

February 7, 2023

USPSTF Coordinator

c/o USPSTF

540 Gaither Road

Rockville, MD 20850

Re: Opportunity for Comment - U.S. Preventive Services Task Force Draft Research Plan for Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Falls and Fractures in Community-Dwelling Adults: Preventive Medication

The Council for Responsible Nutrition (CRN)¹ appreciates the opportunity to comment on the U.S. Preventive Services Task Force (USPSTF) Draft Research Plan for Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Falls and Fractures in Community-Dwelling Adults.

¹ The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement and functional food manufacturers and ingredient suppliers. CRN companies produce a large portion of the dietary supplements marketed in the United States and globally. Our [member companies](#) manufacture popular national brands as well as the store brands marketed by major supermarkets, drug stores and discount chains. These products also include those marketed through natural food stores and mainstream direct selling companies. CRN represents more than 200 companies that manufacture dietary ingredients and/or dietary supplements, or supply services to those suppliers and manufacturers. Our member companies are expected to comply with a host of federal and state regulations governing dietary supplements in the areas of manufacturing, marketing, quality control and safety. Our supplier and manufacturer member companies also agree to adhere to additional voluntary guidelines as well as to CRN's Code of Ethics. Learn more about us at www.crnusa.org.

CRN has organized its comments according to the questions posed by the USPSTF in the USPSTF Public Comment Form.

Proposed Analytic Framework

- a. I agree with it; I have no comments
- b. Generally, I agree with it; see comments below
- c. I have concerns; see comments below
- d. I do not wish to give comments on this question

Do you have any comments about the Analytic Framework?

The proposed analytic framework (as well as all other aspects of the draft research plan) is focused on supplementation with vitamin D, calcium, or vitamin D and calcium in combination. Vitamin D status is included in the framework as an intermediate outcome rather than a component of Key Questions 1 and 2. However, CRN considers vitamin D status (indicated by serum concentrations of 25-hydroxyvitamin D [25(OH)D]) to be a critical component of any research that is conducted to investigate the relationship between vitamin D and health outcomes, and recommends that vitamin D status be the focus of the proposed research plan.

Supplementation with a particular dose of vitamin D will not have the same impact across individuals in a population group. It may provide benefits to some individuals but may not have an effect in others, depending on the individual's vitamin D status at baseline, along with other factors (such as absorption, metabolism, and polymorphisms in key vitamin D dependent genes). As an example, using the Institute of Medicine's classifications of vitamin D status², an individual who is vitamin D-deficient [25(OH)D levels <30 nmol/L] could benefit from supplementation with 25 mcg (1,000 IU) vitamin D, whereas the same dose of vitamin D may not confer additional benefits in an individual who is already considered sufficient [25(OH)D levels ≥50 nmol/L]. Assessing fracture and fall risk, as well as other health outcomes (including potential harms) based on vitamin D dose in isolation does not provide meaningful information. Instead, vitamin D status, which may be altered by vitamin D

² Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press, 2010.

supplementation, is a determinant of health outcomes. Therefore, CRN recommends that the proposed analytic framework be modified to reflect vitamin D status as a central component of the research plan.

CRN recognizes that currently there are no measures of calcium status; therefore, a separate analytic framework for calcium supplementation alone may provide clarity.

Proposed Key Question 1

- a. I agree with it; I have no comments
- b. Generally, I agree with it; see comments below
- c. I have concerns; see comments below
- d. I do not wish to give comments on this question

Do you have any comments about Key Question 1?

CRN has concerns about Key Question 1 because it focuses on the role of vitamin D and/or calcium supplementation in fractures and falls, as well as fracture- and fall-related related morbidity and mortality, instead of vitamin D status. As discussed in CRN's comments regarding the proposed analytic framework, vitamin D status should be an essential component of the research plan, and this should be reflected in the key questions. Therefore, CRN recommends the following wording for Key Question 1: Does modifying vitamin D status by vitamin D supplementation alone or vitamin D combined with calcium supplementation prevent fractures and falls or reduce fracture-and fall-related morbidity and mortality?

CRN does not have comments about Key Question 1 for calcium supplementation alone.

Proposed Key Question 2

- a. I agree with it; I have no comments
- b. Generally, I agree with it; see comments below
- c. I have concerns; see comments below
- d. I do not wish to give comments on this question

Do you have any comments about Key Question 2?

CRN has concerns about Key Question 2, which asks, “What are the harms of supplementation with vitamin D, calcium, or both?”

The phrasing of the question as currently written assumes that there are harms associated with vitamin D and/or calcium supplementation; however, harms have not been established. Further, as stated previously, vitamin D status should be a central consideration in researching health outcomes, including harms. In addition, the term “harms” should be replaced with “adverse events.” The latter term is used in biomedical literature to describe undesirable clinical outcomes resulting from treatment.

CRN recommends that the first sentence be re-worded as follows: Are there adverse events associated with modification of vitamin D status by supplementation with vitamin D alone or vitamin D combined with calcium?

Proposed Approach to Assessing Health Equity and Variation in Evidence Across Populations

- a. I agree with it; I have no comments
- b. Generally, I agree with it; see comments below
- c. I have concerns; see comments below
- d. I do not wish to give comments on this question

CRN recommends that USPSTF assess the effects of different preparations of vitamin D (e.g., vitamin D₂ versus vitamin D₃) or different calcium formulations on the rate of vitamin D and calcium absorption.

Proposed Research Approach

- a. I agree with it; I have no comments
- b. Generally, I agree with it; see comments below
- c. I have concerns; see comments below
- d. I do not wish to give comments on this question

Do you have any comments about the research approach?

CRN recommends that the research approach for vitamin D include the assessment of vitamin D status. In the “Population” section, “studies for which patient eligibility is determined by testing to identify vitamin D deficiency or bone measurement testing, with selection based on low vitamin D or bone density level” are excluded. It is unclear how “low vitamin D” level is defined or why studies that select participants with low vitamin D levels are excluded. Without data on vitamin D deficient subjects, it would not be possible to parse out the potential relationship between vitamin D status and risk of fracture and falls, or fracture and fall-related morbidity and mortality. The research approach should include studies with vitamin D deficient subjects.

In the “Intervention” section, oral and intramuscular vitamin D administration are both included. Since the effects of these routes may differ, CRN recommends evaluating them separately.

Under “Comparators,” vitamin D and/or calcium are compared to placebo or no treatment. Alternative dosages of vitamin D, calcium, or both are excluded as comparators. Applying this criterion would eliminate valuable information from studies that compare multiple doses of vitamin D and/or calcium from the body of research evaluated by the USPSTF, leaving an incomplete picture of the available scientific evidence. We note that under the Proposed Approach to Assessing Health Equity and Variation in Evidence Across Populations, USPSTF indicates it will “explore variation in effectiveness and harms by dosage and duration of supplementation where data are available by stratifying results based on dosage groupings derived from the empiric evidence available.” However, CRN recommends that the dose-response relationship for vitamin D, calcium, or both be included in the research approach.

In the “Outcomes” section, studies should be included for both KQ1 and KQ2 if vitamin D status [indicated by serum 25(OH)D levels] was measured at baseline and end of intervention. Accordingly, studies should be excluded for both KQ1 and KQ2 if vitamin D status was not measured at baseline and end of intervention. Further, the research approach should include other factors that may impact the bone-related response to vitamin D supplementation, including resistance exercise, lean body mass, and excess body fat.

For KQ2 under “Study design,” prospective cohort studies are included if their primary study aim was to evaluate the use of vitamin D or calcium supplementation. CRN recommends that such studies should only be included if they also adequately measured and controlled for non-supplemental sources of vitamin D or calcium.

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CRN also recommends that the analytical method used to measure 25(OH)D be considered when evaluating each study included in the Evidence Review. Analytical methods for 25(OH)D vary in accuracy and precision, leading to diverse results. Therefore, efforts should be made to calibrate the different methods of analysis when assessing vitamin D status across studies. At minimum, analytical methods should be included as a confounding variable in the Evidence Review.

Respectfully Submitted,

A handwritten signature in black ink, appearing to read 'Andrea Wong', with a stylized flourish at the end.

Andrea Wong Ph.D.

Senior Vice President, Scientific & Regulatory Affairs

Council for Responsible Nutrition