



Summary of evidence-based review on vitamin D efficacy and safety in relation to bone health¹⁻⁴

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ABSTRACT

The objective of this evidence review was to synthesize the literature on the effectiveness and safety of nutritional and ultraviolet radiation sources of vitamin D with respect to bone health outcomes at all stages of life. The goals were to identify knowledge gaps for the research community and to highlight areas that required further research. We completed an extensive literature search of multiple databases and a multilevel selection process with synthesis of results from 167 included studies. We included a variety of outcomes (eg, falls, bone mineral density, fractures, and adverse events). This report provides an overview of the methods and a summary of the key findings. In addition, we discuss areas where the evidence is inconclusive, as well as methodologic issues that we encountered. We found inconsistent evidence of an association between serum 25-hydroxyvitamin D [25(OH)D] concentration and bone mineral content in infants and fair evidence of an association with bone mineral content or density in older children and older adults. The evidence of an association between serum 25(OH)D concentration and some clinical outcomes (fractures, performance measures) in postmenopausal women and older men was inconsistent, and the evidence of an association with falls was fair. We found good evidence of a positive effect of consuming vitamin D–fortified foods on 25(OH)D concentrations. The evidence for a benefit of vitamin D on falls and fractures varied. We found fair evidence that adults tolerated vitamin D at doses above current dietary reference intake levels, but we had no data on the association between long-term harms and higher doses of vitamin D. *Am J Clin Nutr* 2008;88(suppl):513S–9S.

INTRODUCTION

Osteoporosis-related fractures constitute an important socioeconomic burden. In the United States, 1.5 to 2 million incident fractures occur annually, and the direct medical costs of osteoporosis are estimated to be \$13.7–20.3 billion (1). The burden of fractures is likely to increase over the next few decades as a result of the expanding aging population. Guidelines have recommended adequate calcium and vitamin D intakes in addition to antiresorptive medications for the prevention of osteoporotic fractures.

The 1997 US Institute of Medicine report on dietary reference intakes for calcium and related nutrients defined circulating 25-hydroxyvitamin D [25(OH)D] as the functional indicator of vitamin D status (2). Circulating 25(OH)D concentrations reflect the combined contribution of cutaneous synthesis and dietary intake, including vitamin D supplements. The Institute of Med-

icine was unable to establish estimated average requirements on which to base recommended daily allowances for vitamin D because of insufficient scientific data, so it provided adequate intake levels instead. An adequate intake of vitamin D should provide the amount needed to maintain a defined criterion of adequacy, eg, prevention of rickets or osteomalacia in all members of a healthy population. The tolerable upper intake level (highest level of daily nutrient intake likely to pose no risk of adverse health effects to almost all individuals in the general population) of 2000 IU per day of vitamin D for individuals 1 y of age or older (or 1000 IU per day for infants) is based on limited evidence (2).

Although several available assays can measure serum 25(OH)D concentrations, they have methodologic limitations. The lack of standardization of the different analytic methods used to measure circulating 25(OH)D concentrations, resulting in both interassay and interlaboratory variability, and the lack of standard reference preparations and calibrating materials, make vitamin D status assessments difficult (3–6).

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In 2005, the Office of Dietary Supplements of the National Institutes of Health and the Agency for Healthcare Research and Quality funded a systematic review of the evidence on the efficacy and safety of vitamin D in relation to bone health outcomes. The goal of this review was to inform the research community of knowledge gaps and limitations in the existing evidence to help identify future research priorities. Another goal was to assist the review's sponsors in developing information on the use of vitamin D supplements for healthcare providers and consumers.

This article summarizes the report's key findings and highlights challenges that we encountered in conducting a systematic review of nutritional forms and ultraviolet sources of vitamin D. The full report is available on the Internet at <http://www.ahrq.gov/clinic/tp/vitadtp.htm>.

SYSTEMATIC REVIEW PROCESS

In contrast with a narrative review that focuses on the results of individual studies, a systematic review of research evidence minimizes bias by providing a reproducible, comprehensive summary of the overall body of evidence (7). As a result, a systematic review can increase the likelihood of appropriate decision making based on the totality of evidence (8). Many people use systematic reviews to evaluate medical therapies or diagnostic tests, but fewer people use them to evaluate nutritional supplements (9).

The University of Ottawa Evidence-based Practice Center team synthesized the published literature on 5 key questions:

1) Are specific circulating concentrations of 25(OH)D associated with bone health outcomes across age groups (infants, children, women of reproductive age, and older men and women)?

2) Does food fortification, sun exposure, or vitamin D supplementation affect circulating concentrations of 25(OH)D?

3) What is the evidence regarding the effect of supplemental doses of vitamin D on bone mineral density (BMD) and fracture or fall risk?

4) Is a specific level of sunlight exposure sufficient to maintain adequate vitamin D levels without increasing the risk of non-melanoma skin cancer or melanoma?

5) Does vitamin D intake above current reference intake levels lead to toxicities (eg, hypercalcemia, hypercalciuria, or nephrolithiasis)?

An independent panel of vitamin D content experts (nutrition scientists, biochemists, and medical specialists) and representatives from the National Institutes of Health and Agency for Healthcare Research and Quality provided input during the review process and helped to refine the key questions (10). To address the 5 key questions, the team developed an analytic framework that outlined linkages among populations of interest, different vitamin D sources (dietary intake, supplements, and ultraviolet B radiation), and relevant outcomes (Figure 1; 11).

Search strategy and eligibility criteria

The team searched multiple databases, without language restriction, including MEDLINE (National Library of Medicine, Bethesda, MD; 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

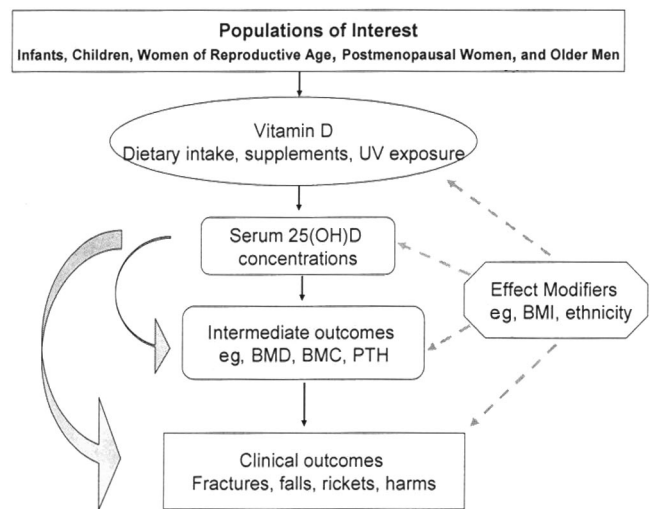


FIGURE 1. Analytic framework for evidence review on vitamin D. UV, ultraviolet; 25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density; BMC, bone mineral content; PTH, parathyroid hormone; BMI, body mass index.

(2nd quarter 2006). The team restricted the studies selected to those published in English and involving human participants.

The team focused on randomized controlled trials (RCTs), whenever possible, to minimize bias and focus on the highest level of evidence for questions. The team only included studies for questions 2–5 that assessed either vitamin D₂ or D₃ (with or without calcium) versus control. The team broadened the inclusion criteria for question 1 to include prospective cohort, case-control, and before-after studies that addressed the association between serum 25(OH)D concentrations and bone health outcomes, especially in infants and children, due to the lack of RCTs in this area, and restricted question 4 to existing reviews.

Study selection

The team assessed the results of the search by using a 3-step process. First, one reviewer screened bibliographic records, including title and abstract. Second, 2 reviewers screened potentially relevant records by using the full-text report and applied strict eligibility criteria. The 2 reviewers resolved any conflicts through consensus or adjudication by the third reviewer. Third, the team assessed relevant studies for study design and categorized these studies by relevance to each question.

Data extraction

Two reviewers abstracted data on study and population characteristics, type of 25(OH)D assay, vitamin D intervention (type, dose, frequency of administration), co-interventions, reported confounders or covariates, and relevant bone health outcomes. The team resolved differences through consensus.

Assessment of study quality

The team assessed the quality of the randomized trials included in the review by using the Jadad 5-point scale, which assesses randomization, double-blinding, and the description of dropouts and withdrawals (12). The team rated adequacy of allocation concealment as adequate, inadequate, or unclear by using the Schulz method (13). For observational studies, the team evaluated methodologic quality (poor, fair, or good) by using a



grading system adapted from Harris et al (11). The team based the aggregate level of evidence (good, fair, or inconsistent) on the quantity, quality, and consistency of results (14).

Data synthesis

Where possible and appropriate, the team conducted meta-analyses of RCTs that assessed the efficacy of vitamin D interventions by using a random effects model, with assessment of statistical heterogeneity. The team did not attempt to calibrate serum 25(OH)D concentrations across studies because of the different assays (ie, radioimmunoassay, enzyme-linked immunoassay, competitive binding protein assay, and HPLC) used in the studies.

For continuous outcomes [eg BMD and serum 25(OH)D], the team used the difference in means between treatment groups in the meta-analyses. For the pooling of BMD results, the team used the difference in the percentage change in BMD from baseline. For pooling of 25(OH)D, absolute changes in 25(OH)D were used. Combined odds ratios were generated for dichotomous outcomes, eg, falls, by using the number of individuals who had an event. The team conducted meta-analyses using a weighted mean method. The team initially used the fixed effects model to obtain combined estimates of weighted mean differences and their standard errors. The assessment of the degree of statistical heterogeneity across studies was based on chi-square (Q) and I^2 statistics. When study heterogeneity was significant ($P < 0.10$), the team used a random-effects method to obtain combined estimates across the studies (15). The team evaluated the degree of statistical heterogeneity with the I^2 statistic (16–18). If the Forest plot, or I^2 statistic, indicated a high degree of heterogeneity (16–18), the team explored this through subgroup, sensitivity, and meta-regression analyses, if appropriate.

OVERVIEW OF RESULTS

The literature search identified 9150 potentially relevant citations; reviewers nominated an additional 59 studies. The team excluded 2643 review or duplicate articles and 5119 articles based on title and abstract screening. The team reviewed 1447 full-text articles; 682 of these met the inclusion criteria and the team classified these by study design. The team included 167 studies that met the pre-established study design criteria in the evidence synthesis (112 RCTs, 19 prospective cohort studies, 30 case-control studies, and 6 before-after studies).

Of the RCTs, 52% had study quality scores of 3 or higher on the Jadad 5-point scale (12), and 29% of these had a score of 4. Overall, most of the higher-quality evidence on vitamin D status and bone health outcomes came from studies of postmenopausal women and men over age 60 y; the review found relatively few high-quality controlled studies in infants, children, and adolescents. Most studies were in white populations only.

Association between 25-hydroxyvitamin D concentrations and bone health outcomes

Seventy-two studies assessed the relation between 25(OH)D concentrations and bone health outcomes (both intermediate and clinical) across the life span. Most (41) of these focused on postmenopausal women and older men. Very few included women of reproductive age, perimenopausal women, infants, or children. We provide a summary of the results by age group and bone health outcome in **Table 1**.

The authors of individual studies did not always assess relevant confounders, and assessing the relation between 25(OH)D concentrations and bone health outcome was only a secondary objective in several studies. The assays used to assess 25(OH)D and baseline 25(OH)D concentrations across studies varied, and this might have affected our results. Many reports did not provide details of assay precision, presumably because of the state of the science at the time of publication.

We found inconsistent evidence of an association between serum 25(OH)D concentration and bone mineral content in infants and fair evidence of an association with bone mineral content or BMD in older children and older adults. We found inconsistent evidence of an association between serum 25(OH)D concentration and some clinical outcomes (fractures, performance measures) in postmenopausal women and older men and fair evidence of an association with falls. Although several authors tried to define 25(OH)D concentration thresholds, we had difficulty defining an overall 25(OH)D threshold because of the inaccuracy and imprecision of the different assays and the lack of a validated method for measuring 25(OH)D.

Effect of vitamin D supplementation, ultraviolet B radiation, or food fortification on 25-hydroxyvitamin D concentrations

Several studies examined the effect of vitamin D supplementation on 25(OH)D concentrations, but few high-quality studies examined the effect of ultraviolet B radiation, the predominant source of vitamin D worldwide, or of food fortification on 25(OH)D concentrations. Seventy-four trials (including 35 of higher quality) evaluated the effect of vitamin D₃ or vitamin D₂ supplements on 25(OH)D concentration. These studies used a variety of different assays to measure 25(OH)D concentrations; most used either competitive protein binding assays or immunoassays. Most of the trials included postmenopausal women or older men, and few high-quality trials included infants, children, pregnant women, or lactating women.

Fifty-five RCTs used vitamin D₃ (dose range: 200–10 000 IU/d), and 15 trials used vitamin D₂ (400–10 000 IU/d). In 3 trials that compared supplemental vitamin D₂ and D₃, vitamin D₃ had a greater effect on serum 25(OH)D concentrations, possibly because of vitamin D₂'s more rapid clearance from the circulation (19).

A meta-analysis of 16 vitamin D₃ trials found consistent support for a dose-response effect on serum 25(OH)D concentration, although the results were heterogeneous, possibly because of differences in population, assay, dose, and treatment duration. Subgroup analyses (dose, population, assay) did not sufficiently explain this heterogeneity, but an exploratory meta-regression analysis found a significant association between dose and serum 25(OH)D concentration [an increase of 1–2 nmol/L in 25(OH)D for each additional 100 units of vitamin D₃]. We found good evidence that vitamin D increased serum 25(OH)D concentrations, although most trials did not explore the role of effect modifiers such as body mass index. Given the lack of standardization and calibration of 25(OH)D assays, we cannot offer recommendations on adequate intake of vitamin D on the basis of this systematic review.

Eight RCTs (4 using an artificial ultraviolet B light source and 4 using solar exposure) examined the effect of ultraviolet light exposure on circulating 25(OH)D concentrations. Of these, 7 enrolled white adults and almost all were of lower quality. We

TABLE 1Evidence for an association between 25-hydroxyvitamin D [25(OH)D] concentrations and bone health outcomes by age group¹

| Population and outcome | Number of studies | Results |
|--|-------------------|---|
| Infants and young children | | |
| Rickets | 13 | Fair evidence of an association between low 25(OH)D concentration and established rickets, but inconsistent evidence for a specific threshold, with mean or median 25(OH)D concentrations ranging from <30 nmol/L (6 studies) to 50 nmol/L (1 study). Most cases of rickets occurred in nonwhite infants, and low-calcium diets confounded case definition. |
| Infants | | |
| PTH | 7 | Fair evidence that PTH is inversely associated with 25(OH)D, but inconsistent evidence for a specific threshold. |
| BMC/BMD | 7 | Inconsistent evidence of an association between serum 25(OH)D concentration and BMC/BMD. |
| Older children and adolescents | | |
| PTH | 7 | Fair evidence of an inverse association between 25(OH)D concentration and PTH. |
| BMC/BMD | 7 | Fair evidence of an association between 25(OH)D concentration and baseline or change in BMD or BMC. |
| Pregnant and lactating women | | |
| BMD | 4 | Insufficient evidence of an association between 25(OH)D concentration and change in BMD during pregnancy and good evidence of no association during lactation. Fair evidence that serum 25(OH)D concentration correlates inversely with PTH in pregnancy. |
| Postmenopausal women and older men | | |
| Fractures | 15 | Inconsistent evidence of an association between lower 25(OH)D concentration and increased risk of fractures. |
| Falls | 5 | Fair evidence of an association between lower 25(OH)D concentration and increased risk of falls in institutionalized elderly. |
| Performance measures (eg, body sway, gait speed) | 7 | Inconsistent evidence for an association between changes in 25(OH)D and a variety of performance measures. |
| BMD | 19 | Fair evidence of an association between 25(OH)D concentration and change in BMD of the hip, with variable thresholds of 25(OH)D concentration below which bone loss increased. |

¹ PTH, parathyroid hormone; BMC, bone mineral content; BMD, bone mineral density.

had difficulty determining the ultraviolet dose used, and heterogeneity with respect to age, area of skin exposed, and outcomes reported limited our synthesis. Two trials in nursing home residents with low baseline 25(OH)D concentrations found that suberythemal ultraviolet light exposure resulted in median increases of 28–42 nmol/L after 3 mo (20). We could not determine the potential impact of effect modifiers such as race, ethnicity, age, or latitude from these studies. We found fair evidence that ultraviolet light exposure increased serum 25(OH)D concentration in participants with a low or normal baseline 25(OH)D concentration.

Dairy products were the vitamin D–fortified food that most of the 11 food fortification RCTs used (dose: 137–1000 IU/d). Vitamin D₃ was the form used in 7 trials, and the type of vitamin D was not specified in the remaining trials. Six of the 11 trials were of higher quality. As with the supplementation trials, heterogeneity of the food fortification trials limited our ability to quantitatively synthesize the results from these studies. We found good evidence of a positive effect on 25(OH)D concentrations; the magnitude of treatment effect varied from 15 to 40 nmol/L. However, we could not determine whether the effect of eating food fortified with vitamin D on serum 25(OH)D concentration varied by age, body mass index, or ethnicity. The food fortification trial reports did not list any adverse events.

Effect of vitamin D supplementation on bone mineral density in adults

Seventeen RCTs evaluated the effects of vitamin D₂ or vitamin D₃ supplementation (dose: 300–2000 IU) on BMD, primarily in postmenopausal women and older men. Most of these trials were relatively small. Vitamin D₃ alone (dose: 300 or 400 IU/d) did not have a significant effect on BMD, except for an increase in femoral neck BMD in one trial. We found consistent evidence that vitamin D₃ at daily doses of ≥700 IU with calcium (500–1200 mg/d) prevented bone loss in the lumbar spine, femoral neck, and total body compared with placebo in whites. The Women's Health Initiative demonstrated a significant effect of 400 IU vitamin D₃ combined with calcium on BMD of the total hip (21). One trial in African American women did not observe a benefit of vitamin D₃ in combination with calcium compared with calcium alone on BMD (22).

Effect of vitamin D supplementation on fractures and falls in postmenopausal women and older men

Fifteen RCTs evaluated the effect of vitamin D supplements on fractures in postmenopausal women and older men. Nine trials were of higher quality, but loss to follow-up of >20% and

unclear reporting of allocation concealment was a limitation in some of these trials. Most trials used oral vitamin D₃ supplements as the intervention, with doses ranging from 300 to 800 IU/d. The combined results from 13 individually randomized trials ($n = 58\,712$) resulted in a nonsignificant reduction in fractures with heterogeneity of treatment effect. Vitamin D₃ supplementation (dose: 400–800 IU/d) without calcium (5 trials) did not reduce the risk of fractures. Vitamin D₃ (dose: 700–800 IU/d) reduced the risk of nonvertebral fractures and hip fractures, although this benefit might only occur in older persons living in institutionalized settings and not in all community-dwelling elderly individuals. Compliance with vitamin D supplementation was lower in the larger pragmatic community-based fracture trials, and this might have affected the results (23, 24).

Fourteen RCTs evaluated the effect of vitamin D on the incidence of falls in postmenopausal women and older men (7 RCTs included community-dwelling elderly and 7 included elderly in institutional settings). Combined results from 12 RCTs ($n = 14\,101$) were consistent with a small benefit of supplementation on falls (OR 0.89; 95% CI: 0.80, 0.99; $I^2 = 23.2\%$), but the extent of the benefit was inconsistent across trials. We found a significant reduction in falls when we combined the results from 6 trials that adequately ascertained falls (OR: 0.79; 95% CI: 0.65, 0.96; $I^2 = 0\%$) or combined results from 8 trials that used oral vitamin D (700–800 IU vitamin D₃ or 1000 IU vitamin D₂) and calcium (500–1200 mg; OR: 0.84; 95% CI: 0.76, 0.93; $I^2 = 0\%$). In sensitivity analyses combining results from 10 RCTs ($n = 8566$) in which the allocation concealment was unclear, there was a significant reduction in falls (OR: 0.85; 95% CI: 0.76, 0.96). The evidence for a benefit of vitamin D on falls varied, possibly because of differences in methods of ascertaining falls, differences in dose, or administration. These results are similar to the findings of some other meta-analyses (25, 26), but not to those of earlier meta-analyses that did not include trials published after 2004 (27, 28). The incomplete ascertainment of vitamin D status in several trials limited our ability to explore the effect of baseline and attained 25(OH)D concentrations on fall and fracture risk.

We did not retrieve any reviews relevant to question 4 on the level of sun exposure sufficient to maintain 25(OH)D concentrations while minimizing the risk of nonmelanoma skin cancer or melanoma. Estimated sun exposure times for adequate vitamin D synthesis vary by individual and environmental characteristics, such as skin pigmentation (melanin) and latitude.

Vitamin D supplementation and toxicity

Twenty-two vitamin D trials reported data on adverse events; 19 included adult populations only, and we found few data on adverse events in infants and children. In general, the harms were secondary outcomes, and the duration of vitamin D exposure in many trials was too short to observe adverse events. Daily doses ranged from 400 to 4000 IU/d of vitamin D₃ (19 trials) and from 5000 to 10 000 IU of vitamin D₂ (2 trials).

Biochemical abnormalities, such as hypercalcemia and hypercalciuria, were the most frequently reported adverse events. Although more of these events occurred in vitamin D groups, the difference in the rates of these events between vitamin D and placebo groups was not significant, and the events were not associated with clinical symptoms. Seven trials reported kidney stone incidence; 5 of these trials reported no cases, 1 did not find differences in kidney stone rates between the vitamin D and

placebo groups (24), and 1 (Women's Health Initiative, whose vitamin D study included 36 282 women) reported an absolute increase in kidney stones in women taking 400 IU vitamin D₃ in combination with 1000 mg Ca per day compared with women taking calcium only (5.7 events per 10 000 women-years of exposure) (21). Overall, we found fair evidence from the trials included in our review that adults tolerated vitamin D at doses above current dietary reference intake levels, although we had no data on the association between long-term harms and higher doses of vitamin D.

LIMITATIONS OF THE EVIDENCE

We encountered several limitations, described below, during the review.

General limitations associated with health research

Some of the studies included in the review did not report data on all outcomes. For example, we often had difficulty finding and synthesizing studies that reported harms data, because authors did not provide complete data on harms (29). This limited our ability to produce quantitative syntheses to answer some of our 5 questions. In addition, many vitamin D trials did not have sufficient statistical power to assess harms. Authors could improve their outcome reporting by following the evidence-based recommendations for reporting RCT results from the Consolidated Standards of Reporting of Trials (CONSORT) statement (30, 31).

Other limitations included the failure to report whether trials adequately concealed allocation, controlled for relevant confounders (such as comorbid conditions), or considered the impact of effect modifiers (such as body mass index or ethnicity). In addition, several of the studies experienced large losses to follow-up or followed study participants for very short periods of time.

Finally, because knowledge in the vitamin D field is evolving rapidly and the review process is resource intensive, we had difficulty ensuring that the review was current (32). For example, the Women's Health Initiative trial leaders published their results after we completed our draft report, so we updated our search and subsequently included the Women's Health Initiative and an additional 37 studies.

Limitations specific to vitamin D research

The limitations of the studies we reviewed that were specific to vitamin D research included the lack of direct comparisons of the efficacy of different vitamin D sources on 25(OH)D concentrations, failure to consider the impact of effect modifiers (such as body mass index and ethnicity), and the challenges of assessing 25(OH)D concentrations accurately (33). Several reports did not provide complete details on the vitamin D source, such as the vitamin D content of supplements and fortified foods, and many did not provide data on baseline dietary intake of vitamin D. The presence in supplements and diets of other dietary components, such as calcium, phosphate, genistein, and acid load, that can affect vitamin D or bone metabolism is another potential limitation. Finally, few of the studies compared different doses of vitamin D, and we had difficulty separating the relative effects of vitamin D and calcium.



SUMMARY OF RESEARCH NEEDS

We identified several research needs in response to the knowledge gaps we encountered in the review:

- **Consensus on endpoints for vitamin D adequacy and insufficiency**
Researchers have used a variety of intermediate and clinical outcomes to help define vitamin D adequacy. The vitamin D research community needs to reach consensus on which outcomes are meaningful measures of vitamin D adequacy at all stages of life.
- **Validated laboratory assays of 25(OH)D concentration**
We had difficulty defining thresholds of circulating 25(OH)D concentrations consistent with optimal bone health because of the imprecision of the 25(OH)D assays. The National Institute of Standards and Technology and the Office of Dietary Supplements should develop standard reference preparations that laboratories can use to validate 25(OH)D assays. Such materials will allow researchers to identify the thresholds of 25(OH)D concentrations associated with adequate vitamin D status across the life cycle.
- **Bone health outcome data on infants, children, and adolescents**
Most of the higher-quality trials included postmenopausal women and older men. We need high-quality randomized trials of the relation between vitamin D status and bone health outcomes in infants, children, and adolescents to determine adequate and safe levels vitamin D intakes.
- **Dose-response relation of vitamin D in infants, children, and pregnant and lactating women**
Few studies have examined the effect of incremental doses of vitamin D from fortified foods and supplementation on vitamin D and calcium metabolism in infants, pregnant women, and women of reproductive age. We need more research in this area.
- **Consistent reporting of efficacy and harms data in vitamin D trials**
We need consistent reporting of outcomes, including harms, to facilitate synthesis of the evidence on vitamin D (29, 34).
- **High-quality studies in underserved populations**
We found few data on the effects of vitamin D in African American, Hispanic, and Native American populations. We therefore need studies to evaluate the association between specific 25(OH)D concentrations and bone health outcomes in these populations.
- **Better understanding of the modifiers of vitamin D's effect**
Another gap that requires further research relates to the limited information on the impact of effect modifiers (eg, latitude, season, ethnicity, and body mass index) on 25(OH)D concentrations and bone health outcomes.
- **Vitamin D responses to and risks and benefits from ultraviolet light exposure**
We need a focused systematic review of the sun exposure literature to evaluate the benefits and harms of the ultraviolet radiation levels that provide adequate vitamin D photosynthesis to maintain bone health.

CONCLUSION

We summarized the results our systematic evidence review of the literature on the safety and effectiveness of vitamin D from nutritional supplements and ultraviolet B light exposure on bone health outcomes at different stages of life. We reviewed reports of 167 studies that met our study design criteria. We found some evidence that vitamin D supplementation increases 25(OH)D concentrations and improves bone health. However, for many outcomes and populations of interest, such as infants, adolescents, and pregnant or lactating women, we found few or primarily low-quality studies, inconsistent results, or limited information. To address the research gaps we identified, the vitamin D research community needs to achieve consensus on endpoints for vitamin D adequacy and insufficiency, conduct more high-quality trials of vitamin D's impact on bone health in a broader range of populations, and report all relevant outcomes (including adverse events) in a complete and consistent format.

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The contribution of the authors were as follows—AC, HAW, SOD, and LP: contributed to the writing, revision, and editing of the manuscript. All authors and those listed in footnote no. 1 to the title contributed to the evidence-based review. The authors had no conflicts of interest.

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