieve recommended vitamin D intakes. These results highlighted the role of food fortification in reaching adequate intakes, because fortified foods provided...
EFFECT OF VITAMIN D–FORTIFIED FOODS ON 25(OH)D CONCENTRATIONS

METHODS

Data sources and searches

We searched MEDLINE (1966 to June week 3 2006), Embase (2002 to 2006 week 25), CINAHL (1982 to June week 4 2006), AMED (1985 to June 2006), Biological Abstracts (1990 to February 2005), and the Cochrane Central Register of Controlled Trials (CENTRAL; 2nd quarter 2006). Our search strategy was developed in MEDLINE and modified for the other databases. We included investigator- and reviewer-nominated trials and contacted the primary or corresponding authors for additional information.

Study selection

Eligible studies included randomized controlled trials (RCTs) comparing foods fortified with vitamin D with no intervention, regular diet, or unfortified foods and reporting the serum 25(OH)D concentrations in all populations. We limited our inclusion criteria to published English-language reports on human studies in all populations (ie, no age limits).

A number of authors were involved in the initial screening of the search results (SO, AC, TH, HAW, SAA, DAH, DSO, LW, AT, FY). First, bibliographic records, including title, keywords, and abstract, were screened. Potentially relevant records were then screened independently with the use of the full text report. Discrepancies were resolved through consensus of the reviewers (SO, AC, DSO, HAW, AT, FY).

Data extraction and quality assessment

Two of us (SO and AC) independently assessed each trial and extracted data on the characteristics of trial participants, interventions ie, type of fortified food, vitamin D content, and frequency of administration), 25(OH)D assay, and outcomes ie, 25(OH)D concentrations including baseline, end of study, and absolute or percent change—or both). The Jadad scale was used to assess the methodologic and reporting quality of RCTs (9).

This validated scale includes 3 items that help to assess the methods used to generate random assignments, blinding, and reporting of dropouts and withdrawals. Jadad scoring ranges from 1 to 5; scores ≥3 indicated higher quality. In addition, concealment of the treatment allocation was ascertained (ie, adequate, inadequate, or unclear) by using the instrument by Schulz et al (10). Discrepancies were discussed and resolved through consensus of the reviewers (NB, MF, TH, DSO).

Data synthesis and analysis

Treatment effects were summarized as the weighted mean difference (WMD) (and 95% CIs) by using the absolute mean change in 25(OH)D concentrations between the treatment and control groups. The S<sub>D</sub>s were calculated from S<sub>E</sub>s or 95% CIs, and the absolute mean change in serum 25(OH)D concentrations from baseline to study endpoint was also calculated.

When statistical heterogeneity was present, estimates from individual trials were combined by using the random-effects model of DerSimonian and Laird (11). The presence of heterogeneity of treatment effect between studies was assessed by using the Cochran Q test and the degree of statistical heterogeneity with the I<sup>2</sup> statistic (12). An I<sup>2</sup> of <25% was felt to be consistent with low heterogeneity, an I<sup>2</sup> of 25–50% corresponded to moderate heterogeneity, and an I<sup>2</sup> of >50% indicated a high degree of heterogeneity (13). Heterogeneity was explored through the following a priori subgroup analyses: 1) population (ie, younger or older adults); 2) most common vitamin D intake from a fortified food source (ie, 10 µg/d); 3) vitamin D assay [eg, radioimmunoassay (RIA)]; and 4) the type of fortified food (ie, milk or other).

To ensure the consistency of reporting and data synthesis of serum 25(OH)D concentrations, all values (ie, nmol/L, ng/mL, µg/dL, and µg/L) were converted to a common unit of nmol/L. Similarly, for vitamin D intake (eg, µg, nmol, IU, and mg), µg was chosen as the standard unit. All statistical analyses were performed by using STATA software (version 9.0; STATA, College Station, TX).

RESULTS

This systematic review is part of a larger report on the evidence for vitamin D and bone health, which yielded 9150 potentially relevant records. After a full text review, 11 RCTs initially met the eligibility criteria: 10 were a parallel design (14–23), and 1 was a factorial design (24). However, after a more detailed review, 2 trials did not specify the vitamin D content of the dietary source, and they were subsequently excluded (18, 21). Therefore, a total of 9 trials (14–17, 19, 20, 22–24) satisfied our inclusion criteria (n = 889 participants; 437 in the intervention group and 452 in the control group) (Figure 1).

Population characteristics

All 9 trials included community-dwelling participants. The population studied included young adults (mean age < 30 y) in 3 trials (17, 19, 23) and older persons in the remaining 6 trials (14–16, 20, 22, 24) (Table 1). The ethnicity of the participants was reported in only 3 trials (14, 16, 22), and BMI was reported in 4 trials (14, 22–24). Five trials excluded participants who were taking vitamin D supplements on a regular basis (15, 17, 20, 22, 23), 1 trial excluded those using multivitamins (19), 1 trial excluded participants taking multivitamins but included those taking single-nutrient supplements (24), and 2 trials did not report on the use of supplements (14, 16). Vitamin D dietary intake was

≈65–86% of the total daily vitamin D intake from foods (and fortified milk contributed 40–64% of that amount) (7). One way to improve vitamin D status would be to recommend vitamin D supplementation in high-risk groups; however, supplementation may not be practical on a population level. Therefore, in response to concerns about widespread vitamin D deficiency, many countries have implemented either mandatory or discretionary food fortification (6, 8).

The serum 25-hydroxyvitamin D [25(OH)D] concentration is a widely accepted indicator of vitamin D status. The primary objective of this systematic review was to assess the effect of vitamin D–fortified foods on circulating concentrations of 25(OH)D. The secondary objective was to determine the effect of individual characteristics, such as age, BMI, ethnicity, and baseline vitamin D status. The present work is part of a larger evidence report on vitamin D and bone health (Internet: http://www.ahrq.gov/clinic/tp/vitadtp.htm).

Figure 1

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evaluated at baseline in 3 trials (20, 23, 24). During the intervention, the total intake of vitamin D from diet was reported in one trial (24) and that from diet and supplements was reported in another trial (20). Sun exposure was assessed in 3 trials (15, 17, 20). For example, Lau et al. (16) investigated the benefits of daily supplementation with vitamin D3 (20 μg) on serum 25(OH)D concentrations (16) and 1 did not provide an estimate of the increase in serum 25(OH)D concentrations.

### Interventions

Most trials (7 of 9) used dairy products as the source of vitamin D, while 1 trial (22) evaluated the effect of fortified foods in general. Dietary interventions included fortified milk (14–17, 22), nutrient-dense fruit- and dairy-based products (24), fortified orange juice (19), and fortified bread (23). The factorial RCT (24) had 2 other intervention groups: an exercise program and a combined program of exercise and nutrient-dense fruit- and dairy-based products (24), fortified orange juice (19), fortified cheese (20), and fortified bread (23).

### Comparators

Comparators were usual diet or no intervention (14, 16, 22, 24), unfortified milk (15, 17), unfortified orange juice (19), unfortified cheese or no cheese (20), and regular wheat bread or regular wheat bread and a vitamin D3 supplement (23).

### Study and reporting quality

Five trials had a total score of ≥3 on the Jadad scale (15, 16, 19, 20, 22). Eight trials provided data on losses to follow-up (14–17, 20, 22–24); of these trials, only one reported losses of >20% (24). In all trials, the information on the methods used for allocation concealment was unclear. Of the 9 trials, 8 did not report whether they had included an intention-to-treat analysis; Daly et al. (22) reported performing an analysis that was similar to an intention-to-treat analysis.

### Efficacy outcomes: serum 25(OH)D concentrations

#### Meta-analysis

Seven trials provided sufficient data for calculation of the absolute mean change from baseline in total 25(OH)D or 25-hydroxyvitamin D3 [25(OH)D3], and these results were combined (14, 15, 17, 19, 22–24). The remaining 2 RCTs were summarized descriptively, because there were insufficient data from which to derive the absolute mean change in 25(OH)D concentrations between the treatment and control groups (16, 20).

Providing an overall treatment estimate from 7 trials (n = 585) was not feasible because of the high heterogeneity of the treatment effect (I² = 70.6%); however, the individual WMDs showed a significantly greater increase in absolute mean change in serum 25(OH)D in the treatment group than in the control group [range: 14.5 (95% CI: 10.6, 18.4) to 34.5 (17.64, 51.36) nmol/L] (14, 15, 17, 19, 22–24) (Figure 2).

#### Subgroup analyses

Subgroup analysis by population or intake level did not explain the heterogeneity with respect to the treatment effect. In contrast, combining results from 4 trials (n = 446; 3.45–20 μg vitamin D3/d) that used an RIA to measure serum 25(OH)D concentrations showed a statistically significant increase in serum 25(OH)D [WMD = 15.70 (95% CI: 12.62, 18.77) nmol/L; F = 0.0%; P = 0.77] (14, 17, 22, 23). Similar results were noted when combining results from 4 trials (n = 466; 3.45–20 μg vitamin D3/d) that used milk as the fortified food source [15.63 (12.79, 18.48) nmol/L; F = 0.0%; P = 0.77] (14, 15, 17, 22). Of the 2 trials not included in the meta-analyses, 1 showed an increase in serum 25(OH)D concentrations (16) and 1 did not (20). For example, Lau et al. (16) investigated the benefits of daily milk supplementation (6 μg vitamin D3 plus 800 mg calcium) in postmenopausal Chinese women over a period of 2 y. At 12 mo, serum 25(OH)D was higher in the vitamin D-fortified milk group than at baseline (P < 0.05); however, baseline and follow-up serum 25(OH)D concentrations in the control group and a comparison of serum 25(OH)D concentrations between the intervention and control groups were not reported (16). In the second of these trials, Johnson et al. (20) compared the effect of vitamin D-fortified cheese (15 μg vitamin D3/d) with that of unfortified cheese or no cheese in older adults over a 2-mo period; despite a significantly higher vitamin D dietary intake in the fortified-cheese group, the serum 25(OH)D concentration decreased by a mean of 6 ± 2 nmol/L (P < 0.001). Whereas this decrease was not clinically significant, the authors speculated...
that it could reflect a higher baseline serum 25(OH)D concentration in the fortified-cheese group than in the control group (20).

Serum parathyroid hormone concentrations were evaluated in 6 trials (14, 16, 19, 20, 22, 23), of which 3 (16, 19, 22) showed a significantly lower concentration at the end of the study in the intervention group than in the control group.

Effect of baseline 25-hydroxyvitamin D concentrations

The positive treatment effect on 25(OH)D from foods fortified with vitamin D was consistent, but it varied according to baseline serum 25(OH)D concentrations (Table 2). Across trials, participants with lower baseline 25(OH)D concentrations (ie, <50 nmol/L) (15, 19, 23, 24) were more likely to reach the higher end of study serum 25(OH)D concentrations than were those with higher baseline concentrations (ie, >50 nmol/L) (14, 16, 17, 20).

Harms

In one trial, 5 participants in the intervention group (vitamin D–fortified milk with added calcium compared with the usual diet) dropped out of the study as a result of gastrointestinal side-effects (22). In another trial, one participant in the intervention group (vitamin D–fortified milk powder with added calcium compared with no intervention) withdrew from the study because of gastrointestinal discomfort (16). In a third trial, 2 participants withdrew from the study because of gastrointestinal problems; however, the treatment group was not specified (20).

DISCUSSION

In 8 of the 9 trials, vitamin D fortification of food had a beneficial effect on vitamin D status in younger and older adults with various baseline 25(OH)D concentrations (14–17, 19, 22–24). It is notable that this benefit was attributed to the fortified foods alone in ≥4 of the 8 trials that excluded participants who were taking vitamin D supplements from the onset (15, 17, 22, 23). The estimation of the combined treatment effect was limited by heterogeneity between trials; however, the combination of 4 trials (n = 446; 3.45–20 μg vitamin D/d) that used an RIA to measure 25(OH)D, resulted in a statistically significant and beneficial treatment effect (14, 17, 22, 23), as did the combination of 4 trials (n = 466; 3.45–20 μg vitamin D/d) that used milk as the fortified food source (14, 15, 17, 22). In 4 of the included studies, the serum 25(OH)D concentration attained was >80 nmol/L, (14, 16, 19, 22), which is a cutoff recommended by many researchers for optimal vitamin D status. In addition, the increment in the 25(OH)D concentration attained appears to be larger than the increment of 1 nmol·L⁻¹·μg⁻¹ that was previously reported in studies of vitamin D supplementation (25, 26). There were insufficient data in these 4 studies for definitive evaluation of the effect of participant characteristics such as age, BMI, ethnicity, and baseline vitamin D status on the treatment effect.

Increases in serum 25(OH)D from vitamin D–fortified foods may be influenced by a number of factors, including total vitamin...
D intake, bioavailability (19), and the actual vitamin D content within the fortified food source [because previous analytic studies showed that actual vitamin D amounts are often outside the stated fortification range (27–29)], the assay used, and the baseline 25(OH)D concentrations.

Based on our review, the treatment effect did vary with baseline serum 25(OH)D concentrations (ie, participants with lower baseline 25(OH)D concentrations tended to reach the higher end of study 25(OH)D concentrations); however, the strength of this observation was limited because it was based on an indirect comparison of the individual trials, and different assays were used.

Furthermore, previous research with vitamin D supplements has suggested that the required treatment duration to reach a steady state of 25(OH)D is ≈3 mo, and a similar duration should apply to fortified foods (30). Seven of the 9 included trials had treatment durations of ≥3 mo (14–17, 19, 22, 24).

The findings of the present review show that the fortification of food with vitamin D was associated with statistically significant improvements in serum 25(OH)D concentrations that have important implications for the maintenance of vitamin D status in the population. Nevertheless, in evaluations of the effect of food fortification on bone health outcomes such as 25(OH)D, parathyroid hormone, and bone mineral density (14, 16, 22), it is important to acknowledge the potential confounding effect generated by the food source used, because a diet high in calcium and phosphorus may decrease calcitriol synthesis, and lower calcitriol concentrations would be associated with less catabolism of 25(OH)D (31).

The exploration of heterogeneity in the present systematic review was limited because we did not have access to individual patient data, which could have allowed us to adjust for population differences and effect modifiers such as BMI and ethnicity. In addition, we could not assess the presence of publication bias, given the limited number of trials with sufficient data (32).

Harms were not adequately described, and it was unclear whether gastrointestinal side effects were secondary to additional calcium or vitamin D.

The ascertainment of the methodologic quality of the included trials was limited by the fact that none of the study authors adequately reported on the methods used for allocation concealment. Previous evidence indicated that trials using inappropriate methods for allocation concealment may overestimate the size of the treatment effect (10).

A lack of information on the dietary intake of vitamin D, the degree of participant compliance, and the analysis of vitamin D content within the food source were another limitation. Finally, the measurement of 25(OH)D is analytically challenging because it is highly protein-bound, and results vary both between assays and between laboratories using the same assay (33, 34).

<table>
<thead>
<tr>
<th>Dietary source (continued)</th>
<th>Absolute mean change in serum 25(OH)D</th>
<th>Fasting sample</th>
<th>Season of sample</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily intake from fortified food (vitamin D/calcium) Duration Assay</td>
<td>IG</td>
<td>CG</td>
<td>Assay</td>
<td>Fasting sample</td>
</tr>
<tr>
<td>µg/g</td>
<td>nmol/L</td>
<td>nmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IG: 10/1.2 24 mo</td>
<td>17.3 ± 13.3</td>
<td>2.8 ± 13.1</td>
<td>RIA</td>
<td>Y</td>
</tr>
<tr>
<td>IG: 20/1.0 24 mo</td>
<td>4.2 ± 20.0</td>
<td>14.4 ± 20.3</td>
<td>RIA</td>
<td>Y</td>
</tr>
<tr>
<td>IG: 10/NR 4 mo</td>
<td>35 ± 18</td>
<td>5 ± 9</td>
<td>CPBA</td>
<td>Y</td>
</tr>
<tr>
<td>IG: 15/NR 2 mo</td>
<td>−6.0 ± 11.49</td>
<td>CG1: 3.5 ± 7.29</td>
<td>RIA</td>
<td>Y</td>
</tr>
<tr>
<td>IG: 5/0.8 CG: 0.1/0.6 12 mo</td>
<td>22.25 ± 10.90</td>
<td>CG2: 0.75 ± 10.05</td>
<td>CPBA</td>
<td>NR</td>
</tr>
<tr>
<td>IG: 6/0.8 24 mo</td>
<td>23.2 ± 13.2</td>
<td>Not estimable</td>
<td>CPBA</td>
<td>NR</td>
</tr>
<tr>
<td>IG: 3.4/0.44 CG: 0.9/0.36 5 mo</td>
<td>15 ± 21.1</td>
<td>31.0 ± 24.2</td>
<td>RIA</td>
<td>NR</td>
</tr>
<tr>
<td>IG1: 10/NR 3 wk</td>
<td>IG1: 16.3 ± 21.89</td>
<td>CG1: 19.5 ± 30.3</td>
<td>RIA</td>
<td>Y</td>
</tr>
<tr>
<td>IG2: 10/NR</td>
<td>IG2: 14.9 ± 19.61</td>
<td>CG2: −0.3 ± 13.27</td>
<td>CPBA</td>
<td>NR</td>
</tr>
<tr>
<td>IG: 25/0.35 3 mo</td>
<td>57.0 ± 26.19</td>
<td>22.3 ± 17.32</td>
<td>CPBA</td>
<td>NR</td>
</tr>
</tbody>
</table>

1 CG, control group; IG, intervention group; RIA, radioimmunoassay; CPBA, competitive protein–binding assay; Y, yes; NR, not reported.
2 Jadad score is calculated from 1 to 5, with the higher scores being better.
3 x SD (all such values except when indicated otherwise).
4 Absolute mean change calculated from baseline and end-of-study data.
5 SEM or 95% CI converted to SD.
6 Median; (range).
The present review highlights the need for stronger data on food fortification. Future research should include analytic assessment of vitamin D food content with the use of quality-control food materials (35), support for dose-response studies, and trials of food fortification in different age and ethnic groups with the use of different food matrices.

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The authors’ responsibilities were as follows—all authors: the design of the study; MS: developing the search and retrieving articles; AC, SO, TH, DSO, AT, and FY: data extraction; SO, AC, TH, NB, MF, SAA, DAH, HAW, DSO, and LW: analysis or interpretation of the data (or both); SO: drafted the manuscript with AC; and all authors: contributed to the initial draft and revisions of the manuscript. None of the authors had a personal or financial conflict of interest.

FIGURE 2. Forest plot of the effect of food fortification of vitamin D (with or without calcium) compared with control on absolute mean change in total serum 25-hydroxyvitamin D [25(OH)D] or 25-hydroxyvitamin D$_3$ [25(OH)D$_3$] concentrations (in nmol/L). WMD, weighted mean difference. The 7 trials shown in the figure (out of 9 trials included in the study) provided sufficient data for calculation of the absolute mean change from baseline in 25(OH)D. Weights are from random-effects analysis.

TABLE 2
Intervention group baseline, end-of-study, and absolute mean change in serum 25-hydroxyvitamin D [25(OH)D] concentrations relative to controls at different estimated daily vitamin D intakes

<table>
<thead>
<tr>
<th>Intake and study</th>
<th>Study group</th>
<th>Subjects</th>
<th>Estimated vitamin D intake from fortified food</th>
<th>25(OH)D in IG</th>
<th>Absolute mean change in 25(OH)D relative to controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>µg/d</td>
<td>baseline</td>
<td>end of study</td>
</tr>
<tr>
<td>&lt;10 µg/d</td>
<td>Keane et al (15)</td>
<td>Elderly persons</td>
<td>18</td>
<td>5&lt;sup&gt;2&lt;/sup&gt;</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Lau et al (16)</td>
<td>Postmenopausal women</td>
<td>95</td>
<td>6</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>McKenna et al (17)</td>
<td>Young adults</td>
<td>52</td>
<td>3.4</td>
<td>77</td>
</tr>
<tr>
<td>&gt;10 µg/d</td>
<td>Chee et al (14)</td>
<td>Postmenopausal women</td>
<td>91</td>
<td>10</td>
<td>69.1</td>
</tr>
<tr>
<td></td>
<td>Daly et al (22)</td>
<td>Ambulatory men</td>
<td>76</td>
<td>20</td>
<td>77.2</td>
</tr>
<tr>
<td></td>
<td>de Jong et al (24)</td>
<td>Elderly persons</td>
<td>37</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Johnson et al (20)</td>
<td>Persons &gt;60 y old</td>
<td>33</td>
<td>15</td>
<td>57.5</td>
</tr>
<tr>
<td></td>
<td>Natri et al (23)</td>
<td>Women 25–45 y old</td>
<td>30</td>
<td>10</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Tangpricha et al (19)</td>
<td>Persons 19–60 y old</td>
<td>14</td>
<td>25</td>
<td>37</td>
</tr>
</tbody>
</table>

<sup>1</sup> IG, intervention group.
<sup>2</sup> Isoform of vitamin D not specified.
<sup>3</sup> Insufficient data.
REFERENCES