Project title: Vitamin D or Calcium and Health Outcomes in Infants and Children Less than Three Years Old: A systematic review for the World Health Organization (WHO)

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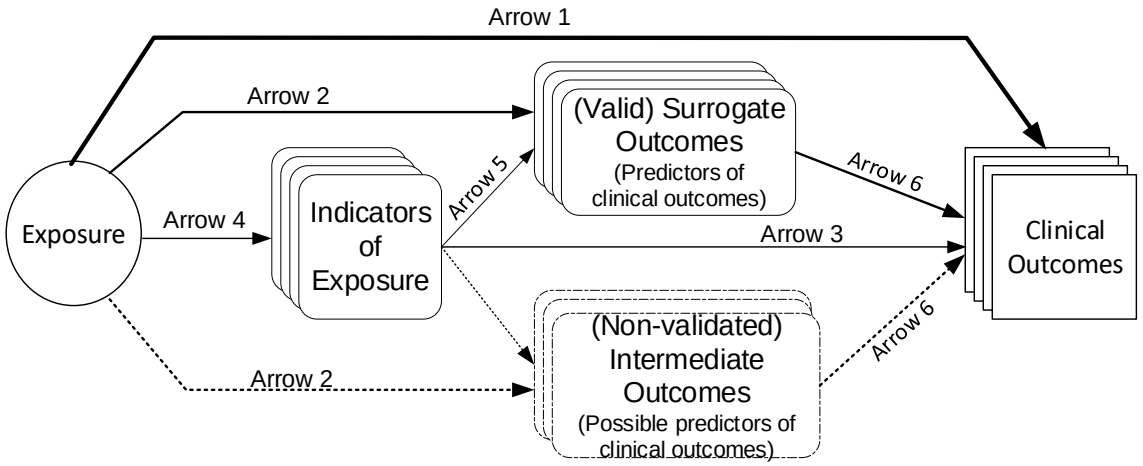
Background

The federal agencies of the U.S. and Canadian governments involved in the Dietary Reference Intake (DRI) process utilize a generic analytic framework (Figure 1)[1] to formulate the Key Questions (KQs) for the systematic reviews to support the development of DRI values. The term "Indicators of Exposure (Nutrient Intake)" as defined within DRI context are measures that correlate with dietary intake of a nutrient, such as nutrient biomarkers, nutritional status, or markers of nutritional status. Indicators of vitamin D exposure (i.e., vitamin D intake and sun exposure) included serum 25(OH)D and $1,25(OH)_2D$ concentrations. Indicators of dietary calcium intakes included calcium balance (i.e., calcium accretion, retention, and loss).[2] Dose-response randomized controlled trials (RCTs) that assess the effects of different nutrient intake levels on age-specific clinical outcomes of public health importance (Arrow 1 in Figure 1) would provide the best direct evidence for setting DRIs. However, such evidence is often lacking for chronic disease endpoints, same as the case shown in the scoping review of vitamin D or calcium and health outcomes in infants and children less than three years old (refer to as "the scoping review" herein). In the absence of direct evidence, it was suggested that a "piecemeal approach" as an option for setting DRIs.[3] For example, data that address the dose-response relationship between nutrient intake and indicators of exposure or surrogate outcomes (Arrows 4 and 5 in Figure 1) can be synthesized with data that address the relation between indicator of exposure and clinical outcomes (Arrow 3 in Figure 1) to set DRIs. This "piecemeal approach" has the advantage of relying on a wider

breadth of the available evidence but the approach would be fraught with uncertainties.[3]

Figure 1. A generic analytic framework to assist formulation of Key Questions for the development of DRIs.



Arrow 1: Association of exposure with clinical outcomes of interest.
Arrow 2: Association of exposure with surrogate or intermediate outcomes (with good or possible evidence for linkage with clinical outcomes).
Arrow 3: Association of indicators of exposure to clinical outcomes.
Arrow 4: Association between exposure and indicators of exposure.
Arrow 5: Association of indicators of exposure to surrogate or intermediate outcomes (with good or possible evidence for linkage with clinical outcomes).
Arrow 6: Association between surrogate outcomes (with good or possible evidence for linkage) and clinical outcomes.

Preliminary Key Questions

Findings in the scoping review and the generic analytic framework (Figure 1) were used to draft the preliminary KQs. The population of interest for all KQs is generally healthy infants or children less than three years old. KQs 1, 2, and 4 will synthesize randomized controlled trial (RCT) evidence, while KQs 3 and 5 will synthesize evidence from prospective cohort studies and nested case-control or case-cohort studies. Evidence for Arrow 6 (the associations between surrogate or intermediate outcomes and clinical outcomes) is not assessed, because it is typically

relied on expert opinions. The list of outcomes of interest in the KQs were chosen based on the findings in the scoping review with regards to the amount of available evidence for those outcomes, as well as their public health importance.

KQ 1: What is the effect of vitamin D, calcium, or combined vitamin D and calcium intakes on clinical outcomes, including growth, neuropsychological development, infectious disease, autoimmune disease, asthma/wheezing, and fracture? (Arrow 1 in Figure 1)

Sub-question 1a. Is there a dose-response relationship between vitamin D or calcium intake levels and the clinical outcomes?

Sub-question 1b. Is the effect differed by types of vitamin D or calcium intake (e.g., food source versus supplements, or different formulation of supplements)?

KQ 2. What is the effect of vitamin D, calcium, or combined vitamin D and calcium intakes on bone mineral density (BMD) or bone mineral content (BMC)? (Arrow 2 in Figure 1)

Sub-question 2a. Is there a dose-response relationship between vitamin D or calcium intake levels and BMD or BMC?

Sub-question 2b. Is the effect differed by types of vitamin D or calcium intake (e.g., food source versus supplements, or different formulation of supplements)?

KQ 3. What is the association between serum 25(OH)D concentrations and clinical outcomes, including growth, neuropsychological development, infectious disease, autoimmune disease, asthma/wheezing, and fracture? (Arrow 3 in Figure 1)

Sub-question 3a. Is there a dose-response relationship between serum 25(OH)D concentrations and the clinical outcomes?

KQ 4. What is the effect of vitamin D or combined vitamin D and calcium intakes on serum 25(OH)D concentrations? (Arrow 4 in Figure 1)

Sub-question 4a. Is there a dose-response relationship between vitamin D or calcium intake levels and serum 25(OH)D concentrations?

Sub-question 4b. Is the effect differed by types of vitamin D or calcium intake (e.g., food source versus supplements, or different formulation of supplements)?

KQ 5. What is the association between serum 25(OH)D concentrations and bone mineral density or bone mineral content? (Arrow 5 in Figure1)

Sub-question 5a. Is there a dose-response relationship between serum 25(OH)D concentrations and BMD or BMC?

References

1. Russell R, Chung M, Balk EM, 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*. Mar 2009;89(3):728-733.

2. Chung M, Balk EM, Brendel M, et al. Vitamin D and calcium: a systematic review of health outcomes. *Evid Rep Technol Assess (Full Rep)*. Aug 2009(183):1-420.

3. Yetley EA, MacFarlane AJ, Greene-Finestone LS, et al. Options for basing Dietary Reference Intakes (DRIs) on chronic disease endpoints: report from a joint US-/Canadian-sponsored working group. *Am J Clin Nutr*. Jan 2017;105(1):249S-285S.