PERSPECTIVE

Perspective: Appraisal of the Evidence Base to Update DRI Values—Lessons from the Past, Thoughts for the Future

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ABSTRACT

Updating evidence-based nutrient guidance is challenging. One set of recommendations for which a robust evidence base is essential is the DRIs. In the past 10 y, DRI values for 4 essential nutrients have been re-evaluated in 2 groups: vitamin D and calcium, and sodium and potassium. To support the work of the committees tasked with evaluating the available evidence, the federal agencies that sponsor the DRI reviews contracted with the Agency for Healthcare Research and Quality to perform systematic reviews on predefined questions for these nutrient groups. Our aims were to tabulate the studies included in these systematic reviews and then, within the context of prespecified outcomes, summarize the totality of the available evidence and identify areas for consideration to maximize the value of the end products for future DRI committees. For the outcomes of interest, the available studies did not tend to report age data consistent with the current DRI categories. For some life stage categories, particularly pregnancy and lactation, there is a dearth of data. A wide range of study interventions were used, making it challenging to combine data to accurately derive or re-evaluate DRI values. There is also an under-representation of data on race/ethnicity and overweight/obesity, which is of concern, given the shifting demographic in the US and Canadian populations. Moving forward, it may be advantageous to develop a process to prospectively target research funding for studies designed to generate data that will most closely support re-evaluation of DRI values. *Adv Nutr* 2022;13:975–981.

Statement of Significance: Updating evidence-based nutrient guidance is challenging. Garnered from recent experiences using systematic reviews to update the Dietary Reference Intake values for calcium and vitamin D, and sodium and potassium, are some considerations for the future.

Keywords: vitamin D, calcium, sodium, potassium, Dietary Reference Intake Intakes, systematic reviews, USA, Canada

Introduction

Updating evidence-based nutrient guidance is challenging, particularly when formulating numerical recommendations for a wide range of ages and life stages. Much of the challenge rests on limitations in the available evidence base. One set of recommendations for which a robust evidence base is essential is the DRIs, first issued by the Institute of Medicine and now under the auspices of the National Research Council of the National Academies of Sciences, Engineering, and Medicine (NASEM) (1). Specific intake values are given for micronutrients (vitamins, minerals, and elements) and intake ranges for energy, macronutrients and non-essential nutrients (fiber, cholesterol) and water on the basis of age, sex and life stage (e.g., pregnancy and lactation) categories.

The RDAs were first issued in 1941. Over time, as the essentiality of additional nutrients was established, new RDA values were derived. The mid to late 1990s saw a major revision in the approach used to develop the RDA values. The age group 70 years and older was added, as were additional nutrient categories: the Estimated Average Requirement (EAR), Adequate Intake (AI), Tolerable Upper Intake Level (UL) and Adequate Macronutrient Distribution Range (AMDR), and later Chronic Disease Risk Reduction (CDRR). These categories were added to reflect the evolving uses of recommendations, limitations of the database from

which the values were derived, and contemporary public health concerns. The approach used to derive the values was based on a review of the literature, in some cases expert opinion, and, as necessary, interpolation of the values for age categories lacking data.

In the past 10 y, DRI values for 4 essential nutrients have been re-evaluated: vitamin D (VitD), calcium (Ca), sodium (Na), and potassium (K). The approach used was to consider these nutrients in 2 groups: vitamin D and calcium (VitD/Ca) (2), and sodium and potassium (Na/K) (3). Within each of the 2 groups, biological interrelations had been well established, hence, re-evaluating them together allowed for consideration of the nutrients as they were frequently studied. Of the 4 nutrients, 1 is of public health concern for overconsumption (Na), and 3 are of public health concern for underconsumption (K, Ca, VitD) (4). To support the work of the committees tasked with evaluating the available evidence for these nutrients, the federal agencies that sponsor the DRI reviews contracted with the Agency for Healthcare Research and Quality (AHRQ) to perform systematic reviews on predefined questions for these nutrient groups; the approach used was for the NAM to request that the AHRQ commission systematic reviews for the nutrient groups.

Critical to the work of the committees tasked with revising the DRI values is the available evidence. The aim of this commentary was to tabulate the studies included in the AHRQ systematic reviews commissioned for the DRI committees (5–8) to *1*) summarize the totality of the available evidence for prespecified outcomes and identify gaps, *2*) identify areas for consideration to maximize the value of the end products for future DRI committees, and *3*) based on these findings, reflect on possible modifications to the DRI rubric in the future.

Methods

Data were extracted from the controlled trials included in the AHRQ systematic reviews that reported the prespecified outcomes of interest. For VitD/Ca those outcomes were bone mineral content and/or density (BMC/BMD) from studies included in the 2007 (5), 2009 (6), and 2014 updates (7). For Na/K those outcomes were systolic and diastolic blood pressure (SBP/DBP) (8). These outcomes were chosen because they were most frequently reported for the respective nutrients. The entire team decided on the data elements to be extracted and operationalized their definitions. Data extraction was performed individually by 2 investigators (DSC and SPS). Both investigators extracted information both from VitD/Ca studies and Na/K studies. Extracted data included participant characteristics: number; age (range or mean ± SD or SEM); race/ethnicity; inclusion criteria related to the outcome measures and sex; intervention, duration, and type; and comparator. Forty-five studies for VitD/Ca and 80 studies for Na/K met the inclusion criteria. Data for age were extracted according to the categories used in the VitD/Ca systematic reviews, with an additional category for pregnant women. None of the studies reported the age categories according to those predefined in DRI tables. Based on age range or mean ± SD, participants in all studies spanned multiple DRI categories. Hence, studies appear in >1 category in the table and figures.

Results

The VitD/Ca and BMD/BMC studies centered on participants 51 y and older, whereas the Na/K and SBP/DBP studies included a wider age range of participants, 19–70 y old (**Table 1**, **Figure 1**). This pattern was reflected in the total number of individuals studied (Table 1). From the late 1990s to the early 2000s, no temporal trend in this pattern was observed. This distribution of studies across age categories may be related to the life stage at which the health outcomes of interest most frequently manifest.

The studies conducted for VitD/Ca predominantly included a relatively high proportion of females, likely a reflection of their higher risk of osteoporosis than for males (Table 1) (9). A more even female/male distribution was observed for Na/K studies. The majority of VitD/Ca studies (82%) were conducted in participants described as healthy. The majority of Na/K studies (74%) were conducted in participants with hypertension and related comorbidities; type 2 diabetes; 10-y cardiovascular disease risk >10%, overweight-obesity, and chronic kidney disease.

Race/ethnicity was reported in 49% of the VitD/Ca studies and 56% of the Na/K studies. It was more frequently reported in studies involving participants 19 y and older than in studies involving children (Table 1). One potential explanation for the slightly higher reporting of race/ethnicity of the Na/K than the VitD/Ca studies may be the higher risk of hypertension in blacks than in whites, particularly in males (10). No temporal relation for reporting race/ethnicity was identified for studies of Na/K or VitD/Ca (**Figure 2**).

Of the VitD/Ca studies, 87% provided the nutrients as a supplement, 9% as fortified foods, and 4% as a combination of fortified foods and supplements (**Supplemental Table 1**). There was considerable heterogeneity among studies in terms of comparison groups. In addition to a control/placebo

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Abbreviations used: AHRQ, Agency for Healthcare Research and Quality; AMDR, Adequate Macronutrient Distribution Range; BMC, bone mineral content; BMD, bone mineral density; CDRR, Chronic Disease Risk Reduction; DBP, diastolic blood pressure; NASEM, National Academies of Sciences, Engineering, and Medicine; SBP, systolic blood pressure; UL, Upper Levels of Tolerance; VitD, vitamin D.

TABLE 1 Number of studies according to age categories, total number of participants, percentage female, and race/ethnicity reporting[1]

	Unique studies,[2] *n*	Total participants,[3] *n*	% Female[3]	Race/ethnicity reported (N/Y)[3]
VitD/Ca and BMD/BMC ($n = 45$)				
0–6 mo	3	302	50	1/2
7 mo–2 y	0	0	—	—
3–8 y	0	0	—	—
9–18 y	7	1258	93	1/6
19–50 y	6	745	74	3/3
51–70 y	27	46,837	99	15/12
≥71 y	11	5764	97	10/1
Pregnant	0	0	—	—
Age NR	1	51	55	1/0
Na and SBP/DBP ($n = 62$)				
0–6 mo	1	476	48	1/0
7 mo–2 y	1	58	NR	0/1
3–8 y	2	378	55	2/0
9–18 y	7	1896	54[4]	4/3
19–50 y	21	6894	42[5]	11/10
51–70 y	34	4161	49	20/14
≥71 y	3	1131	61	3/0
Pregnant	3	673	0	1/2
Age NR	4	327	0[6]	4/0
K and SBP/DBP ($n = 21$)				
0–6 mo	0	0	—	—
7 mo–2 y	0	0	—	—
3–8 y	0	0	—	—
9–18 y	2	286	50[7]	0/2
19–50 y	12	1323	39[8]	2/10
51–70 y	9	575	42[9]	6/3
≥71 y	0	0	—	—
Pregnant	0	0	—	—
Age NR	1	50	NR	1/0

[1] BMC, bone mineral content; BMD, bone mineral density; DBP, diastolic blood pressure; NR, not reported; N/Y, no/yes; SBP, systolic blood pressure; VitD, vitamin D.
[2] Study tallies were derived using mean age and age range data. Hence, studies reporting participant age range were frequently included in multiple age categories.
[3] Studies reporting participant age range that included multiple categories and did not report category breakdown, hence, the data in the table represent the total study populations only.
[4] Female (%) of 1064 total participants in 6 studies.
[5] Female (%) of 6062 total participants in 20 studies.
[6] Female (%) of 77 total participants in 1 study.
[7] Female (%) of 210 total participants in 1 study.
[8] Female (%) of 1096 total participants in 9 studies.
[9] Female (%) of 485 total participants in 7 studies.

group, studies included a VitD-only group, Ca-only group, and/or combined VitD/Ca group. The control/placebo intervention likewise varied among studies (Supplemental Table 1).

For the studies designed to reduce Na intake, 63% involved dietary advice/lifestyle counseling compared with standard care or habitual diet (Supplemental Table 1). The other 37% of studies were designed to reduce Na intake by providing placebo pills (compared with salt-containing pills), low-sodium water (compared with high-sodium water), salt substitutes (compared with table salt), low-sodium formula (compared with regular-sodium formula), or other low-sodium items (e.g., tomato juice and bread) for substitution of habitually consumed items. For studies designed to increase K intake, 90% provided the nutrient as a supplement or a placebo (lactose, microcrystalline cellulose, or unstated composition). The remaining 10% of studies compared K-enriched bread with conventional bread or counseling for increasing dietary K in the habitual diet.

The duration of the VitD/Ca studies ranged from 3 mo to 9 y (Supplemental Table 1). The duration of the Na/K intervention studies ranged from 3 to 36 mo. The intervention periods appeared to be related to the natural course of the outcomes.

Discussion

Systematic reviews are now an indispensable component of the process used to establish and re-evaluate DRI values. The usefulness of these reviews is dependent on the study design and statistical power, participant characteristics, nutrient

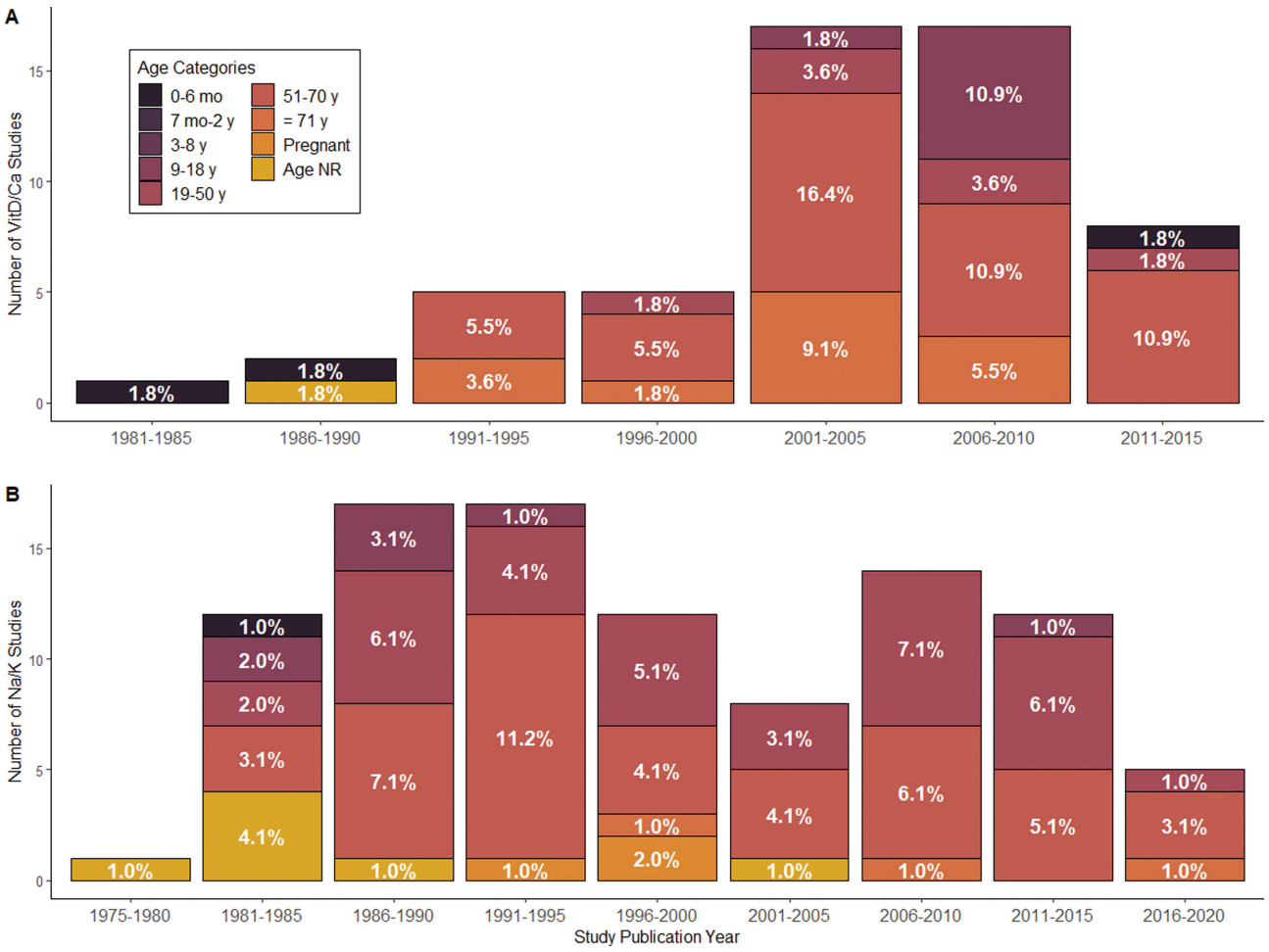

FIGURE 1 VitD/Ca (A) and Na/K studies (B) reporting mean age or age range by publication year. Study tallies were derived using mean age or range data. Studies reporting participant age ranges spanning >1 category appear multiple times. NR, not reported; VitD, vitamin D.

dosages and comparator, and format in which the data are reported in the included studies (11). In the past 10 y, 2 groups of DRI values, VitD/Ca and Na/K, have been re-evaluated. To facilitate this work, the federal agencies that sponsor the DRI reviews contracted with the AHRQ to perform systematic reviews on predefined questions to support the DRI committees' deliberations. For this perspective, we examined 125 trials that met the inclusion/exclusion criteria for the systematic reviews and included data for BMD/BMC and SBP/DBP for VitD/Ca and Na/K, respectively. We identified some common issues that might facilitate future NAM approaches to re-evaluating DRI values.

In terms of age, sex, pregnancy and lactation, and nutrient dosage, primary studies of essential nutrients are seldom designed to yield data tailored for the needs of the DRI committees. No predefined guidance or a priori recommendations currently exist to encourage the design, execution, and funding of studies that target essential nutrients for which data are lacking, or toward age, sex, and pregnancy and lactation categories of public health concern. In the future, consideration should be given to identifying areas of highest need by developing criteria on which to base this assessment. For example, re-evaluating the current age/sex categories for each nutrient individually, or, for the case of children and potentially adults, formulating recommendations based on body weight or energy needs. Of note, in terms of human clinical controlled trials, generating data is a lengthy process; thus, there is typically a time lag between identifying a need and data becoming available. This should be taken into consideration when formulating timelines for re-evaluation. Newer design approaches are being explored such as N-of-1 studies (12, 13) and application of artificial intelligence (14). With respect to research funding priorities, consideration should be given to developing criteria to identify which DRI values—Estimated Average Requirement (EAR), RDA, UL, AMDR, and CDRR—are of highest priority and relevance for each individual nutrient.

Approximately half of the studies included in the systematic reviews provided data for racial or ethnic distributions of the study participants. The importance of this biological variable has yet to be adequately adjudicated. In terms of demographic changes, the populations of the United States

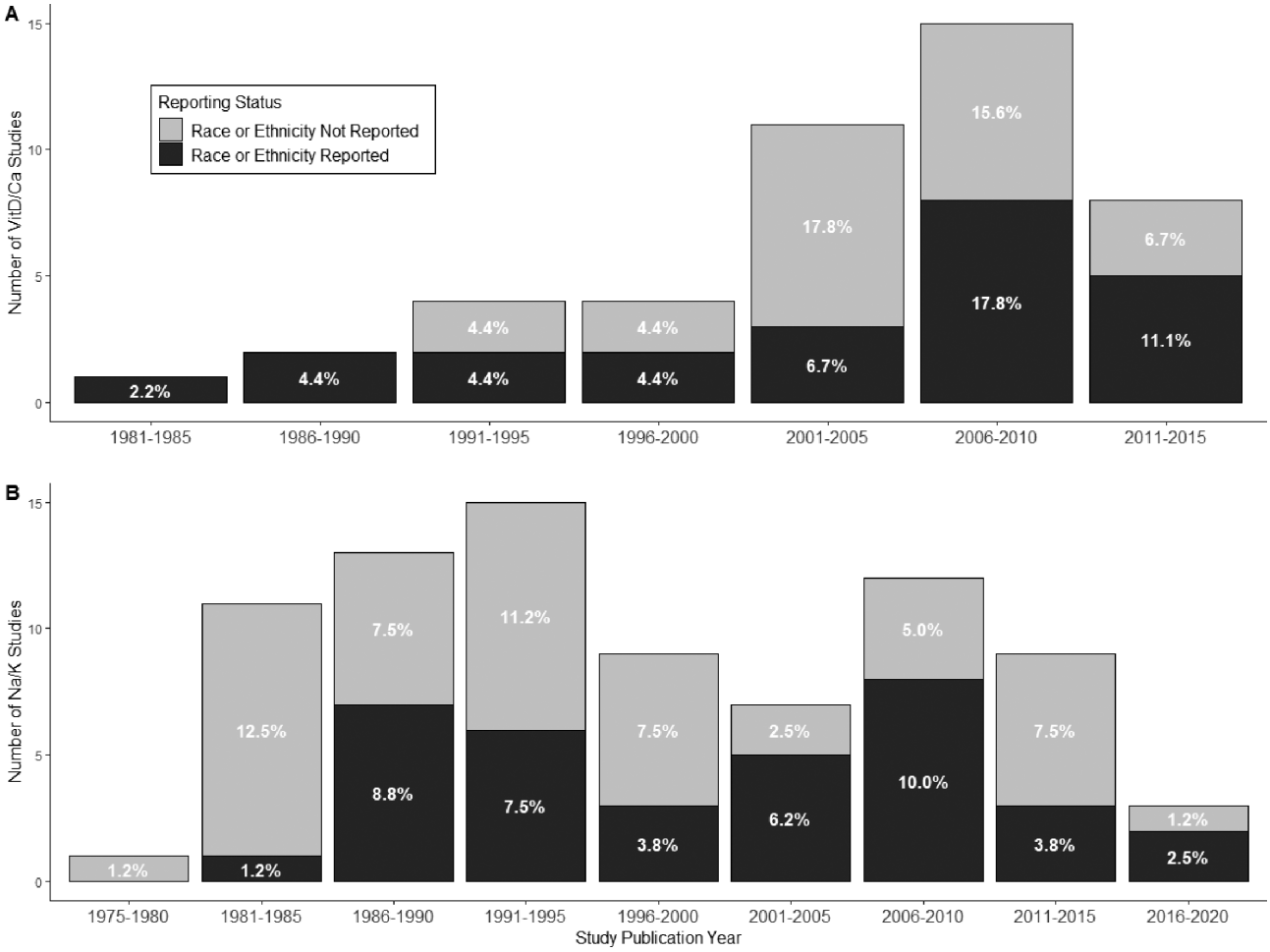

FIGURE 2 VitD/Ca (A) and Na/K (B) studies reporting data on race/ethnicity by publication year. VitD, vitamin D.

and Canada are shifting toward becoming majority-minority. Hence, the importance of developing a better understanding of this biological variable continues to increase. Incomplete reporting of race/ethnicity and inadequate statistical power to address the variable restrict the degree to which the DRI values are generalizable.

As defined in 1994 by the Food and Nutrition Board of the NAM, RDA values are intended to be recommended nutrient intake values "… judged on the basis of available scientific evidence to meet the known nutritional needs of practically all healthy persons …" (15). The challenge now is whether the definition is current. In the United States, ∼42% of adults have obesity and ∼67% have overweight or obesity (16, 17). In Canada, ∼27% of adults have obesity and ∼63% have overweight or obesity (18). Similarly, there are high rates of individuals with chronic diseases, such as cardiometabolic disorders. Body weight and chronic disease risk frequently coexist. The current range and distribution of body weights, body compositions, and chronic disease risk factors will likely have direct relevance when establishing future DRI values. One example is the apparent sequestration of vitamin D in adipose tissue (19, 20). The biological consequences have yet to be fully elucidated.

There was a wide range of approaches used to modify nutrient intakes among the trials included in the systematic reviews. They included providing all foods and beverages; enriching or depleting the nutrient content in selected foods and beverages; nutrient supplements; and counseling to modify dietary patterns to promote a change in nutrient intake. Likewise, the absolute amounts of the nutrients were manipulated using a variety of approaches. They included using commercially available foods, specially formulated foods, and supplements. A wide range of control interventions/placebo substances were used, as well as approaches to assess food intake in response to the interventions. After identifying data gaps, it may be of value to develop standardized intervention foods and supplements, diet assessment tools, and protocols for behavior change assessment to facilitate the combination of data from multiple trials.

The most recent approach used to re-evaluate DRI values was to consider nutrients associated with common outcomes: Na and K, and blood pressure; and Ca and VitD, and bone

health. VitD/Ca also tend to be consumed together (e.g., in cow and plant-based milks) or as supplements (calcium plus vitamin D). For Na/K, there is no direct relation between their occurrence in food sources or supplements. In terms of translating the DRI values into the most efficacious guidance, an analysis of the benefits and risks of studying nutrients independently or in combination warrants exploration. This issue extends beyond those nutrients for which biological relations have been established. Given the widespread enrichment and fortification of the food supply, along with accessible over-the-counter supplements in the United States and Canada, teasing out the independent effect of each nutrient may no longer be feasible or relevant. One example is mandatory enrichment of refined grains with thiamin, niacin, riboflavin, and folate. Modeling scenarios where nutrients are considered independently and in combinations based on biological function and occurrence in the food supply may be of benefit.

In 2017, a 2-part consensus study of the Dietary Guidelines for Americans development process was conducted by an ad hoc committee under the auspices of the National Academies of Sciences, Engineering, and Medicine in response to a request from Congress (21, 22). The DGAs tend to be food based, whereas the DRIs are nutrient based. Among other issues addressed, one that may be helpful to consider in terms of the DRI re-evaluation process was the recommendation that the sponsoring agencies prioritize topics to be reviewed in each cycle, and redistribute the current functions of the Dietary Guidelines Advisory Committee to 3 separate groups: Dietary Guidelines Planning and Continuity Group to monitor and curate evidence generation, to identify and prioritize topics for inclusion in the Dietary Guidelines for Americans, and to provide strategic planning support across Dietary Guidelines for Americans cycles; technical expert panels to provide content and methodological consultation during evaluation of the evidence; and a Dietary Guidelines Scientific Advisory Committee to interpret the scientific evidence and draw conclusions. Applying some of these recommendations to the DRI re-evaluation process may help target and focus the efforts to those aspects of the nutrients under review for which there is the highest public health concern.

Summarized in this commentary were the studies for specific outcomes included in the AHRQ systematic reviews commissioned for DRI committees tasked with re-evaluating VitD/Ca and Na/K. Several important issues were identified. The available studies did not report the age data in a manner consistent with the current DRI categories. In some categories for which DRI values are derived, including pregnancy and lactation, there is a dearth of data. A wide variety of study interventions was used. This makes it challenging to combine data to accurately derive or re-evaluate DRI values. There is an under-representation of data on the basis of race/ethnicity, an understudied biological variable. Currently, the DRI values are intended for a "healthy" population. Much of the US and Canadian populations are not classified as "healthy" based on body weight alone. Consideration should be given to establishing values for the majority of individuals. Moving forward, it would be advantageous to develop a process to prospectively target research funding for studies designed to generate data that will most closely support re-evaluation of DRI values. To this end, potential approaches may be through the Agriculture and Food Research Initiative competitive grants program, USDA Human Nutrition Research Centers, and requests for proposals from the NIH. Generating new data takes time. Taking a long view by defining future needs and developing a process to fulfill those needs may be a valuable first step.

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