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Scanning for new evidence to prioritize updates to the Dietary Reference Intakes: case studies for thiamin and phosphorus[1,2]

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ABSTRACT

Background: Dietary Reference Intakes (DRIs) are fundamental to inform national nutrition policy. However, a regular systematic review of the 51 nutrients that have DRIs has limited feasibility, and many DRIs have not been reviewed in >15 y.

Objective: To address this issue, individuals (nutrient review group) who were members of the Food and Nutrition Board developed a streamlined, evidence-based methodology that could be used to identify nutrients potentially in need of a systematic review.

Design: The proposed methodology, termed an evidence scan, comprises several steps. First, an analytic framework is developed to identify markers of associations between intake of a nutrient and a corresponding clinical outcome. Next, the framework is used to direct the identification of keywords for a scan of published research that is potentially relevant to intake requirements or upper intake levels for a nutrient. Last, a panel of content experts selects the abstracts that are likely to be relevant and reviews the full publications. The results may be used to determine whether a revision of the nutrient's DRI is an immediate priority but would not supplant a comprehensive systematic evidence review.

Results: To illustrate the process, 2 nutrients were selected as case studies: thiamin and phosphorus (DRIs were last set in 1998 and 1997, respectively). Using the evidence scan for thiamin, we identified 70 potentially relevant abstracts, of which 9 full publications were reviewed. For phosphorus, 127 potentially relevant abstracts were identified, and 29 full publications were reviewed.

Conclusions: From the review of these 2 nutrients, the nutrient review group concluded that there was insufficient new evidence to assign a high priority to a comprehensive systematic review for either thiamin or phosphorus. Evidence scanning is an efficient method of identifying DRI nutrients that are most in need of either a new or an updated systematic review. *Am J Clin Nutr* 2016;104:1366–77.

Keywords: Dietary Reference Intakes, phosphorus, risk-assessment framework, evidence scan, thiamin

INTRODUCTION

From 1997 to 2005, the Dietary Reference Intakes (DRIs),[9] the nutrient reference values for the United States and Canada, were set by a series of consensus panels convened by the Institute of Medicine (IOM). The panels considered both historical outcomes of the prevention of nutrient deficiency and other health outcomes including, explicitly for the first time, the prevention of chronic disease (1–6). DRIs include the Estimated Average Requirement (EAR) that meets the needs of 50% of the generally healthy individuals in a population; the Recommended Dietary Allowance, which is derived from an EAR and meets the needs of 97.5% of the population; an Adequate Intake, which is set when insufficient evidence is available to specify an EAR and thus a Recommended Dietary Allowance but is assumed to ensure nutritional adequacy; and a Tolerable Upper Intake Level, which represents maximal daily intake that is unlikely to have an adverse health outcome. At its completion in 2005, the DRI study panels recommended intakes for 51 nutrients, including energy, macronutrients, fiber, vitamins and minerals, for 22 age-, life stage–, and sex-specific subgroups. **Table 1** shows the dates when DRIs were specified for each nutrient.

Since the completion of the initial DRIs, only those for calcium and vitamin D have been re-examined and updated (7). At the time that calcium and vitamin D were re-examined, there was no precedent in the previous DRI review for the use of a systematic evidence review in the DRI process, and thus, a previously published systematic review and a new systematic review on vitamin D were used as the basis for an updated review of the evidence.

Because of the length of time since the other nutrients were reviewed as well as the absence of systematic reviews of the evidence for most of the nutrients, the currency of these recommended

[1] The authors reported no funding received for this study.

[2] Supplemental Tables 1 and 2 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[9] Abbreviations used: DRI, Dietary Reference Intake; EAR, Estimated Average Requirement; IOM, Institute of Medicine; PICOD, Population, Intervention, Comparator, Outcomes, and Study Design; RCT, randomized controlled trial.

Received December 7, 2015. Accepted for publication August 22, 2016.
First published online October 12, 2016; doi: 10.3945/ajcn.115.128256.

TABLE 1
Summary of DRI-specification dates[1]

Year of DRI specification	Nutrient
2011	Vitamin D and calcium
2005	Energy, fiber, protein, and amino acids
2004	Water, potassium, sodium, and chloride
2002	Vitamin A, vitamin K, boron (UL only), chromium, copper, iodine, iron, manganese, molybdenum, nickel (UL only), vanadium (UL only), and zinc
2000	Vitamin C, vitamin E, and selenium
1998	Thiamin, riboflavin, niacin, vitamin B-6, folate, vitamin B-12, pantothenic acid, biotin, and choline
1997	Calcium, vitamin D, phosphorus, magnesium, and fluoride

[1] DRIs for nutrients that included only the UL are indicated. DRI, Dietary Reference Intake; UL, Tolerable Upper Intake Level.

intakes is a concern, particularly in light of the range of evidence currently available and the importance of the DRIs in national nutrition policies (8).

Important uses of the DRIs include the formulation of national dietary guidance as well as the assessment of nutritional adequacy and the improvement of nutritional intakes of targeted and at-risk subgroups through federal nutrition-assistance programs (9). For example, in the United States, the nutritional principles of the DRIs are foundational to the development and application of food-group intakes and food patterns recommended in the *Dietary Guidelines for Americans* (10). By Congressional mandate, the *Dietary Guidelines for Americans* is used as the basis for establishing nutrient-based food plans for participants in federally funded nutrition-assistance programs such as the Supplemental Nutrition Assistance Program, the National School Lunch and Breakfast Programs, and the Special Supplemental Nutrition Program for Women, Infants, and Children (10). These important uses of the DRIs provide a rationale for periodic nutrient reviews and updates, as needed, of DRI values.

The DRI process must be informed by objective systematic reviews, which provide a means for assessing the quality of all available evidence, which is a critical constituent of DRI development (11). Systematic evidence reviews provide a basis for assessing the strengths and limitations of the totality of the evidence and determining whether there is concordance between RCTs and observational evidence in support of DRI development. However, the time and cost commitment of a comprehensive systematic review for every nutrient is high, and feasibility becomes a barrier to the process. Accordingly, there is a need for the initial prioritization and assessment of new evidence available for a given nutrient since its last DRI review to determine whether it is sufficient to support the more comprehensive re-examination of the DRIs with the use of a systematic review process. The development of such an initial assessment of the new evidence does not replace the need for an eventual full systematic review for a nutrient. Rather, the use of such an approach to scanning the new evidence serves as an early indicator of sufficient new evidence that could prioritize a new comprehensive systematic review or an update to an existing review of the full range of new evidence. In addition, this approach recognizes the need for cost-benefit considerations in times of fiscal constraint in both the US and Canadian federal agencies.

METHODS

The process that is currently used for specifying DRIs follows a risk-assessment approach that has 4 steps as follows: *1*) hazard identification (in this case, the hazard is a clinical outcome resulting from nutrient inadequacy or excess), *2*) hazard characterization (in this case the dose-response), *3*) intake assessment, and, finally, *4*) risk characterization (12). In this context, evidence scanning examines published research and identifies new findings from the literature that can contribute to an additional hazard identification or characterization for a specific nutrient. Thus, the results can indicate whether there is a need to update the evidence base for a nutrient for DRI consideration. Similar scanning approaches have been described as an alternative to conducting a full systematic review when there is uncertainty about the availability of relevant evidence and when frequent or timed updates to existing systematic reviews may be costly or infeasible (13, 14).

By providing a streamlined and efficient assessment of recent evidence that could be used in selecting the relevant clinical outcomes and for determining the dose-response relation, evidence scanning can play a crucial role in determining the importance of initiating a full re-examination of a nutrient's DRI. In addition, each nutrient's DRI should be based on an analytic framework that assesses the relation of a nutrient intake to clinical outcomes as described in **Figure 1**. In this framework, alternate pathways from nutrient exposure to clinical outcome are considered. A risk-assessment framework is particularly appropriate for specifying nutrient intake recommendations because, such as with DRIs, it uses a probability approach for determining the distribution of risk and enhances the transparency of decision making.

Objective

The objective of the case studies presented herein was to pilot an evidence-scanning methodology that would examine and evaluate research published since 1996 that might indicate the need for a comprehensive systematic review to support the re-examination of DRIs for thiamin and for phosphorus, which were last specified in 1998 and 1997, respectively. The goal was not to conduct a full systematic review for the purpose of revising DRI values. Instead, the goal was to conduct a thorough evidence-based literature scan to determine whether there was sufficient new and relevant evidence since the last specification of the DRIs to prioritize a new or updated full systematic review of the

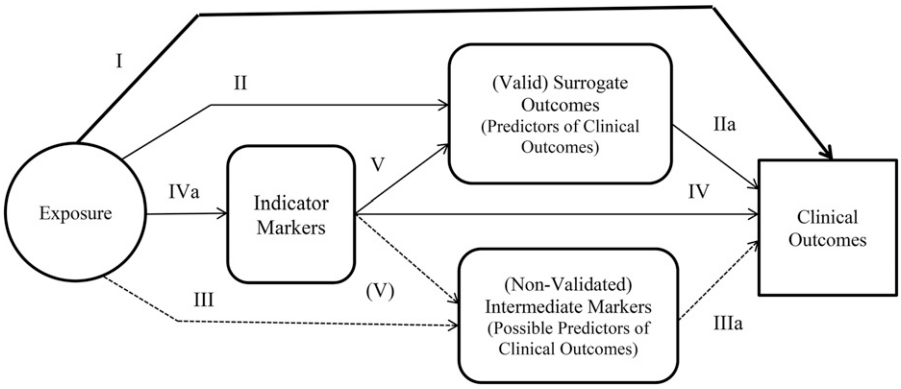

FIGURE 1 Generic analytic framework for Dietary Reference Intakes to assess the relation of nutrient intake (exposure) to health outcomes. Solid arrows represent established associations between factors. Line thickness represents the relative directness of an association and the strength of the relation with clinical outcomes. Dotted arrows represent associations to surrogate markers for which there is no direct evidence of an association with clinical outcomes. Associations are designated as follows: I, association of exposure with clinical outcomes of interest; II, association of exposure with surrogate outcomes for which there is good evidence of a linkage with clinical outcomes; IIa, association between surrogate outcomes and clinical outcomes (good evidence for linkage); III, association of exposure with surrogate markers for which the linkage with clinical outcome is uncertain; IIIa, association between surrogate markers and clinical outcomes (uncertain linkage); IV, association of indicator markers to clinical outcomes; IVa, association between exposure and indicator markers; and V, association of indicator markers to surrogate outcomes (with good or possible evidence for linkage with clinical outcomes). Adapted from reference 11 with permission.

evidence for each nutrient. Critical to such a scan is the evaluation of evidence for established or new health outcomes and dose-response evidence that could be considered across an analytic framework. This report describes the approaches used and findings for cases studies on thiamin and phosphorus and the lessons learned from the process.

Although the evidence scan process may be used to examine health outcomes related to both nutrient requirements and nutrient excesses, the 2 case studies focused only on requirements. From these case studies, the nutrient review group derived recommendations to guide the periodic evidence scanning of all nutrients with DRIs. In the future, this process might lead to a method of strategic prioritization of those nutrients with evidential support for new or updated systematic reviews to support the re-examination and updates of DRIs. Again, this type of evidence scanning is not a replacement for a comprehensive systematic review but, rather, is a more objective approach to assessing if such a comprehensive review is a high priority on the basis of the new evidence available since the last DRI review.

Case-study approach

For both thiamin and phosphorus, the nutrient review group first considered the criteria to evaluate whether the evidence was sufficient to recommend new or updated systematic reviews to support a re-examination of DRIs. These criteria were based on

TABLE 2
Prespecified criteria for assessing relevance of identified evidence for revising the DRIs[1]

Major criteria	Specific criteria
Relevant and needs evaluation	Selection of health-outcome indicator
	Randomized controlled trials
	Observational prospective cohort or nested case control
	Cross-sectional, case control, case report, or case series
	Factors affecting requirement and dose response
	Randomized controlled trials
	Observational prospective cohort or nested case control
	Cross-sectional, case control, case report, or case series
Possibly relevant but uncertain generalizability to setting DRIs	Populations with high prevalence of nutritional deficiency or malnutrition
	Well-nourished European, Asian, or other population
	Not current methodology but might still be relevant
Not relevant	No original data and not a systematic review
	Mechanistic studies worth reviewing for background but not informative to DRI
	Not related to selection:
	a) of health-outcome indicator or factors
	b) affecting requirement and dose response
	Not generally healthy population
	Not able to assess nutrient of interest independently

[1] For both thiamin and phosphorus case studies, major criteria were established on the basis of the relevance of the evidence to the selection of a health-outcome indicator; specific criteria were identified to characterize the relation of nutrient intake to an identified outcome. DRI, Dietary Reference Intake.

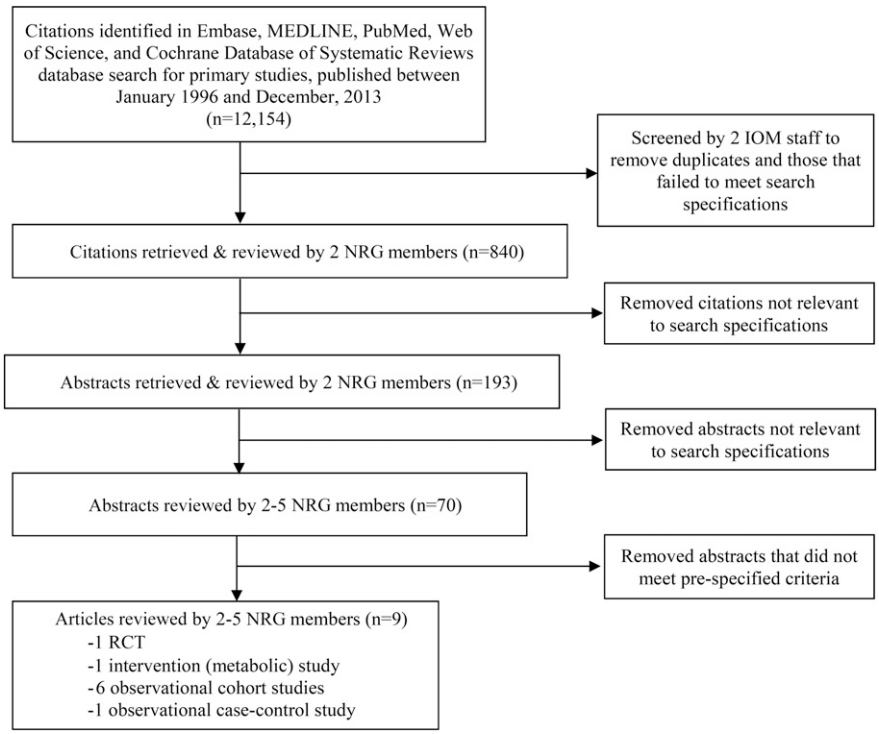

FIGURE 2 Screening strategy flow diagram for thiamin showing the screening and review process followed by the nutrient review group to identify nutrients that were potentially in need of a systematic evidence review. Cochrane Database of Systematic Reviews, http://www.cochranelibrary.com/cochrane-database-of-systematic-reviews/; Embase, http://www.ovid.com/site/?cmpid=Database%2520Landing:%2520RecomendMedicine%2520-%2520Embase; MEDLINE/PubMed, http://www.ncbi.nlm.nih.gov/pubmed; Web of Science, http://thomsonreuters.com/en/products-services/scholarly-scientific-research/scholarly-search-and-discovery/web-of-science.html. IOM, Institute of Medicine; NRG, nutrient review group; RCT, randomized controlled trial.

the first 2 steps of the risk-assessment framework to characterize the dose relation between dietary intake of a nutrient and the identified health outcomes (12). A set of prespecified criteria, which are described in **Table 2**, were formulated before initiating the evidence scan for each case study. A key aspect was the relevance to the selection of a health-outcome indicator. Also important was the identification of evidence for the dose-response relation between health outcomes and dietary intake and factors that affected this relation.

Several rounds of initial screening identified and removed duplicate citations and abstracts that were not relevant to the search specifications. In its review, the nutrient review group gave strongest consideration to randomized controlled trials (RCTs); less-strong consideration was given to observational prospective cohort studies and nested case-control studies. Observational cross-sectional or case control or case series were noted but not heavily weighted in the evidence scan.

In the evaluation of identified studies, trials that were not relevant for the following reasons were excluded in the evidence-selection process: no original data were reported; not a systematic review; mechanistic studies that were useful for background but not informative for the DRI process; not related to the selection of a health outcome; not informative for a dose-response relation; not conducted in generally healthy populations; or not able to assess nutrients of interest independent of other nutrients. Because of the purpose of the evidence scans, the quality of identified studies per se was not assessed systematically. If sufficient relevant evidence is identified to initiate a re-examination of a DRI, a full systematic review, including the assessment of the quality of the studies, would be warranted.

TABLE 3
Thiamin case study: abstracts shown to not be relevant to prespecified criteria for relevance to DRIs[1]

Reason not relevant	Abstracts reviewed, *n*
No original data and not a systematic review	14
Mechanistic studies worth reviewing for background but not informative to DRIs	3
Not related to selection of thiamin health-outcome indicator or factors affecting thiamin requirement and dose response	31
Not a healthy population	14
Total	62

[1] Specific criteria were identified to characterize the relation of nutrient intake to an identified outcome. DRI, Dietary Reference Intake.

TABLE 4
Assessment of relevance of reviewed studies to thiamin DRIs on the basis of prespecified criteria identified to characterize the relation of nutrient intake to an identified outcome[1]

Relevance (reason why not relevant)	Study authors, year (ref)	Study type and population	Intervention or exposure	Comparator	Outcome	Additional comments
Not related to requirement[2]	Ortega et al., 2004 (15)	Longitudinal study 82 healthy women in the third trimester of pregnancy or lactating	Participants with intakes below RI; thiamin intake based on weighed-food records and supplements	Participants with intakes at or above RI	Serum erythrocyte transketolase: no difference Milk thiamin content: no difference	—
Not related to health outcome[3]	Fattal et al., 2011 (16)	Follow-up study 59 Israeli children (5–7 y old) fed thiamin-deficient formula ≥1 mo during infancy	Thiamin deficiency during first 12 mo of life	35 age-matched control children (5–10 y old) who were not exposed to thiamin-deficient formula	Syntatic and lexical retrieval language development: impaired abilities in 57 exposed infants; $n = 3$ controls	Observational study raises possible new health outcome of concern but did not provide a causal linkage
Could not assess nutrient[4]	Jiang, 2006 (17)	RCT; school children (9–11 y old) in Beijing	Supplement for 37 d with riboflavin alone or riboflavin, thiamin, nicotinic acid, and folate	No supplement of riboflavin, thiamin, nicotinic acid or folate	Effect (%) of thiamin pyrophosphate on erythrocyte transketolase activity: decreased in thiamin-supplemented group but not to a normal level (<15%)	Intervention: multiple B vitamins fortified
Not related to health outcome[3]	Zhang et al., 2013 (18)	Rural and urban community-dwelling Chinese older adults (50–70 y old)	Depressive symptoms assessed (Center for Epidemiologic Studies Depression Scale)	Participants without depressive symptoms	Erythrocyte thiamin and TMP amounts: significantly lower in depressive symptoms or depressive symptoms increased as erythrocyte thiamin and TMP decreased	Observational case-control study that suggested a potential health outcome of depression that merits further study
Not related to requirement and dose response or health outcome[2,3]	Attias et al., 2012 (19)	Case study 11 Israeli infants fed a thiamin-deficient soy-based formula ≥3 mo	Early infancy thiamin deficiency	None	Auditory abnormalities in all Language developmental delay at 6–8 y of follow-up in all subjects	Observational case study that was not informative for the health outcome or dose response
Could not assess nutrient[4]	McKay et al., 2000 (20)	80 US adults aged 50–87 y	Double-blind RCT Daily multivitamin and mineral supplement: 100% DV for 13 vitamins (including thiamin) and 14 minerals for 8 wk	Placebo	Plasma thiamin unchanged	Daily multivitamin and mineral supplement
Not related to requirement and dose response[2]	Essama-Tjani et al., 2000 (21)	26 institutionalized elderly French adults followed longitudinally for 360 d	Dietary intake assessment for multiple vitamins including thiamin	Follow-up compared with baseline	Erythrocyte transketolase coefficient: baseline normal although 50% had intakes less than one-half the French RDA; unchanged at 360 d although intakes were less than the French RDA Erythrocyte thiamin pyrophosphate decreased	Observational study without informative dose-response information

(Continued)

TABLE 4 (*Continued*)

Relevance (reason why not relevant)	Study authors, year (ref)	Study type and population	Intervention or exposure	Comparator	Outcome	Additional comments
Not related to requirement and dose response or health outcome[2,3]	Schröder et al., 2008 (22)	1150 men, 1094 women; Spanish adults (>65 y old)	Two cross-sectional surveys; self-selected diet assessed by FFQ	First compared with third tertiles of energy density	Thiamine intake: higher in first tertile (low energy density) than in third tertile and higher percentage that met recommended intake	—
Not related to requirement and dose response or health outcome[2,3]	Elmadfa et al., 2001 (23)	12 healthy men (n = 6) and women (n = 6) residing in Vienna	Stepwise isocaloric increase for 4 d of dietary carbohydrate intake from baseline (55%) to phase 2 (65%) to 75%; thiamin intake: 0.110–0.13 mg/mJ across 3 phases	Baseline carbohydrate intake	Plasma and urinary thiamin decreased with increased carbohydrate Erythrocyte transketolase was unchanged	Small metabolic study that raised the possibility of a potential relation of carbohydrate intake to thiamin requirements that merits further study with a controlled thiamin dose response

[1] See Table 2 for prespecified criteria regarding the decision on relevance to DRI re-examination. DV, daily value; DRI, Dietary Reference Intake; FFQ, food-frequency questionnaire; RCT, randomized controlled trial; RDA, Recommended Dietary Allowance; ref, reference; RI, required intake; TMP, thiamin monophosphate.
[2] Not related to selection affecting requirement and dose response.
[3] Not related to selection of health-outcome indicator or factors.
[4] Not able to assess nutrient of interest independently.

RESULTS

Thiamin case study

Thiamin was selected as the first case study of a nutrient's DRI. It was expected that there might not be sufficient new evidence to initiate a re-examination of the thiamin DRI and that no new functions would have been identified for this nutrient.

Literature search strategy

Because of the uncertainty about the range of new evidence and to capture all possible relevant citations, a broad and inclusive search was conducted on peer-reviewed literature published from 1996 through 2013. For thiamin, no analytic framework was available from 1998, nor was one developed initially, to inform the literature search. With the use of the initial search results, the nutrient review group held a series of discussions by conference call to plan its strategy for identifying new evidence on thiamin intakes and health outcomes that were relevant to the DRI process for the evaluation of nutrients. A decision was made not to limit the search by specifying the population of interest beyond humans in all age groups. Interventions were specified broadly and included dietary thiamin, biomarkers of thiamin exposure (urinary thiamin), and supplemental thiamin. No comparator was specified. Health outcomes were also widely inclusive to ensure that any newly identified outcomes would also be included. No study designs were excluded, again with the intent of scanning the evidence as widely as possible.

After the previously described discussions, IOM staff searched a range of online bibliographic databases including Academic Search Premier (https://www.ebscohost.com/academic/academic-search-premier), AGRICOLA (https://www.ebscohost.com/academic/agricola), Embase (http://www.ovid.com/site/?cmpid=Database%2520Landing:%2520RecomendMedicine%2520-%2520Embase), PubMed/MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed), Science Direct (https://www.elsevier.com/solutions/sciencedirect), the Web of Science (http://thomsonreuters.com/en/products-services/scholarly-scientific-research/scholarly-search-and-discovery/web-of-science.html), and WorldCat/First Search (https://www.worldcat.org/) according to the nutrient review group's strategy. To identify primary literature, the staff first conducted general searches with the use of search terms that were identified by the nutrient review group (**Supplemental Table 1**). With the use of the results of the initial search, staff, in consultation with the nutrient review group, developed key search terms and conducted secondary searches. Search terms were selected on the basis of the relevance to the DRI process and likely health outcomes that were identified in the initial search. On the basis of the search criteria, the staff developed a comprehensive search strategy. Searches were limited to English-language publications. Search terms incorporated relevant Medical Subject Headings terms as well as terms from the EMBASE thesaurus.

The initial broad search retrieved a total of 12,154 citations, which were reviewed for their relevance to the specified search terms, and 11,961 inappropriate and duplicate citations were discarded. Two members of the nutrient review group reviewed a second tier group of 193 citations and identified 70 third-tier abstracts that were potentially relevant. The group of 70 third-tier abstracts was screened by 2 to 5 members of the nutrient review group with the removal of abstracts that did not meet the prespecified criteria. The remaining abstracts were categorized

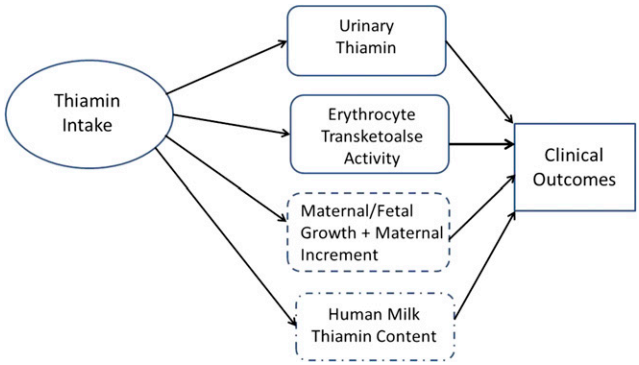

FIGURE 3 Analytic framework for thiamin. Dotted lines represent associations with surrogate markers for which there is no direct evidence of an association with clinical outcomes.

according to the prespecified criteria discussed previously. The nutrient review group examined the remaining full-text articles. For articles for which there was disagreement, the working group discussed the study approach, methods, and outcomes and reached a consensus on whether they were relevant. **Figure 2** illustrates the screening and review process.

Thiamin evaluation

Table 3 summarizes the review of thiamin abstracts. Of reviewed abstracts for thiamin, only 9 publications were identified for further assessment for relevance (15–23) (**Table 4**). The nutrient review group evaluated the complete report for each of the 9 potentially relevant publications. None of the publications were finally determined to be relevant to the DRI criteria, and the reasons are summarized in Table 4. Principally, none of the publications provided either causal evidence related to a relevant health outcome or informative dose-response data from a relevant population that were needed to re-examine the DRI.

One potential new clinical outcome relative to thiamin (i.e., depression) emerged from a single observational study in elderly Chinese (17), but further research on this as a potential health outcome for specifying the DRI is needed. The current evidence for causality is limited. Another potential new clinical outcome relative to thiamin (i.e., wound healing) emerged from one additional abstract, but this outcome was examined only in hospitalized and unhealthy subjects (24). Future research is needed in generally healthy individuals who experience wounding to determine whether this is a relevant and new health outcome for specifying the DRI for thiamin. If so, dose-response data would be needed for this health outcome in those individuals.

The lack of an analytic framework (see Lessons learned) was noted during the review process. The thiamin DRI specified in 1997 did not include such a framework, and thus, the nutrient review group developed its own framework (**Figure 3**) to facilitate the review of the selected abstracts. The nutrient review group's framework provided greater clarity in the assessment of the relevance of the abstracts to the identification of clinical outcomes and dose-response data that were relevant to the DRI.

Phosphorus case study

Phosphorus was selected for the second case study because the understanding of certain aspects of its physiology has advanced since the establishment of the DRIs in 1997. For example, the role of fibroblast growth factor-23 has been identified in the homeostatic regulation of circulating concentrations of phosphorus through the regulation of phosphorus absorption and renal excretion as part of a hormonal bone-parathyroid-kidney axis (25). On the basis of the experience with the thiamin evidence scan, an analytic framework for phosphorus was developed at the start of the process (**Figure 4**). Although the phosphorus framework did not identify any intermediate predictors of clinical outcomes, as shown in Figure 1, it was helpful to prespecify intermediate outcomes such as fibroblast growth factor-23 concentrations.

Literature search strategy

Similar to the thiamin search strategy, a broad and inclusive multidatabase literature search was conducted on articles published from 1996 to 2013 to identify studies that were related to phosphorus, with the exclusion of review articles, animal studies, and non-English language studies. Medical Subject Headings terms used in the search are summarized in **Supplemental Table 2**. After the search, the nutrient review group used Abstrackr, which is a continuously updated web-based abstract screening, tracking, and annotation tool (26), to facilitate the screening of abstracts for further review.

The initial search retrieved 810 citations, which were reviewed for their relevance to the search terms, and inappropriate citations were discarded. After this initial review, 127 citations remained. Two members of the nutrient review group reviewed this second-tier group of citations and identified 29 potentially relevant abstracts from the total number of abstract for further review. **Table 5** shows the reasons for exclusion of 98 abstracts from the initial review. Two to 3 members of the nutrient review group screened the 29 third-tier full-text articles to identify those abstracts that were relevant for further review. For citations on which there was disagreement, the nutrient review group discussed the abstracts and reached a consensus on whether the citations were relevant or not.

Phosphorus evaluation

From the screening of the 29 third-tier full-text articles, only 15 articles received a consensus as being potentially relevant to either a full systematic review or useful in providing information

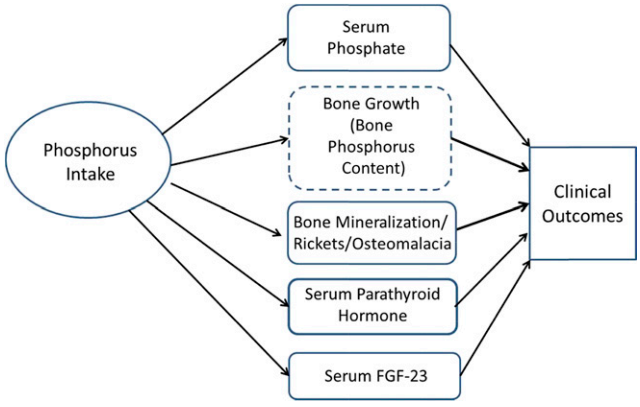

FIGURE 4 Analytic framework for phosphorus. Dotted lines represent associations with surrogate markers for which there is no direct evidence of an association with clinical outcomes. FGF-23, fibroblast growth factor-23.

TABLE 5
Phosphorus case study: abstracts that were shown to be not relevant to prespecified criteria for relevance to DRIs[1]

Reason why not relevant	Abstract, *n*
No original data and not a systematic review	25
Mechanistic studies worth reviewing for background but not informative to DRIs	11
Not related to selection of phosphorus health-outcome indicator or factors affecting phosphorus requirement and dose response	25
Not a healthy population	37
Total, *n*	98

[1] Specific criteria were identified to characterize the relation of nutrient intake to an identified outcome. DRI, Dietary Reference Intake.

about factors that influence requirements (27–41) (**Table 6**). In addition, none of the 15 publications reviewed by the nutrient review group were considered relevant for the initiation of a formal DRI review because most of the associational, prospective, and balance studies did not enable the assessment of only phosphorus and, therefore, did not permit the determination of the effect of phosphorus per se on any of the outcomes indicated in the analytic framework (Figure 1). Some of the reviewed articles could be informative in the determination of a dose response. However, in terms of the effect of dietary phosphorus on serum phosphorus concentrations, for those factors that either influenced phosphorus absorption or showed no dose, none of the articles had relevant effect data because of an absence of a measure of a health outcome for phosphorus (30, 33, 34).

The evidence-scan methodology described here resulted from a multistep process that developed as the review group moved from an initial review (of thiamin) to a more defined review (of phosphorus). For thiamin, the nutrient review group performed a literature scan with the use of the traditional approach that was informed by nutrition experts but was unguided by the explicit Population, Intervention, Comparator, Outcomes, and Study Design (PICOD) question formulation, and review criteria were not established as typical evidence-based methodology. The group used the lessons learned from the thiamin case study and applied evidence-based methods (i.e., an analytic framework PICOD approach to formulate questions and eligibility criteria and technical expert input) and experiences reported in the literature for systematic reviews of nutrients to the case study of phosphorus. Finally, members of the nutrient review group compared the advantages and limitations of the 2 approaches with the use of the insights gained from these exercises and developed an evidence-scanning approach that could be applied to other nutrients with the aim that it would be both feasible and efficient. This scanning process, as previously noted, in no way replaces the need for a comprehensive systematic review. Rather, it enables a cost-effective and more objective means whereby the need for such a comprehensive systematic review can be given a high priority on the basis of indicators of sufficient new evidence to warrant further review in support of the DRI process. The specific lessons learned from this process were as follows.

Lessons learned

In the first case study on thiamin, the need for an analytic framework emerged during the review of third-tier citations. The review process showed that such a framework would facilitate the framing of systematic literature scan terms and questions and enhance the clarity of predicted relations between dietary exposure and selected clinical outcomes (11). In addition, the framework would facilitate the evaluation of the relevance of the evidence. The 1997 IOM report *DRIs for Thiamin, Riboflavin, Niacin, Vitamin B-6, Folate, Vitamin B-12, Pantothenic Acid, Biotin, and Choline* did not include such a framework, and thus, the nutrient review group developed a framework on the basis of selected clinical outcomes and a consideration of dietary exposures in the specification of the DRIs for thiamin (2). Such an analytic framework would have been helpful from the beginning of the literature scan to guide the search strategy and develop an appropriate and broad PICOD for the search. However, the thiamin analytic framework (Figure 3) that was subsequently developed was useful in facilitating the nutrient review group's review of evidence and its ability to reach a consensus assessment of abstracts that lacked initial agreement. For the phosphorus review, an analytic framework (Figure 4) was developed at the outset to inform the systematic search strategy and the review of abstracts. This analytic framework enabled the nutrient review group to conduct a more appropriately focused search while still ensuring the necessary breadth of scanning the literature for emerging health outcomes.

During the evidence scan for phosphorus, the nutrient review group identified the need for consultation with colleagues who are experts in phosphorus requirements. These experts assisted with both the specification of the analytic framework and with a review of the results of the evidence scan. The inclusion of one or more experts in the process was determined to be necessary to confirm that the scan was comprehensive.

As the nutrient review group initiated its review of abstracts, the process itself revealed a need for training on and discussion about the use of the first 2 steps of the risk-assessment framework and the prespecified criteria and about how the relevance of the evidence was determined. Likewise, the need for a more focused and efficient search strategy became apparent. The group showed that the process could be enhanced and more efficient if such training occurred before the individual review of citations.

The nature of evidence differed between that for clinical outcomes and that for dose-response outcomes. A consideration of separate literature scans, framed differently, could facilitate each more effectively than could a single literature scan on combined outcomes.

The advantages of a broad and inclusive literature search require the weighting of such an approach against the ability to identify the most-relevant research obtained through a less-rigorous approach (i.e., an evidence scan). The evidence scan conducted by the nutrient review group would have benefited from a broad definition of the PICOD that included study designs without the loss of the crucial breadth of search at the expense of unknown or poorly understood outcomes. For example, systematic reviews should be included, but all other reviews should be excluded. One purpose of the evidence scan was to identify new clinical outcomes. To do so would have required an open and relatively unspecified search; however, such an approach would have identified many more irrelevant citations. Therefore, it is necessary to balance the need for breadth while ensuring the relevance of identified citations.

TABLE 6
Assessment of relevance of reviewed references to the DRI for phosphorus on the basis of prespecified criteria identified to characterize the relation of nutrient intake to an identified outcomes[1]

Relevance (reason why not relevant)	Study authors, year (ref)	Population	Intervention or exposure	Comparator	Outcome	Additional comments
Not related to requirement[2]	Alonso et al., 2010 (27)	13,444 adults in 2 cohorts, the Atherosclerosis Risk in Communities and Multi-Ethnic Study of Atherosclerosis	Prospective 6.2-y mean follow-up; n = 3345 cases of hypertension	Highest compared with lowest quintiles	High phosphorus reduced blood pressure from dairy only HR: 0.86 (95% CI: 0.76–0.97; P = 01)	Observational study
Not related to health outcome or requirement[2,3]	Brot et al., 1999 (28)	510 perimenopausal women in Denmark aged 45–58 y	Cross-sectional	NA	Calcium:phosphorus intake but not phosphorus intake alone was related to BMD	Observational study of calcium:phosphorus intake but not of phosphorus alone
Not related to requirement[2]	de Boer et al., 2009 (29)	15,513 individuals from NHANES	Cross-sectional	NA	Diet phosphorus was weakly related to serum phosphorus but not to CVD risk	—
Not related to requirement[2]	Delgado-Andrade et al., 2011 (30)	20 male adolescents	2- to 3-d balance studies with diets high in Maillard products	Diets high and low in Maillard products	Maillard products increased fecal phosphorus	Supported information on phosphorus digestibility but had no range of phosphorus intake
Not related to requirement[2]	Elliott et al., 2008 (31)	4680 women and men aged 40–59 y	Cross-sectional	Comparisons made with supplement users and diagnosis for CVD or diabetes	Dietary phosphorus was inversely related to blood pressure	Observational study that raised the possibility that dietary phosphorus might influence blood pressure, but phosphorus was highly correlated with calcium and magnesium
Not related to requirement[2]	Elmståhl et al., 1998 (32)	6576 men aged 46–68 y	Prospective cohort for 2.4 y	Lowest quintile	Lowest quintile of phosphorus was associated with increased fracture risk	Observational study
Not related to requirement[2]	Grimm et al., 2001 (33)	10 women aged 20–30 y	6-wk high phosphorus (3088 mg/d) and calcium (1995 mg/d)	4-wk normal phosphorus (1700 mg/d) and calcium (1500 mg/d)	No significant changes in bone hormones	Potentially informative for safety of high phosphorus on renal function
Not related to health outcome[3]	Haraikawa et al., 2012 (34)	193 Japanese young adults	Cross-sectional	NA	Serum phosphorus and serum BAP were correlated	No measure of phosphorus health outcome
Not related to health outcome or requirement[2,3]	Heaney and Nordin, 2002 (35)	543 women aged 35–65 y and 93 men and women aged 19–78 y	Balance studies	Range of phosphorus intakes but other nutrient intakes varied	As calcium intake increased by 25 mmol, phosphorus absorption decreased by 10.8 mmol	Compilation of balance studies raised the possibility of an interaction effect with calcium, but many nutrients were varied
Not related to health outcome[3]	Heppe et al., 2013 (36)	2819 children	Maternal first-trimester diet	NA	Phosphorus and protein, calcium, and vitamin B-12 were associated with lower bone mass	Cross-generational comparison
Not related to requirement[2]	Ito et al., 2011 (37)	441 Japanese women aged 18–22 y	Cross-sectional	NA	Phosphorus and calcium and the ratio of the 2 were related to distal radius BMD but not to the femoral neck or spine	No independent effect of phosphorous

(Continued)

TABLE 6 (*Continued*)

Relevance (reason why not relevant)	Study authors, year (ref)	Population	Intervention or exposure	Comparator	Outcome	Additional comments
Not related to requirement[2]	Méndez et al., 2002 (38)	47 Mexican postmenopausal women aged 45–63 y	Cross-sectional	NA	No relation between phosphorus and BMD	Observational study
Not related to health outcome or requirement[2,3]	Nishimuta et al., 2012 (39)	178 Japanese women from 17 studies	8- to 12-d balance studies	Range of phosphorus intakes but other nutrient intakes varied	Equilibration intake of 18.7–19.3 mg · kg body weight^{-1} · d^{-1}	Small range of phosphorus intake, and phosphorus was not independently manipulated
Not related to health outcome or requirement[2,3]	Nishimuta et al., 2004 (40)	109 young Japanese adults	5- to 12-d balance studies	Range of phosphorus intakes but other nutrient intakes varied	22.6 mg · kg body weight^{-1} · d^{-1} for a zero phosphorus balance	Small range of phosphorus intake, and phosphorus was not independently manipulated
Not related to requirement[2]	Whiting et al., 2002 (41)	57 men aged 39–42 y	Cross-sectional	NA	Phosphorus, calcium, protein, and potassium were correlated with BMD at the total body, hip, lumbar, and spine	Observational study

[1] See Table 2 for prespecified criteria regarding the decision on relevance to DRI re-examination. BAP, bone-specific alkaline phosphatase; BMD, bone mineral density; CVD, cardiovascular disease; DRI, Dietary Reference Intake; NA, not applicable.
[2] Not related to selection affecting requirement and dose response.
[3] Not related to selection of health-outcome indicator or factors.

DISCUSSION

The importance of the DRIs for policy, including the assessment and monitoring of the nutritional health of US and Canadian populations, informing public health policy through dietary guidance, supporting nutritional requirements for nutrition-assistance programs, and informing nutrition labeling, requires a set of DRIs that are based on the current scientific evidence. With the exception of calcium and vitamin D (7), no DRI nutrient rereviews have been conducted to our knowledge, and the current DRI recommendations are 10–18 y old. As stated previously, an objective assessment of the totality and quality of the evidence with the use of a comprehensive systematic review is required to update a DRI (11). Two such systematic reviews were used for the update of the DRIs for calcium and vitamin D (7). The previous DRI review (1997–2005) included 51 identified nutrients, although the DRI review process at the time did not entail a comprehensive systematic review of every nutrient. It was not until the 2010 review of calcium and vitamin D that systematic reviews were recognized as an essential component of the DRI review process. The cost and time commitment of the 2 comprehensive systematic reviews to support the calcium and vitamin D DRI process were high and suggested a possible barrier to carrying out future comprehensive systematic reviews on the remaining DRI nutrients that have not been updated since the 1997–2005 review process. The approach piloted in these 2 case studies for thiamin and phosphorus showed a potential mechanism for the assessment of the status of new evidence that may be relevant to the DRI process and showed that an evidence scan can be used to determine whether sufficient new evidence is available to prioritize a comprehensive systematic review to update specific DRIs. In addition, even in the absence of sufficient evidence, this approach can identify potential new health outcomes that merit additional research (e.g., depression and wound healing for thiamin) of a given nutrient of interest.

Key steps in this approach are as follows: *1*) the determination of an analytic framework on the basis of appropriate clinical and biochemical markers of an adequate or excessive intake; *2*) the use of a framework to develop and conduct a literature scan with relevant key words; *3*) the review of abstracts and publications for relevance relative to prespecified criteria; *4*) the consultation of experts on the nutrient or nutrients of interest; and *5*) reaching a consensus on whether relevant new evidence is available. Such an evidence scan, as defined by an analytic framework, is a robust and effective way to determine whether sufficient new evidence on clinical outcomes or dose-response data exists to merit a formal re-examination of a nutrient's DRI.

In conclusion, to ensure that the DRIs are consistent with the current research, a cost-effective process for conducting evidence scans, which would recur in 5-y intervals, is recommended as a preliminary step to determine the need for a formal DRI review. The nutrient review group proposes that a standing committee should be convened to initiate and carry out such a process beginning with the oldest DRIs. If there is insufficient relevant evidence to assign a high priority to a rereview, a statement of this finding, together with the date of the evidence scan, would be made public. Subsequently, if there is sufficient relevant evidence to support a nutrient re-examination, the nutrient could be submitted to the Federal DRI Steering Committee for a formal review that would include a comprehensive systematic review of

the new evidence, an update of the clinical outcomes that are most crucially linked to that nutrient, an evaluation of the relations between the distribution of intake and status for that nutrient and the identified clinical outcomes, and the identification of gaps to prioritize future research. Publicly releasing the findings of the evidence scans would inform users of the status of nutrients and identify whether the DRI for a nutrient is particularly in need of revision. A regular, cyclical review of new evidence for all DRI nutrients would ensure that DRIs that are most in need of updating are identified in a timely, cost-effective manner and are consistent with the current evidence.

We thank Susan Taylor Mayne for contributions to the planning and discussion of this case-study approach during her service on the IOM's Food and Nutrition Board and Mei Chung and Alice Vorosmart for their contributions in conducting the literature searches.

The authors' responsibilities were as follows—PMB and ALY: contributed to the design of the approach; the development of the thiamin search strategy; the review of the thiamin citations, abstracts, and selected articles; the interpretation of the results; and the writing of the manuscript; CMW and SPM: contributed to the design of the approach; the development of the thiamin and phosphorus search strategies; the review of the thiamin and phosphorus citations, abstracts, and selected articles; the interpretation of the results; and the writing of the manuscript; CAMA: contributed to the development of the phosphorus search strategy; the review of the phosphorus citations, abstracts, and selected articles; the interpretation of the results; and the writing of the manuscript; SMD: contributed to the development of the phosphorus search strategy; the review of the thiamin and phosphorus citations, abstracts, and selected articles; the interpretation of the results; and the writing of the manuscript; and all authors: read and approved the final manuscript. None of the authors reported a conflict of interest related to the study. Any views that are not attributed to Institute of Medicine reports are those of the authors and do not necessarily represent the views of The National Academies of Sciences, Engineering, and Medicine. The authors' work was conducted independently of their roles as current or former members of the Food and Nutrition Board (PMB, CMW, CAMA, and SMD are current members and SPM is a former member and chair of the Food and Nutrition Board.).

REFERENCES

1. Institute of Medicine. Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, DC: National Academy Press; 1997.
2. Institute of Medicine. Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington (DC): National Academy Press; 1998.
3. Institute of Medicine. Dietary Reference Intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington (DC): National Academy Press; 2000.
4. Institute of Medicine. Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington (DC): National Academy Press; 2002.
5. Institute of Medicine. Dietary Reference Intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington (DC): The National Academies Press; 2005.
6. Institute of Medicine. Dietary Reference Intakes for water, potassium, sodium, chloride, and sulfate. Washington (DC): The National Academies Press; 2005.
7. Institute of Medicine. Dietary Reference Intakes for calcium and vitamin D. Washington (DC): The National Academies Press; 2011.
8. Yetley EA, Brule D, Cheney MC, Davis CD, Esslinger KA, Fischer PW, Friedl KE, Greene-Finestone LS, Guenther PM, Klurfeld DM, et al. Dietary Reference Intakes for vitamin D: justification for a review of the 1997 values. Am J Clin Nutr 2009;89:719–27.
9. Institute of Medicine. Dietary Reference Intakes: applications in dietary assessment. Washington (DC): The National Academies Press; 2001.
10. US Department of Health and Human Services and US Department of Agriculture. Dietary guidelines for Americans [Internet]. 7th ed. Washington (DC): US Government Printing Office; 2010 [cited 2015 Jun 25). Available from: http:www.health.gov/dietaryguidelines/2010.asp.
11. Brannon PM, Taylor CL, Coates P. Use and application of systematic reviews in public health nutrition. Annu Rev Nutr 2014;34:401–19.
12. Russell R, Chung M, Balk EM, Atkinson S, Giovannucci EL, Ip S, Lichtenstein AH, Taylor Mayne S, Raman G, Ross AC, et al. Opportunities and challenges in conducting systematic reviews to support the development of nutrient reference values: vitamin A as an example. Am J Clin Nutr 2009;89:728–33.
13. Chung M, Newberry SJ, Ansari MT, Yu WW, Wu H, Lee J, Suttorp M, Gaylor JM, Motala A, Moher D, Balk EM, Shekelle PG.. Two methods provide similar signals for the need to update systematic reviews. J Clin Epidemiol 2012;65:660–8.
14. Shekelle PG, Motala A, Johnsen B, Newberry SJ. Assessment of a method to detect signals for updating systematic reviews. Syst Rev 2014;3:13.
15. Ortega RM, Martinez RM, Andres P, Marin-Arias L, Lopez-Sobaler M. Thiamin status during the third trimester of pregnancy and its influence on thiamin concentrations in transition and mature breast. Br J Nutr 2004;92:129–35.
16. Fattal I, Friedmann N, Fattal-Valevski A. The crucial role of thiamine in the development of syntax and lexical retrieval: a study of infantile thiamine deficiency. Brain 2011;134:1720–39.
17. Jiang YY. Effect of B vitamin-fortified foods on primary school children in Beijing. Asia Pac J Public Health 2006;18:21–5.
18. Zhang G, Ding H, Chen H, Te S, Li H, Lin X, Ke Z. Symptoms are inversely associated among older Chinese adults. J Nutr 2013;143:53–8.
19. Attias J, Raveh E, Aizer-Dannon A, Bloch-Mimouni A, Fattal-Valevski A. Auditory system dysfunction due to infantile thiamine deficiency: long term auditory sequelae. Audiol Neurootol 2012;17:309–20.
20. McKay DL, Perrone G, Rasmussen H, Dallal G, Hartman W, Cao G, Prior RL, Roubenoff R, Blumberg J. The effects of a multi-vitamin/mineral supplement on micronutrient status, antioxidant capacity and cytokine production in healthy older adults consuming a fortified diet. J Am Coll Nutr 2000;19:613–21.
21. Essama-Tjani JC, Guilland JC, Fuchs F, Lombard M, Richard D. Changes in riboflavin, niacin, beta-carotene, vitamins C, A, D, and E status of French elderly subjects during the first year of institutionalization. Int J Vitam Nutr Res 2000;70:54–64.
22. Schröder H, Vila J, Marrugat J, Covas M-I. Low energy density diets are associated with favorable nutrient intake profile and adequacy of free-living elderly men and women. J Nutr 2008;138:1476–81.
23. Elmadfa I, Majchrzak D, Rust P, Genser D. The thiamin status of adult humans depends on carbohydrate intake. Int J Vitam Nutr Res 2001;71:217–21.
24. Neiva RF, Al Shammari K, Nociti FH Jr., Soehren S, Wang HL. Effects of vitamin B complex supplementation on periodontal would healing. J Periodontol 2005;76:1084–91.
25. Ramon I, Kleynen P, Body JJ, Karmali R. Fibroblast growth factor 23 and its role in phosphate homeostasis. Eur J Endocrinol 2010;162:1–10.
26. Wallace BC, Small K, Brodley CE, Lau J, Trikalinos TA. Deploying an interactive machine learning system in an evidence-based practice center: abstrackr. In Proceedings of the ACM International Health Informatics Symposium (IHI); 2012. p. 819–24. Available from: http://abstrackr.cebm.brown.edu/.
27. Alonso A, Nettleton JA, Ix JH, de Boer IH, Folsom AR, Bidulescu A, Kestenbau, BR, Chambless LE, Jacobs DR Jr. Dietary phosphorus, blood pressure, and incidence of hypertension in the atherosclerosis risk in communities study and the multi-ethnic study of atherosclerosis. Hypertension 2010; 55;776–84.
28. Brot C, Jorgensen N, Madsen OR, Jensen LB, Sorensen OH. Relationships between bone mineral density, serum vitamin D metabolites and calcium:phosphorus intake in healthy perimenopausal women. J Intern Med 1999;245:509–16.
29. de Boer IH, Rue TC, Kestenbaum B. Serum phosphorus concentrations in the Third National Health and Nutrition Examination Survey (NHANES III). Am J Kidney Dis 2009;53:399–407.
30. Delgado-Andrade C, Seiquer I, Garcia MM, Galdo G, Navarro MP. Increased Maillard reaction products intake reduces phosphorus digestibility in male adolescents. Nutrition 2011;27:86–91.

31. Elliott P, Kestelott H, Appel LJ, Dyer AR, Ueshima H, Chan Q, Brown IJ, Ahao L, Stamler J, INTERMAP Cooperative Research Group. Dietary phosphorus and blood pressure: international study of macro- and micro-nutrients and blood pressure. Hypertension 2008;51:669–75.
32. Elmståhl S, Gullberg B, Janzon L, Johnell O, Elmstahl B. Increased incidence of factures in middle-aged and elderly men with low intakes of phosphorus and zinc. Osteoporos Int 1998;8:333–40.
33. Grimm M, Muller A, Hein G, Funfstuck R, Jahreis G. High phosphorus intake only slightly affects serum minerals, urinary pyridinium crosslinks and renal function in young women. Eur J Clin Nutr 2001;55:153–61.
34. Haraikawa M, Tanabe R, Sogabe N, Sugimoto A, Kawamura Y, Michigami T, Hosoi T, Goseki-Sone M. A study of the association between serum bone-specific alkaline phosphatase and serum phosphorus concentration or dietary phosphorus intake. J Nutr Sci Vitaminol (Tokyo) 2012;58:442–5.
35. Heaney RP, Nordin BD. Calcium effects on phosphorus absorption: implications for the prevention and co-therapy of osteoporosis. J Am Coll Nutr 2002;21:239–44.
36. Heppe DH, Medina-Gomez C, Hofman A, Franco OH, Rivadeneira F, Jaddoe VW. Maternal first-trimester diet and childhood bone mass: the Generation R study. Am J Clin Nutr 2013;98:224–32.
37. Ito S, Ishida H, Uenishi K, Murakami K, Sasaki S. The relationship between habitual dietary phosphorus and calcium intake and bone mineral density in young Japanese women: a cross-sectional study. Asia Pac J Clin Nutr 2011;20:411–7.
38. Méndez RO, Gomez MA, Lopez AM, Gonzalez H, Wyatt CJ. Effects of calcium and phosphorus intake and excretion on bone density in postmenopausal women in Hermosillo, Mexico. Ann Nutr Metab 2002; 46:249–53.
39. Nishimuta M, Kodama N, Shimada M, Toshtake Y, Matsuzaki N, Morikuni E. Estimated equilibrated dietary intakes for nine minerals (Na, K, Ca, Mg, P, Fe, Zn, Cu, and Mn) adjusted by mineral balance medians in young Japanese females. J Nutr Sci Vitaminol (Tokyo) 2012;58:118–28.
40. Nishimuta M, Kodama N, Morikuni E, Yoshioka YH, Takeyama H, Yamada H, Kitajima H, Suzuki K. Balances of calcium, magnesium and phosphorus in Japanese young adults. J Nutr Sci Vitaminol (Tokyo) 2004;50:19–25.
41. Whiting SJ, Boyle JL, Thompson A, Mirwald RL, Faulkner RA. Dietary protein, phosphorus and potassium are beneficial to bone mineral density in adult men consuming adequate dietary calcium. J Am Coll Nutr 2002;21:402–9.