Evidence Report/Technology Assessment Disposition of Comments Report

Research Review Title: *Vitamin D and Calcium: A Systematic Review of Health Outcomes (Update)*

Draft review available for public comment from January 13, 2014 to February 11, 2014.

Research Review Citation: Newberry SJ, Chung M, Shekelle PG, Booth MS, Liu JL, Maher AR, Motala A, Cui M, Perry T, Shanman R, Balk EM. Vitamin D and Calcium: A Systematic Review of Health Outcomes (Update). Evidence Report/Technology Assessment No. 217. (Prepared by the Southern California Evidence-based Practice Center under Contract No. 290-2012-00006-I.) AHRQ Publication No. 14-E004-EF. Rockville, MD: Agency for Healthcare Research and Quality. September 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Comment #	Commentator & Affiliation	Section	Comment	Response
1	Peer Reviewer 1	Structured Abstract	(Page 8) 2nd paragraph of Background: It might be useful to the reader to understand here that the update was only for vitamin D alone and then in combination with calcium, but not of calcium on its own, in relation to the NIH/ODS project which focused on best clinical practices related to vitamin D in primary care settings. It is not an update of exercise to underpin revision of DRI for vitamin D and calcium (if I am correct), but rather than a vitamin D in clinical practice backdrop.	We have added emphasis by specifying the focus on vitamin D alone or D+calcium only in the background.
2	Peer Reviewer 1	Structured Abstract	(Page 9) Conclusion seems a bit short in relation to the amount of underpinning research. Could it/should it be a little more descriptive or comprehensive. No mention of assay issue either despite mention in Purpose.	We have added emphasis to the general agreement between the findings of the 2009 report and the current report, have added brief summaries of two potential findings that emerged in the current report, and included a finding regarding the assay method assessment.
3	Peer Reviewer 1	Executive Summary	(Page 18) Executive summary (and also Chapter 1 – Introduction): To help the reader fully grasp the rationale for the request for an update and also for not considering calcium alone, could a little more detail be included on the mentioned NIH/ODS project/initiative – aims, goals etc? Provision of rationale not to include body weight and composition as well as postnatal growth might help reader.	We have added a paragraph describing NIH/ODS' aims and goals with respect to this report.
4	Peer Reviewer 1	Executive Summary	(Page 19) To maintain the link to original report I can see the logic, however, Key Question 5 could go before Key Question 4 in terms of approach.	As requested by the sponsor, we need to preserve the report's organization.
5	Peer Reviewer 1	Executive Summary	(Page 21) and elsewhere throughout the Report: 'Prostate cancer'….higher serum vitamin D concentrations. Throughout best to use serum 25(OH)D concentrations. Vitamin D will imply circulating cholecalciferol.	Yes. Thank you for noticing this. We have corrected the terminology.

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6	Peer Reviewer 1	Executive Summary	(Page 22) …. were divided by quartiles of vitamin D concentration … vitamin Ds sufficiency. Maybe a policy decision – to avoid confusion on the definitions on terms like deficiency and sufficiency, low status etc (as the will appear in papers, but meaning different things) could the serum 25(OH)D threshold be included in brackets after the term? The lack of agreed definitions is a persisting issue that can cause huge confusion to readerships.	We have provided the study's criteria for deficiency, insufficiency, and sufficiency in the Executive Summary; they also appear in the summary tables.
7	Peer Reviewer 1	Executive Summary	(Page 24) Another UK longitudinal study found a slightly positive association ….. possibly consider rewording on slightly ? significant (state P) or weakly significant or some such ?	We have revised the wording to "small but statistically significant."
8	Peer Reviewer 1	Executive Summary	(Page 25) (Fractures, falls, or performance....) and elsewhere throughout the report. ….association between vitamin D exposure and fracture risk. The phrase vitamin D exposure might need to be qualified. Vitamin D intake or serum 25(OH)D as reflective of overall vitamin D exposure from diet and sun.	We have replaced the phrase "vitamin D exposure" here, in the corresponding text in the body of the report, and in other instances of similar use. When referring to the interventions of RCTs, we have adopted the wording "vitamin D supplementation;" when referring to the outcomes of RCTs or to the "exposures" for observational studies, we now specify "serum 25(OH)D concentration" throughout the report for precision.
9	Peer Reviewer 2	Executive Summary	Page 4 L35-36, 54 & throughout. Consistently note 'rated' before giving the rating. Sometimes this is done, which makes it clearer than when the rating is given such as (1A, 3B) on L.36.	We have made the suggested revisions.
10	Peer Reviewer 2	Executive Summary	Page 7 L36-39 – Summarize finding of the other 2 nested case control studies on PE. Presumably these were negative. Explicitly stating so would be helpful to the reader.	We added the findings of the other two nested case controls.
11	Peer Reviewer 2	Executive Summary	Page 7 L45-53 – One of the nested case control studies on vitamin D and Small for Gestational Age found a U-shaped relationship with significantly increased risk at low and high levels of serum 25OHD. This should be described in the text.	We have corrected and clarified the findings of that study in the ES and the text.
12	Peer Reviewer 2	Executive Summary	Page 10 L25 – Give the rating of the one study in which vitamin D decreased blood pressure.	The rating has been added

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13	Peer Reviewer 2	Executive Summary	Page 10 L48-52. Summarize reported effect of combined vitamin D and calcium on CV events in text.	We had already described the Prentice posthoc analysis of the WHI data both in the executive summary and the main body of the report. However we have now clarified the description and moved it so that it appears after the description of the original WHI findings so that the findings should now make sequential sense.
14	Peer Reviewer 2	Executive Summary	Page 11 L43-45. Summarize the reported effects of combined vitamin D and calcium on muscle strength in the four RCTs.	The studies actually assessed the association between serum 25(OH)D and muscle strength. They were inadvertently included in the summary of Ca and vitamin D studies. We have revised the text and described the studies in full.
15	Peer Reviewer 2	Executive Summary	Page 14 L6-17. Give the rating of quality for the new studies described.	Ratings and additional details have been provided for all new studies
16	Peer Reviewer 2	Executive Summary	Page 16 L53-Page 17 L10. Clarify what 'Reference Standard' means. It appears from the table in Appendix G that none of the studies used the NIST Standard Reference Material (SRM) or the NIST or Ghent standard reference methods (SM). This is worth noting in the text if correct. Some, but not many participated in DEQAS and a limited number participated in other external reference standard groups. Summarizing this in the text here and in Chapter 2 in terms of the percentage of studies participating is useful to the reader. Defining what is meant by 'Reference Standard' and whether use of the NIST SRM or SM was assessed.	We have clarified "reference standard" and added more detail about the use of NIST and DEQAS standards as well as reporting the year of assay.
17	Peer Reviewer 3	Executive Summary	p32 line 26 it is unclear why craniotabes is included as a potential adverse event since this is a clinical sign for vitamin D deficiency rickets?	Craniotabes was reported as an adverse event in a study that was included in the original report: we have omitted it from the text and revised the original AE table. .
18	Peer Reviewer 3	Executive Summary	page 21 line 48 1500 mg/day should read 1500 IUs/day	We have changed this.
19	Peer Reviewer 4	Executive Summary	ES-3 line 30: notes that 3 new RCT's on vitamin D and growth were identified, but results are summarized for only 2 RCT's. Can the 3rd RCT be summarized here?	The 3 RCTs as well as two additional RCTs identified in the update search are now described in full.

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20	Peer Reviewer 4	Executive Summary	ES-4 line 32: states that one new cohort study found no association between total (all-cause) cancer and vitamin D status (rated A). The next sentence states that 7 new cohort studies addressed the association of 25OHD and cancer mortality. Please clarify what "vitamin D status" means in the sentence beginning on line 32. If it refers to 25OHD, shouldn't this study be combined with the 7 cohort studies mentioned in the next sentence?	We appreciate your catching that. The first sentence intended to summarize a study(now two studies, as an additional one was identified in an update search) on cancer incidence, not mortality; this point has now been clarified and "vitamin D status" has been changed to serum 25(OH)D concentration.
21	Peer Reviewer 4	Executive Summary	ES-4 line 38-39: refer to one cohort study and a nested case control study—were both studies rated B?	Yes, the ratings have now been clarified in the text.
22	Peer Reviewer 4	Executive Summary	ES-6 line 10: states that 2 new studies that examined the relationship between vitamin D and calcium intake and breast density were found, but line 13 refers to a case-control study that examined 25OHD rather than intake.	Yes, one study was an RCT and one was a nested case control: we have clarified the study designs.
23	Peer Reviewer 4	Executive Summary	ES-12 line 43: notes that 4 new RCT's that assessed effects on muscle strength were found but results from only one study were summarized.	The numbers for studies of vitamin D only were inadvertently added to the section on vitamin D and calcium; we have corrected the text.
24	Peer Reviewer 4	Executive Summary	ES-16 lines 1-13—the summation of results for "bone health" focus on BMD only and do not mention results for fracture, which is the endpoint of greatest interest for bone health. Can text be added to summarize fracture results here?	We were requested to maintain the structure of the original report, which separated clinical outcomes (fracture) from intermediate outcomes (BMD). We have added brief notes in each section, referring to the other, and a new summary table at the end of the Executive Summary places the bone health findings side by side.
25	Peer Reviewer 4	Executive Summary	ES-16 line 30-31 and 45-52—these groups of sentences both summarize results for 25OHD and cardiovascular outcomes so it isn't clear why they are separated. In particular, lines 46-52 follow text that summarized results for cancer outcomes in the 2009 report.	Thank you for noticing this problem. We somehow inadvertently separated the discussion on CV outcomes into two pieces; the text has been reorganized.
26	TEP 1	Introduction	Very succinct introduction. Purpose described and outline reasonable.	Thank you.

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27	Peer Reviewer 1	Introduction	Introduction was good but largely unchanged from original review. One deficit might have been that it might be useful to the reader to understand here that the update was only for vitamin D alone and then in combination with calcium, but not of calcium on its own, in relation to the NIH/ODS project which focused on best clinical practices related to vitamin D in primary care settings. It is not an update of exercise to underpin revision of DRI for vitamin D and calcium (if I am correct), but rather than a vitamin D in clinical practice backdrop.	We have attempted to clarify the intent of the report.
28	Peer Reviewer 2	Introduction	No comments.	Thank you.
29	Peer Reviewer 3	Introduction	page 37 line 5 24,25-dihydroxyvitamin D and 1,24, 25-trihydroxyvitamin D had similar biologic activities as 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D an animal models. Both of these 24- hydroxylated metabolites are further metabolized to water-soluble in active metabolites one of which is calcitroic acid. This should be corrected.	We are compelled for these systematic reviews to limit the studies we include as well as our background information to studies conducted in humans.
30	Peer Reviewer 3	Introduction	The comment that it is not yet determined whether 1,25-dihydroxyvitamin D directly influences bone mineralization is not accurate. 2 studies demonstrated that vitamin D deficient rodents that received calcium and vitamin D either from diet or intravenously had normal bone mineralization. Furthermore patients with vitamin D resistant rickets and unable to respond to 1,25-dihydroxyvitamin D had good mineralization of the skeleton when infused with calcium and phosphate.	Again, it was beyond the scope of the review to include lab animal studies.
31	Peer Reviewer 3	Introduction	Figure 1 is outdated. For example fibroblast growth factor 23 is a regulator of 1,25-dihydroxyvitamin D. You may want to use a more up-to-date figure such as published in Mayo Clinic proceedings July 2013 a daily	We have replaced the original figure with the figure in your review, and have requested permission to reproduce it.
32	Peer Reviewer 5	Introduction	excellent	Thank you.
33	TEP 1	Methods	Search strategies are explicit. The definitions of the key terms are stated. Diagnostic criteria are appropriate.	Thank you.
34	Peer Reviewer 1	Methods	Methods section was good but largely unchanged from original review bar explanation of update approach.	No response needed

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35	Peer Reviewer 1	Methods	(Page 45 and 46) Title of Figure 3 and 4 … Analytical framework for vitamin D alone or with calcium … ? and/or implies calcium also considered separately which it wasn't in update.	The original titles were suggested by the sponsor; however, we see your point and have modified them slightly.
36	Peer Reviewer 2	Methods	The inclusion and exclusion criteria are well-justified and clearly stated. The search strategies are explicit, clear and appropriate. Page 21 L22-25 – Give more detail how 'reference standard' was defined as detailed above for the Introduction. The concern stated above about the need to include osteomalacia as a bone health outcome for the questions concerning the relationship of vitamin D alone or in combination with calcium is important. To include only the childhood adverse bone health outcome, rickets, and not the adult one is problematic. This problem is magnified by the importance of the findings of Priemel et al. (BMR 2010; 25:305-12) to the IOM 2011 DRI committee's deliberations. The Priemel study post-dates the Tufts AHRQ review, but it and any others on osteomalacia since the ARHQ review should be included in this update.	We have added information to the Methods chapter on the reporting of assay and reference standard. Regarding the evidence on the important concern of vitamin D deficiency and adult osteomalacia, we would not have identified this study in our search as the data were collected postmortem; we did however, include studies, both trials and observational studies of vitamin D or calcium and vitamin D supplementation or serum 25(OH)D status in adults.
37	Peer Reviewer 3	Methods	For the most part yes unclear why for the subset analysis for breast cancer for the WHI study was not included	We have added the post hoc analysis for breast and colorectal cancer and for hip fracture conducted by Prentice and colleagues of the 7-year data. It was omitted in error. We did not include the analysis by Cauley et al., as it follows a period of no intervention.

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38	Peer Reviewer 3	Methods	Regarding cancer risk and the WHI trial subset analyses of those women who were not previously taking calcium and vitamin D supplementation who complied with taking calcium and vitamin D had a statistically significant reduced risk for breast cancer and trend for reduced risk for colorectal cancer. Also it was reported that women who had a blood level of 25-hydroxyvitamin D <12 ng/mL and followed for 8 years had a 253% higher risk of developing colorectal cancer compared to women who had a baseline 25-hydroxyvitamin D >23 ng/mL. To be fair it would seem that these should be included rather than simply dismissing that providing suboptimal 400 IUs of vitamin D provided no benefit for reducing risk of cancer. It would also seem that since it had been reported to postmenopausal women who took 1100 IUs of vitamin D daily for 4 years reduced risk of cancers by more than 60%.	We have added the post hoc analysis for breast and colorectal cancer and for hip fracture conducted by Prentice and colleagues of the 7-year data. It was omitted in error. We did not include the analysis by Cauley et al., as it follows a period of no intervention.
39	Peer Reviewer 3	Methods	Bolland et al Calcium and vitamin D supplements and health outcomes: A reanalysis of the Women's Health Initiative limited-access data set Am J Clin Nutr 2011. 94:1144-1149 this in fact is a major issue with most of these reports. They do not pointed out that compliance was a major issue in some of the largest studies and thus not a surprise that if you didn't take the vitamin D and calcium that they would not be a benefit. Also the WHI as well as many of the large RCTs did not have baseline end of the study 25-hydroxyvitamin D to know whether the amount of vitamin D was having a desired effect.	We have expanded on the brief mention of compliance and provided several references, including Bolland, which support the concern regarding compliance.
40	Peer Reviewer 4	Methods	Methods are appropriate overall. The term "vitamin D status" is used throughout the report but it isn't always clear whether this refers to 25OHD or vitamin D intake. My recommendation would be to identify the specific variable (25OHD or dietary intake) rather than using a broader term. Alternatively, 'vitamin D status' could be reserved for 25OHD only, since it reflects the sum of dietary intake and skin production, while results based on dietary intake would be specified as such. In either case, it would be useful to define this term early in the report and then apply this definition consistently.	We have revised the wording throughout, accordingly.

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41	Peer Reviewer 5	Methods	search strategies are well described and appropriate	No response needed
42	TEP 1	Results	The studies are presented in detail. The tables are somewhat difficult to read. The dose response graphs are particularly informative on pages 314- 317. But there is no stratification by 25OHD assay which may be important in understanding how different measurement tools can provide variable results.	We have added the graphs that stratify by assay method.
43	Peer Reviewer 1	Results	The data is presented clearly and succinctly from textual perspective and supported greatly by the tables and evidence tables which provide the core data on the studies. The use of bold text has allowed the reader delineate (and yet compare) the new with the older data, which works well. The only downside is that it culminates in a very sizeable final report.	No response needed
44	Peer Reviewer 1	Results	Tables (In Chapter 3 results): best again to used …studies on vitamin D intake and serum 25(OH)D concentration….	We have revised the wording throughout, accordingly.
45	Peer Reviewer 1	Results	Some of the Tables have Comments (e.g. Table 4) – some of these are not intuitive to reader.	We have removed the comments.
46	Peer Reviewer 1	Results	Tabbing on some Tables will need to be checked as some are miss-aligned.	We have formatted the tables
47	Peer Reviewer 1	Results	Consistency of units for serum 25(OH)D – all nmol/L, some use ng/mL Typos on Figures (e.g., page 166; Almquist 2010 … Quartile 1 (<701)	We have made the changes
48	Peer Reviewer 1	Results	(Page 175 and 176) not clear whether higher 25(OH)D2 concentration is associated with increased wheeze (Page 175), or lower levels of D2 (should be 25(OH)D2) and higher levels of wheeze (Page 176). Likewise check 25(OH)D3 .. Possibly might knock on to 9-18 y on page 178.	we have clarified the wording in both sections of text: higher serum concentrations of 25(OH)D3 were associated with higher incidence of wheeze (the term used) and flexural dermatitis.
49	Peer Reviewer 1	Results	(Page 176) As whole page is bolded, maybe underline 'Infection' and 'Asthma, Atopy, and Eczema' sections to show these are separate sections. Likewise with 'Autoimmune' section.	We have underlined the subsections.
50	Peer Reviewer 1	Results	Table 31a. nmol/L versus nm	We have made the revisions
51	Peer Reviewer 1	Results	(Page 218) Possibly provide rationale to 'The outcomes of these studies were not combined with the results of the original report….'	We clarified why none of the newer studies were included: they did not fit the inclusion criteria for the original meta-analysis.

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52	Peer Reviewer 1	Results	Arrow 4 (Page 309 ….) A few comments that might be considered: (Page 310) …supplementation with calcium or use of ergocalciferol in place of cholecalciferol resulted in smaller increases .. Can you clarify whether the vitamin D plus calcium yielded a lower response to vitamin D alone in the quoted systematic review? generally calcium has been suggested to have a sparing effect on serum 25(OH)D.	In fact, simultaneous supplementation with calcium and vitamin D resulted in a non-significantly smaller increase in serum 25(OH)D concentrations. We clarified the text slightly.
53	Peer Reviewer 1	Results	Figures 12-14. The bubble plots are useful but the reader just can't get a feel for the relationship (as crude as that may be) so low 25(OH)D plot versus normal/high 25(OH)D different ? Likewise with < and > 3 months. Are all of these with only vitamin D3 RCTs, is there sufficient data between existing and new) to compare vitamin D3 and vitamin D2 ? the differential between the response to these two different vitamins than < and > 3 months.	We have modified the original bubble plots exactly as requested by ODS. All but one study administered vit D3; this information is noted in table 67.
54	Peer Reviewer 1	Results	Table 67 Molgaard RCT – subjects were 9 to 11, rather than 9 -18 y.	We have revised the table accordingly.
55	Peer Reviewer 2	Results	In general, the detail is necessary and appropriate. For some specific studies some key aspects are not well-described or are not discussed in the text even though important and included in the detailed tables. In general the figures and tables are exceptionally clear and most helpful to the reader. Detailed comments follow.	No response needed
56	Peer Reviewer 2	Results	Page35 L18-19- It would be helpful to state explicitly what the key finding was of the third RCT. Presumably it found no effect.	We actually added several RCTs identified in an update search and all the studies are explicitly described just below the synopsis.
57	Peer Reviewer 2	Results	Table 4 – For Hollis 2011, no comment is made about the lack of full randomization into treatment. Because of IRB stipulation, participants were differentially eligible for treatment assignment based on baseline 25OHD levels. This is an important limitation of this study even though mean 25OHD levels were not different among the three treatment groups at baseline; a comment should be made in the table.	We have added to the table and the text the observation that assignment to intervention arms was not entirely random and partly depended on baseline serum 25(OH) D
58	Peer Reviewer 2	Results	Tables 30b, c & d and 31b, c & d should be identified as New Studies found in this SR update.	We have modified the titles to indicate new studies were added.

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59	Peer Reviewer 2	Results	Page 158 L10=22 and L45-47 and Page 159 L17-19. One of the two cohort studies (Bodnar et al. 2010) reports a U-shaped risk curve of maternal 25OHD levels with the risk for small for gestational age. This is an important difference from the stated effect of only an increased risk at low 25OHD levels. Further, it represents the only U-shaped risk curve for a pregnancy outcome reported to date. Text needs to be modified. Description of results in Table 33B report the increased risk at higher 25OHD levels. Text throughout report needs to be revised to describe this as well.	In reassessing the body of literature after conducting an update search modified the text, we had revised the description of this study to show this unusual finding.
60	Peer Reviewer 2	Results	Page 163, As discussed in the Introduction and Methods sections, osteomalacia should be included as bone health outcomes. The IOM committee used the observational study on osteomalacia in its deliberations and findings, but this study was not included in the original SR. It would be useful to include it in this update. It is also important to assess if any additional studies have been reported on osteomalacia and vitamin D status in adult.	We excluded the study by Sanders as the outcomes were measured in post mortem samples. We did not identify other studies on the specific outcome of osteomalacia that met the inclusion criteria for the report (an initially healthy population and an intervention or follow-up for at least a year) however a number of RCTs are included that assess bone health outcomes in adult populations at risk for bone loss.
61	Peer Reviewer 2	Results	Page 242 It appears that this update found no new studies on the combined effect of vitamin D and calcium on preeclampsia. If so, this should be stated in the text on line 10 and 40.	We have added text to clarify the lack of new studies.
62	Peer Reviewer 2	Results	Page 252 It appears that this update found no new studies on the combined effect of vitamin D and all-cause mortality. If so, this should be stated in the text on line 8.	We have added text to clarify the lack of new studies.
63	Peer Reviewer 2	Results	Page 255 It appears that this update found no new studies on the combined effect of vitamin D and hypertension. If so, this should be stated in the text on line 7.	We have added text to clarify the lack of new studies.

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64	Peer Reviewer 4	Results	The text in the Executive Summary that describes the results of the Prentice re-analysis of WHI data on pg. ES-12 notes that a non-significant relationship was found for total fracture. The text on pg. 245 describing the Prentice results (lines 29-30 and 53-56) also summarizes the Prentice results for total fracture only. However Prentice et al also reported a reduction in hip fracture that just missed significance in the RCT –only portion and they found a significant relationship when results from the WHI observational study and randomized clinical trial were combined. Since hip fracture was a primary outcome in the WHI RCT (whereas total fracture was a secondary outcome), I recommend that the hip fracture findings be noted in the Executive Summary, in the text on Pg. 245 and in table 59. If not, then it would be useful to state why only total fracture findings from the Prentice study were noted.	We have added the data and a discussion of the hip fracture, colorectal cancer, and breast cancer findings to the main body of the report and the executive summary. They were inadvertently omitted.
65	Peer Reviewer 4	Results	Pg. 285. Adverse events reported in RCT's. No mention is made of the Sanders et al RCT (JAMA 2010) in this section. Sanders et al reported an increased risk of fractures and falls with an annual high dose of vitamin D. The Sanders paper is listed in 'Excluded studies, comorbidities not of interest" (pg. F-43) but it is not clear why it received this designation, since fractures and falls are a focus in the study.	The study was excluded because a high proportion of the participants had cardiovascular disease and prior fractures. We were following the inclusion/exclusion criteria of the original report, which excluded studies where more than 20% of participants had chronic conditions.
66	Peer Reviewer 4	Results	Will the literature review be updated to include papers published after April 2013 in the final report? The Discussion (pg. 291, line 46-48) makes reference to a systematic review that was released "coincident with the current draft", which implies it was published after April 2013. If so, then it would seem important to add other studies that have been published since April 2013 as well.	Yes, an update search was conducted in late December while the draft report was in review
67	Peer Reviewer 5	Results	the tables and figures are excellent. all tables have complete data and this is very useful.	No response needed

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68	Peer Reviewer 5	Results	P 112,lines 26seq and page 113, lines 30 seq. Although this is a "B' rated study it should not be for the following reasons. -The cancer data was a secondary outcome -the data in the cancer paper is incomplete because it lacks concomitant medications - in the original abstract on the primary outcome ASBMR abstracts 2006-2007 it says that 50 percent of the women took hormones for part of the study and 15-20 % took bisphosphonates both of which can affect cancer incidence. (Because I am out of the country I could not access the ASBMR abstract).In fact this should invalidate the conclusions. This failure to follow the bone protocol was probably the reason the bone data was never published as a paper.	We assume the reviewer is referring to the Fedirko paper that reports on cancer mortality in the EPIC cohort. We did not include meeting abstracts and thus would not have realized a large part of the study population was taking bisphosphonates (which would have led us to exclude the study at least for bone outcomes). We have added a note to the description regarding the use of medications that would have increased risk for cancer.
69	Peer Reviewer 5	Results	P 201,Line 10 In the study on falls by Prince the data is not completely correct in the table. The OR for fallers was 0.66 (0.41-1.06) . Only after adjustment for baseline height is was significant OR 0.61 (0.37-0.99).	We added the unadjusted figures and noted the adjustment
70	TEP 1	Discussion/Conclusion	The discussion is succinct. The literature is comprehensive and the report does not appear to have omitted any large studies. The tables interfere with the flow of the result section, although it's not clear that this would be improved by putting the tables at the end.	The charge from the sponsor was to add new findings to the existing report, preserving the original structure, so we have done that.
71	Peer Reviewer 1	Discussion/Conclusion	The conclusions and discussion of the main points are in general valid. The report is clear and will be usable. On the point of its use, one suggestion is to clarify the intended use that the NIH/ODS exercise was to/will put the data to. It isn't clear to the reader up front and the reader may find themselves slipping into the mindset that this Systematic review is being updated for the original purpose i.e., to inform DRI decision making. This is particularly the case when much of the text of original review mentions the DRI process. This also relates to what might or could be included under Future research perhaps.	We have modified the introduction to the report to address the intended purpose of the report.

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72	Peer Reviewer 1	Discussion/Conclusion	(Page 325) Possibly qualify the inconsistent results for associations between CVD events and serum 25(OH)D studies (X studies were null, Y studies found an inverse relation etc). Should concluding sentence mention All-cause mortality ?	The findings reported in the original report for vitamin D and all-cause mortality were based on a re-analysis of an earlier meta-analysis with one study added. No new trials were identified for the current report. A large number of observational studies were identified that assessed the association of serum 25(OH)D with all-cause mortality but these studies were also inconsistent in their findings, so we don't see a value in repeating their findings in the Conclusion.
73	Peer Reviewer 1	Discussion/Conclusion	(Page 327) Section dealing with methods/assays etc. Any trend evident across assays – greater response with immunoassay v. MS, irrespective of year, country etc.	We have added text describing the plots based on assay method.
74	Peer Reviewer 1	Discussion/Conclusion	(Page 330) '..overall, there appeared to be a trend for higher vitamin D supplementation dose resulting in higher net change in serum 25(OH)D concentration. Current report found quality systematic review which reported similar results…' Possibly again if the bubble graphs had a relationship included one of the things that might become evident, even visually, is that serum 25(OH)D concentration will plateau at higher vitamin D intakes (which is debated but >1000/1400 IU/d).	It was evident from the data we included in our report as well as the studies included in the 2012 systematic review by Autier that too few studies administer high doses of vitamin D to be able to ascertain whether the increase reaches a plateau. We have now noted this in our description of the findings.
75	Peer Reviewer 1	Discussion/Conclusion	General comment on Discussion: for any of the health outcomes examined and updated, has the evidence base strengthened ? The number of studies have increased considerable for some outcomes (e.g. all-cause mortality).	We have created a summary table that compares primary outcomes of interest between the two reports.
76	Peer Reviewer 2	Discussion/Conclusion	This section is succinct, clear and well-written. I had no additional comments.	No response needed
77	Peer Reviewer 3	Discussion/Conclusion	For the conclusion they should include the subset analysis of the WHI regarding breast cancer. It would seem reasonable to at least ask the question why with men be taking >1500 mg or >2000 mg of calcium daily. It is likely these men were body builders taking large amounts of different supplements including likely androgen supplements which could be associated with increased risk for prostate cancer.	For the current report we did not review studies of calcium supplementation alone; thus we cannot attempt to address the possible association of calcium supplementation and prostate cancer.

Comment #	Commentator & Affiliation	Section	Comment	Response
78	Peer Reviewer 3	Discussion/Conclusion	There is mention of heterogeneity due to lack of reporting for compliance. However the large RCTs often reported poor compliance but this did not appear to be taken into consideration when evaluating the health outcome measures either in the original studies or in this report.	We now further emphasize the issue of compliance in the Discussion section.
79	Peer Reviewer 4	Discussion/Conclusion	There does not appear to be a future research section. However, it would be very useful if the authors could comment or make recommendations regarding steps that might be taken in future studies that could improve the ability to draw conclusions regarding the relationship of vitamin D (or vitamin D and calcium) and health outcomes in systematic reviews.	For the original report, the authors were asked to provide a set of suggestions to future DRI committees. For this report, we have added commentary regarding the choice and reporting of assay methodology, as that was a strong interest of ODS for this update.
80	Peer Reviewer 5	Discussion/Conclusion	very clearly presented. limitations of studies are well described. I particularly liked the section on excluded studies. the worst part -trying to read this on a pdf-it should have been sent as a pre-publication to reviewers	No response needed
81	Peer Reviewer 1	Appendix A.	(Page 372) Would 'Efficacy search in Medline' be better reported at same as that in Original 'Overall search strategy for Outcomes of Estimates Average Requirements' to be consistent with the Update. The same terms were used for search for Upper Limits.	Yes for clarity, the titles should be the same.
82	Peer Reviewer 2	Appendix G	Add a footnote to the table defining what was meant by 'reference standard'.	We have added the footnote.
83	TEP 1	Clarity and Usability	Although the report is well structured, it was difficult at times to make it through the report in order to find a particular result. It will be a usable report as a reference. The bolding for the new findings in this evidence based report is important. Of course, one concern is the absence of data from non-published studies. There appears to be no effort to find those trials, for example, the Lappe trial in Nebraska did not report the effects of calcium and vitamin D on fractures, although that was the primary outcome and cancer, an unplanned outcome.	The charge from the sponsor was to add new findings to the existing report, preserving the original structure, so we have done that . It was not within the scope for the review to include unpublished studies; however, in lieu of searching for unpublished studies, AHRQ requested input by posting a notice in the Federal Register.

Comment #	Commentator & Affiliation	Section	Comment	Response
84	Peer Reviewer 1	Clarity and Usability	The report is clear and will be usable. On the point of its use, one suggestion is to clarify the intended use that the NIH/ODS exercise was to/will put the data to. It isn't clear to the reader up front and the reader may find themselves slipping into the mindset that this Systematic review is being updated for the original purpose i.e., to inform DRI decision making. This is particularly the case when much of the text of original review mentions the DRI process.	We have clarified the intended use of the report inthe introduction.
85	Peer Reviewer 2	Clarity and Usability	The structure is logical. In general the main points are explicit and clear. The conclusions are clearly stated and well-justified by the findings of the updated SR. The nature of the findings in terms of the sustained lack of conclusive and consistent evidence of the relationship of vitamin D with nearly all of the identified health outcomes leaves the formulation of policy and practice a matter of scientific and expert judgment. The value of the updated SR findings lie in the rigorous examination of the new evidence since 2009 and the lack of conclusive evidence of a relationship of vitamin D to health outcomes despite the considerable new evidence documented in this update.	Thank you.
86	Peer Reviewer 3	Clarity and Usability	Overall it is reasonably well structured. However without further clarifications regarding limitations studies evaluated especially regarding compliance and lack of baseline and end of study 25-hydroxyvitamin D levels raises questions as to how useful the information is for policy and practiced decisions.	We have now expanded on our discussion of the limitations. Regarding the compliance issue, we now cite the findings of several of the included studies, where relatively poor compliance appeared to influence and explain the outcomes, We also discuss the implications of the use of different assay methods.

Comment #	Commentator & Affiliation	Section	Comment	Response
87	Peer Reviewer 4	Clarity and Usability	As noted in the my general comments, the report concludes that study results were too inconsistent to allow many conclusions regarding vitamin D's relationship with health outcomes to be drawn. Thus readers must draw their own conclusions in regard to policy or practice decisions. Some possible revisions of the report might improve the reader's ability to grasp the totality of the evidence (if they can be accommodated within the AHRQ format) include the following:	We agree that the organization of the report is difficult to follow (e.g., the separation of intermediate and clinical bone outcomes). Part of the charge for the update report was to add new findings to the existing structure. I response to the concern that the reader is left to draw his/her own conclusions or at least to decide what, if anything, has changed, we have provided a table in the Executive Summary that compares the general findings for each of the outcomes from the original to the current report. Because we did not pool results, the table is necessarily highly qualitative.
88	Peer Reviewer 4	Clarity and Usability	A. Both the update and older report cover studies with different designs (randomized clinical trials, prospective studies and case-control studies) and quality (rated A, B C). Can the results be further distilled in a way that emphasizes the strongest studies more? For example, could more emphasis be placed on RCT results and/or studies rated A or B? Perhaps a summary table that that describe the percentage of RCT's and/or A and B rated studies that did or did not find a significant relationship for each outcome could be added.	We have now provided a table that compares the findings from the original to the current report by study design.
89	Peer Reviewer 4	Clarity and Usability	B. Some re-organization of the material might also make it easier to grasp the totality of the evidence:	While preserving the original report structure, as requested, we hope that the table we have added to the Summary helps organize the material.
90	Peer Reviewer 4	Clarity and Usability	i) The report is organized into sections that summarize studies on vitamin D alone for each health outcome, followed by sections that summarize studies of vitamin D and calcium for each outcome. However, the outcomes considered are quite diverse, and it is possible that the relationship between vitamin D (or vitamin D plus calcium) and these different outcomes varies. Could the information be organized by outcome instead?	The new summary table provides the findings for supplementation with vitamin D with or without calcium together for the same outcomes.

Comment #	Commentator & Affiliation	Section	Comment	Response
91	Peer Reviewer 4	Clarity and Usability	ii) The current report appends the results of the updated literature review to the text from the original 2009 report—leaving it to the reader to merge the new results with the older results. Is it possible to add a 'combined' section which integrates the older (2009 report) and newer (updated report) findings?	The new Summary table compares the findings of the original and update reports for each outcome.
92	Peer Reviewer 4	Clarity and Usability	iii) Pg. 164-183 and 213-224 (Vitamin D only) and pg. 245-252 and 263-274 (combined vit D and calcium). Results for bone-related variables are divided into "clinical outcomes" (rickets, fractures, falls, performance measures) and "bone density/bone mineral content" for both vitamin D alone and combined vit D & calcium. These bone-related sections are separated by sections on non-bone related outcomes (mortality, and hypertension/blood pressure). It is not clear why the bone-related variables were separated in this manner, especially since hypertension and blood pressure are presented together. I think the totality of evidence for "bone health" would be easier to gauge if bone density/bone mineral content section was placed after the material on the clinical bone outcomes.	In the summary table we have added to the Executive Summary, we have now organized the outcomes by body system (e.g., all bone health outcomes are together).
93	Peer Reviewer 5	Clarity and Usability	very clear and well organized. I think this can be a valuable document in making future practice decisions	No response needed
94	TEP 1	General	Quality of the Report: Superior. Overall it is a significant piece of work; The questions were appropriate and the sections were well defined. The table of contents is key and provides an important roadmap for readers to go immediately to a particular section.	No response needed

Comment #	Commentator & Affiliation	Section	Comment	Response
95	Peer Reviewer 1	General	Quality of Report: Good. This is a well-researched and presented Update on the original Systematic Review of Health Outcomes in related to Vitamin D and Calcium. The update has captured the relative studies to my reading and exposure to the literature over the last few years. The methods are similar to those used in the original review and the consistency has been maintained well. The data is presented clearly and succinctly from textual perspective and supported greatly by the tables and evidence tables which provide the core data on the studies. The use of bold text has allowed the reader delineate (and yet compare) the new with the older data, which works well. The only downside is that it culminates in a very sizeable final report. The conclusions and discussion of the main points are in general valid.	Thank you.
96	Peer Reviewer 1	General	The report is clear and will be usable. On the point of its use, one suggestion is to clarify the intended use that the NIH/ODS exercise was to/will put the data to. It isn't clear to the reader up front and the reader may find themselves slipping into the mindset that this Systematic review is being updated for the original purpose i.e., to inform DRI decision making. This is particularly the case when much of the text of original review mentions the DRI process.	We have clarified the sponsors' intended use for the report in the introduction.
97	Peer Reviewer 1	General	There are a number of areas, ranging from minor editorial amendments to some more significant points, which might be considered in terms of enhancing for readership. These are outlined below (I will use the page numbers as they appear on upper right hand side of manuscript as PDF; the number at the bottom seemed to jump)	We are unable to find the suggestions to which the reviewer refers.
98	Peer Reviewer 2	General	Quality of the Report: Good. Yes, the report is clinically meaningful and has generally sufficient detail. The target population and audience for the report is explicitly stated. The key questions are sufficiently detailed and appropriate.	Thank you

Comment #	Commentator & Affiliation	Section	Comment	Response
99	Peer Reviewer 2	General	There is one concern, however, that the key question on vitamin D or vitamin D in combination with calcium on bone health did not include the adult vitamin D deficient outcome of osteomalacia in addition to the childhood vitamin D deficiency outcome of rickets. The IOM 2011 DRI committee used an observational study (Priemel et al. BMR 2010; 25:305-12) on osteomalacia in its deliberations and findings, but this study was not included in the original SR. It would be useful to include it in this update. It is also important to assess if any additional studies have been reported on osteomalacia and vitamin D status in adult.	We excluded the study by Sanders as the outcomes were measured in post mortem samples. We did not identify other studies on the specific outcome of osteomalacia that met the inclusion criteria for the report (an initially healthy population and an intervention or follow-up for at least a year) however a number of RCTs are included that assess bone health outcomes in adult populations at risk for bone loss.
100	Peer Reviewer 3	General	Quality of the Report: Fair. The major problem with the report regarding its clinical utility is that many of the studies used suboptimal doses of vitamin D or did not measure baseline or at the end of study 25-hydroxyvitamin D. Also cutoffs for 25-hydroxyvitamin D were different for different studies making it difficult for a physician to make a clinical judgment regarding vitamin D intake and target level for 25-hydroxyvitamin D. There is no information about issues regarding vitamin D bioavailability including obesity, and factors associated with increased risk for vitamin D deficiency.	We believe we have identified and addressed the limitations in the original studies that prevent us from being able to draw any firm conclusions regarding the effect of vitamin D supplementation on, and indeed the association of serum 25(OH)D status with, health outcomes. We have striven to strengthen these points by including information on differences in assay methods and by elaborating on factors such as adherence and lack of baseline measures that undoubtedly contribute to the lack of effects seen in trials.

Comment #	Commentator & Affiliation	Section	Comment	Response
101	Peer Reviewer 4	General	Quality of the Report: Good. The authors are to be commended for a very thorough job of compiling the recent literature on the topic. The report is comprehensive and will be a valuable resource for researchers in this area. The key questions are explicitly stated. However, despite an additional 126 new studies and 3 new systematic reviews (covering > 562 studies) on the topic since the previous review (which was based on 165 studies and 11 systematic reviews), the updated report concludes that in most cases, it is still not possible to draw many conclusions regarding the relationship between vitamin D (or vitamin D and calcium) and health outcomes because the study results were too inconsistent. The report authors cannot be faulted for the inconsistent study results, but the unfortunate outcome is less clinical meaningfulness because in the absence of conclusions, it is left to each reader to come up with a global view of the evidence. Some possible revisions that might aid readers in this regard, if they can be accommodated within the AHRQ format, are described in section F.	We have attempted to provide a more organized overview of the changes in findings from the original to the current report in the table we created for the summary.
102	Peer Reviewer 5	General	Quality of the Report: Superior. I think an update subsequent to the IOM report is appropriate. The target population is well defined. The key questions to be answered are very clear.	Thank you.

Comment #	Commentator & Affiliation	Section	Comment	Response
103	Public comment: John Aloia	General	The cost of measurement of serum 25-hydroxy D and its burden on healthcare in the U.S. should be addressed. There is confusion in the report over cutoff values and reference ranges. The reference ranges are for nutritional recommendations. The IOM recommendation for an RDA of 50 nmol is a recommendation that when that level is attained 97.5% of the population has adequate vitamin D. The implication, however, in this report is that the recommendation is for values above 50 nmol. Indeed, using the nutritional recommendations, half of individuals who have achieved the EAR have sufficient vitamin D levels. The concept of screening for nutritional status rather than for disease should be addressed. Population screening for adequate nutrition (not even deficiency) would certainly be a unique recommendation.	Assessing the comparative costs of the assay methods was considered to be beyond the scope of this review; we have made sure that the cutoff values and reference ranges, as well as any reference to vitamin D deficiency, insufficiency, and sufficiency, were as reported and defined in individual studies.
104	Public comment: John Aloia	Line 28	Line 28: Systematic literature reviews have shown there is not evidence for a cutoff of PTH at 70-80 nmol/L vs. 50 nmol/L. (References: Aloia, J.F., et al., Optimal vitamin D status and serum parathyroid hormone concentrations in African American women. Am J Clin Nutr, 2006. 84(3):602-9; Sai, A.J., et al., Relationship between Vitamin D, Parathyroid Hormone, and Bone Health. J Clin Endocrinol Metab, 2011. 96(3):E436-46.) The goal in individual should not be to be greater than 50 or 70 nmol/L but rather these should be target goals.	In the current report, we did not attempt to assess any findings related to PTH; we are unable to identify the text in question.

Comment #	Commentator & Affiliation	Section	Comment	Response
105	Public comment: John Aloia	Line 29	Line 29: Reference 15 is not a study. There are multiple studies besides Hansen that show that there is NOT a cutoff for calcium absorption at levels 25D>30 nmol/L (20 ng/mL). (references: Gallagher, J.C., V. Yalamanchili, and L.M. Smith, The effect of vitamin D on calcium absorption in older women. J Clin Endocrinol Metab, 2012. 97(10): 3550-6; Gallagher, C.J., P. Jindal, and M.S. Lynette, Vitamin D does not Increase Calcium Absorption in Young Women: A Randomized Clinical Trial. J Bone Miner Res, 2013; Gallagher, J.C., et al., Effects of vitamin D supplementation in older African American women. J Clin Endocrinol Metab, 2013. 98(3):1137- 46; Aloia, JF, et al, Vitamin D supplementation increases calcium absorption without a threshold effect. Am J Clin Nutr, 2013).	We are unable to identify the reference by Hansen that the commenter is referring to. Reference 15 was provided as background in the original report. For continuity, and because the current report did not update the literature on calcium supplementation, we did not update this background
106	Public comment: John Aloia	Line 44	Line 44: "Deficiency" vs. "Insufficiency" are terms that may be considered. Vitamin D "deficiency" should reflect levels that are associated with symptomatic disease that is less than 12 ng/m/L (30 nmol/L) of 25(OH)D. Saying that individuals less than 50 nmol/L are "deficient" is misleading. At any rate, the terms should be defined in terms of 25(OH)D levels. An example of a more appropriate terminology is given in the following reference. (Aloia, J.F., The 2011 report on dietary reference intake for vitamin d: where do we go from here? J Clin Endocrinol Metab, 2011. 96(10): 2987-96)	We have purposely aimed to include the terms "deficiency" and "insufficiency" only when used by study authors themselves and have include the authors' cutoffs when possible.
107	Public comment: John Aloia	Line 81	Line 81: "Severe Deficiency" should be defined.	We are unable to find this term, although we conducted various searches and also tried to calculate the text lines by dividing the numbers he provided by 60 (his version had continuous numbering, and one page contains 60 lines..
108	Public comment: John Aloia	Line 87	Line 87: "less severe levels of vitamin D deficiency" defined as 10-30 ng/mL accepts the Endocrine Society recommendation as opposed to the IOM. Individuals with 20 ng/mL are not deficient.	We are unable to locate the text the commenters are referring to.

Comment #	Commentator & Affiliation	Section	Comment	Response
109	Public comment: John Aloia	Line 94	Line 94: There are other factors that lower fracture risk in African Americans. (Aloia, J.F., African Americans, 25-hydroxyvitamin D, and osteoporosis: a paradox. Am J Clin Nutr, 2008. 88(2): 545S-550S.	Since the focus of the report was on literature reporting on supplementation with vitamin D with or without calcium and on serum 25(OH)D concentrations and their association with health and disease in people who were healthy at baseline, we included only studies that met these inclusion criteria. . For included studies that reported findings for or by subgroups (including age , sex, and race/ethnicity) we reported the findings by those subgroups.
110	Public comment: John Aloia	Line 130	Line: 130: Again, many individuals < 20 ng/mL will not be deficient based on the dietary intakes and the EAR.	We are unable to identify text that refers to individuals with vitamin D levels less than 20ng/ml (indeed, serum 25(OH)D concentrations were expressed as nmol/L throughout).
111	Public comment: John Aloia	Line 150	Line 150: This sentence is misleading. Again, it is the concept of the RDA and EAR.	We are unable to identify the text in question.
112	Public comment: John Aloia	Line 162	Line 162: There is no rationale for high risk individuals needing higher intakes of vitamin D than the general population. The higher intakes should result in higher serum 25(OH)D levels than in needed.	We would agree: we cannot identify the text that refers to high-risk individuals.
113	Public comment: John Aloia	Line 190	Line 190: The level of evidence that lead to the task force recommendations should be given.	We assume the commenters are referring to the USPSTF report on vitamin D. The studies that comprised that review were included in the original report , on which the current report is based.. .
114	Public comment: John Aloia	Line 227	Line 227: Hypercalciuria has not been specifically studied.	We addressed the issue of hypercalciuria in our assessment of the adverse events reported in studies of vitamin D interventions.
115	Public comment: John Aloia	Line 238	Line 238: The cost of vitamin D assays should be estimated. The use of 50,000 IU in the protocol given is a treatment based on opinion, not evidence.	Again, it is not within the scope of the review to address the costs of the assays,
116	Public comment: John Aloia	Line 263	Line 263: The outcome of giving vitamin D to blacks and obese for bone health has either not been studied or the results have been negative. (Reference: Aloia, J.F., et al., A randomized controlled trial of vitamin D3 supplementation in African American women. Arch Intern Med, 2005, 165(14): 1618-23).	The 2005 study was included in the 2006 evidence review on bone health that was cited in the original 2009 report.
117	Public comment: John Aloia	Line 337	Line 337: The cost should be discussed.	The costs of assay and treatment are not within the scope of this review.

Comment #	Commentator & Affiliation	Section	Comment	Response
118	Public comment: John Aloia	Line 350	Line 350: Definition of “deficiency” is again needed.	We are unable to identify the specific example in question but have provided the authors’ definitions of these terms throughout.
119	Public comment: John Aloia	Line 395	Line 395: It is stated that symptoms may be subtle or mild. There are no symptoms unless it is “severe”.	The wording in question, that symptoms may be subtle or mild, were the words of the authors of the study that was being cited; they were referring to the symptoms, not the deficiency that leads to the symptoms .
120	Public comment: John Aloia	Line 397	Line 397: These are not signs of vitamin D deficiency in these ranges.	We are unable to identify or correct this wording.
121	Public comment: John Aloia	Line 490	Line 490: Was 5,000 units supposed to be “50,000”?	We cannot locate this statement.
122	Public comment: John Aloia	Line 674	Line 674: Was 54,000 IU supposed to be “50,000”?	We cannot locate the reference to 54,000 IU.
123	Public comment: John Aloia	Line 696	Line 696: Hypercalciuria should be reviewed. This is presumed it will result in an increased risk for nephrolithiasis. This should be done by measuring 24-hour urine for calcium because the fasting urine calcium creatinine ratio has not been shown to be accurate.	We believe the commenters are referring to the reported adverse events in RCTs: we described the number of reports of hypercalcemia across the studies, as reported by the study authors.
124	Public comment: John Aloia	Line 727	Line: 727: “Their” review not “they” review.	We are unable to see the suggestion the reviewer mentions
125	Public comment: John Aloia	Line 800	Line 800: The difficulty with 25-hydroxyvitamin D assays and the differences in different types of assays is a reason to avoid screening. Not only are the cutoff points in dispute but so are assay results. This should be documented.	We have added plots of the dose response effects observed in the included RCTs by assay type and we now address the limitations of the assays, both in the main body of the report and in the executive summary.
126	Public comment: John Aloia	Line 802	Line 802: 50 nmol/L is the level where 97.5% of individuals have adequate nutrition. The goal is not to be above 50 nmol/L but to attain it.	We have revised the description of the study population in the study being described.
127	Public comment: John Aloia	Line 812	Line 812: Blacks are not at an increased risk in terms of bone health. Therefore, they should not be considered as a population at risk.	We have revised the wording to “incidence of.”
128	Public comment: John Aloia	Line 829	Line 829: Nutritional recommendations apply to the entire population. Adding a laboratory test for vitamin D in asymptomatic patients would be striking new ground in screening. If this were done, we should be screening for other biomarkers of nutritional constituents such as serum iron and serum magnesium in everyone. Again, the cost of this in addition to the value would be prohibitive.	It would be beyond the charge for this report to suggest screening for vitamin D or using any particular assay. Our charge was to identify the assays used by RCTs included in the report as a way to assess the extent to which study outcomes can be compared. Screening recommendations are under the purview of the USPSTF.

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