The DRI Process: Considerations for Assessing Omega-3 Fatty Acids and Cardiovascular Disease in the DRI Framework of Chronic Disease Risk

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Conflict of Interest

- Member, DRI Committee for Calcium and Vitamin D
- Member, DRI Committee for Sodium and Potassium

Objectives

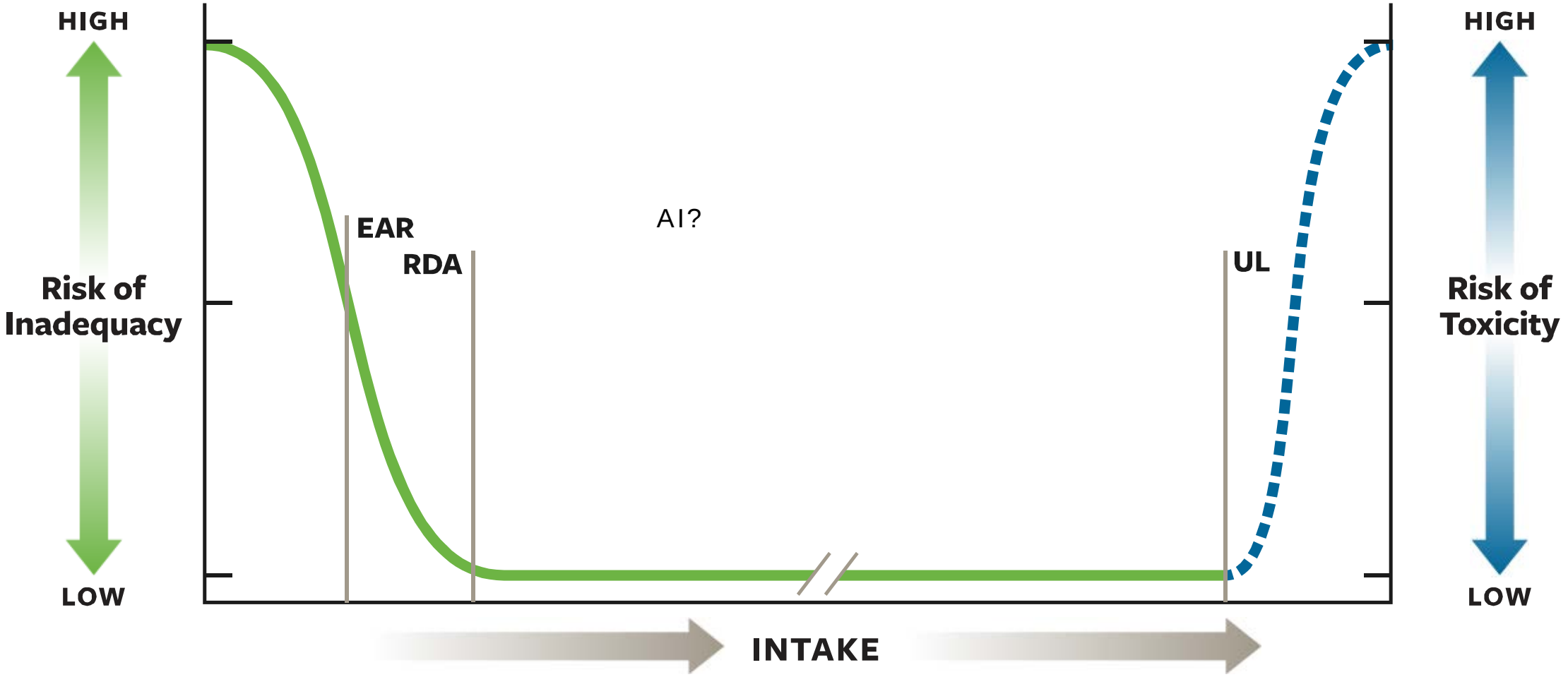
- Understand how the Expanded Dietary Reference Intakes include CDRR and chronic disease outcomes
- Relate what is needed for the nature and strength of evidence to consider a chronic disease outcome
  - Causality of Relationship
  - Intake-Response Relationship
- Consider implications for omega 3 fatty acids

Assumptions of DRI Framework: Adequacy

- **Meets needs of 'apparently healthy population'**
  - **Includes a diverse population**
    - **Many vary in their health conditions (obesity, etc.)**
    - **Many are at risk for one or more chronic diseases**
  - **Excludes those who**
    - **Have chronic disease that requires management with medical foods *and medical nutrition therapy***
    - **Are malnourished or undernourished**
    - **Have diseases resulting in malabsorption or requiring dialysis**
    - **Have altered energy needs due to disability or altered mobility**
- **Need varies, generally normally distributed across population**

Adapted in part from *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease Outcomes.* 2017, National Academies Press

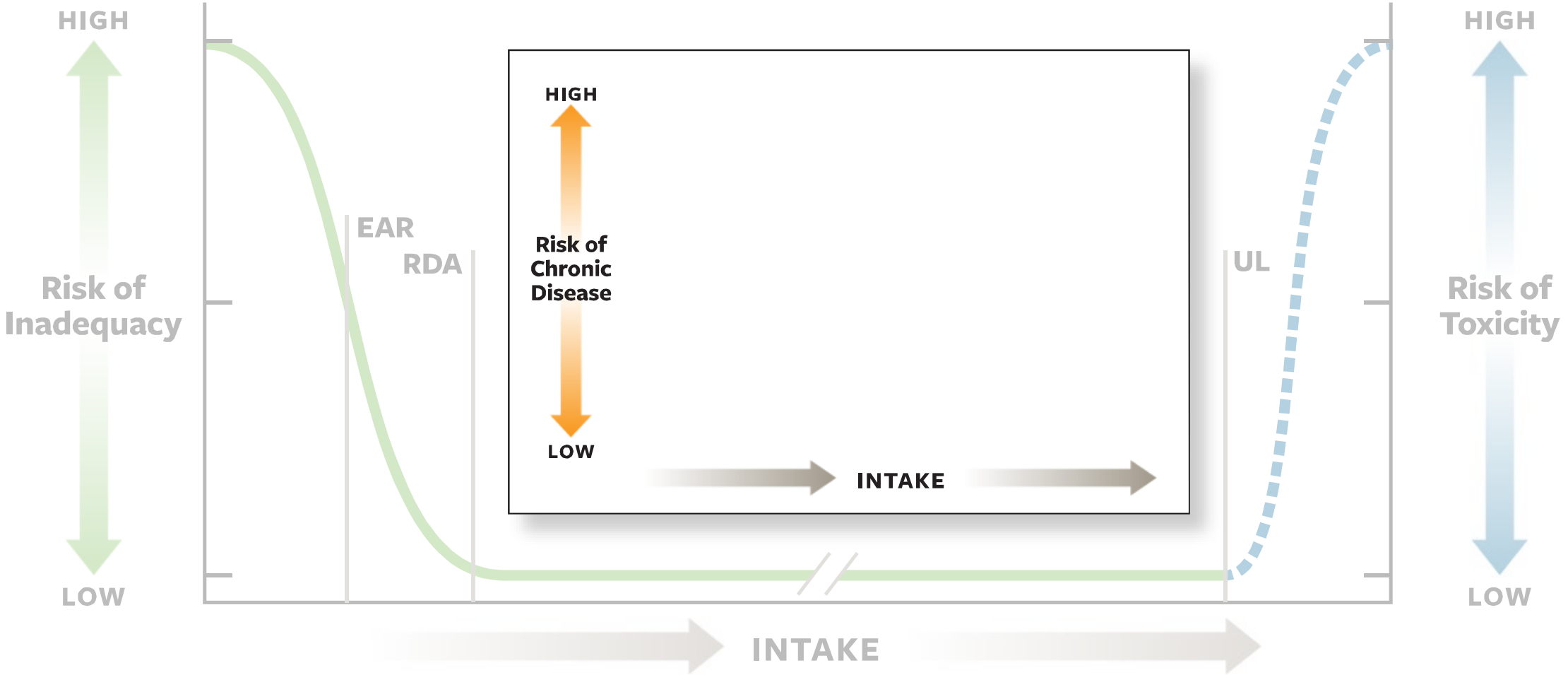
Expanded Dietary Reference Intakes with CDRR and Chronic Disease Outcomes



Expanded DRI Framework Resulted in Change for UL for Sodium in 2019

UL for Sodium	
2005	**2019**
2300 mg/d based on sodium-blood pressure relationship (a ***chronic disease*** indicator outcome)	**Not determined** due to lack of toxicologic indicator

Expanded Dietary Reference Intakes with Chronic Disease Risk Reduction (CDRR) and Chronic Disease Outcomes



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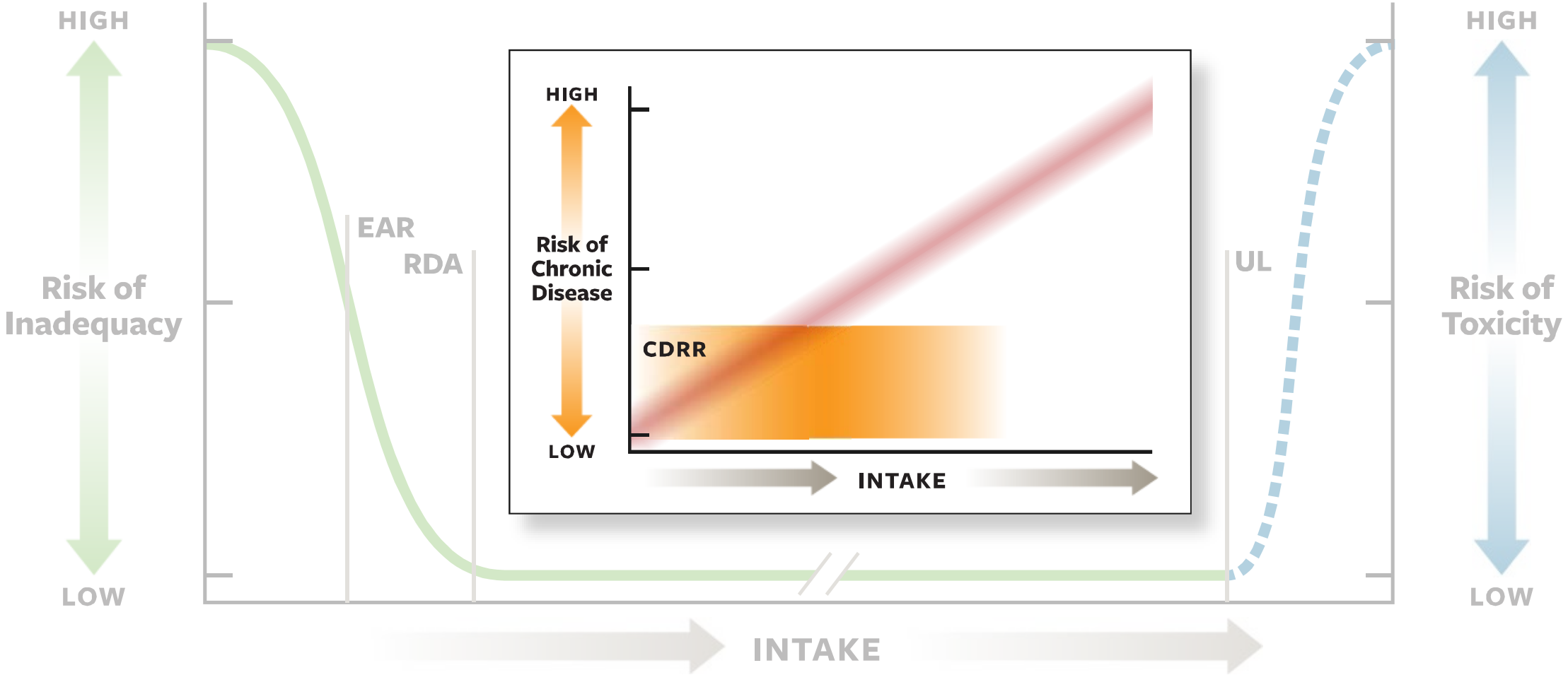

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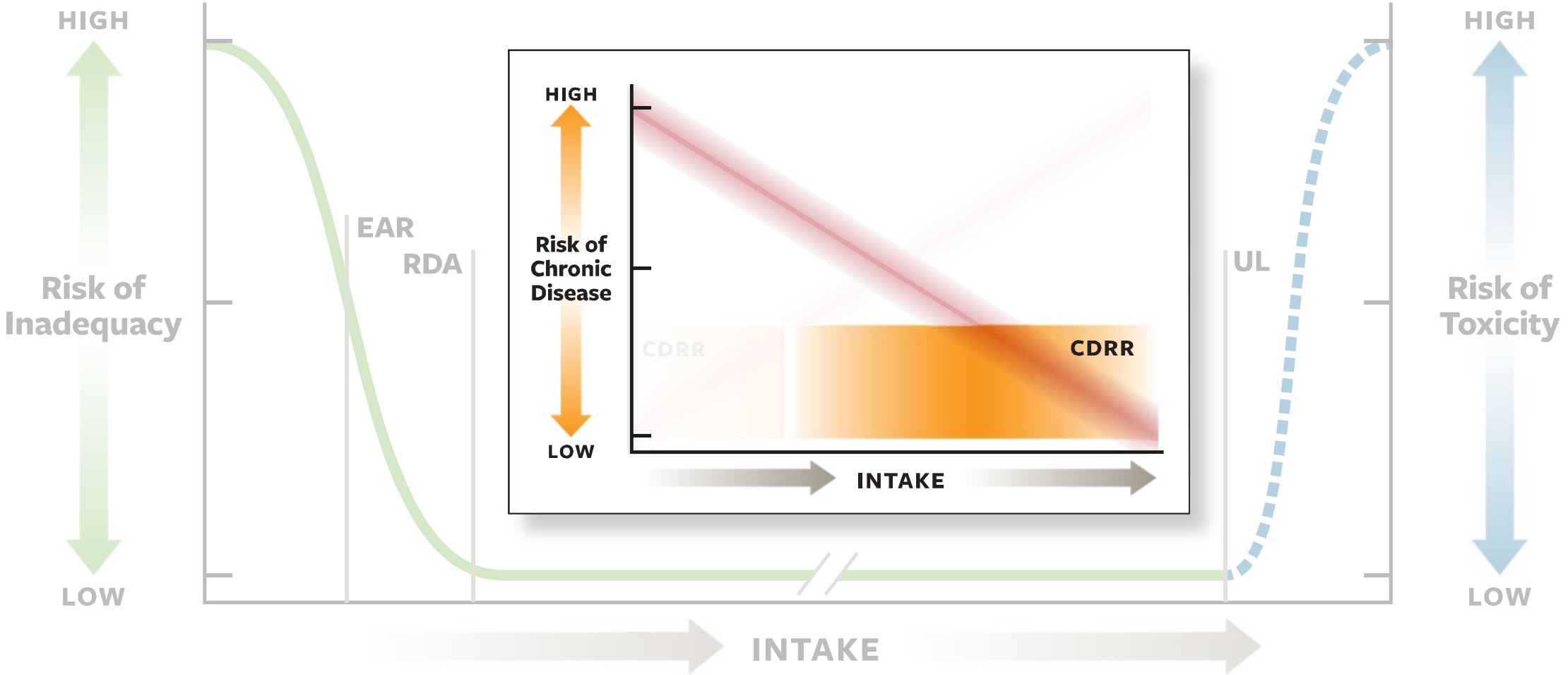

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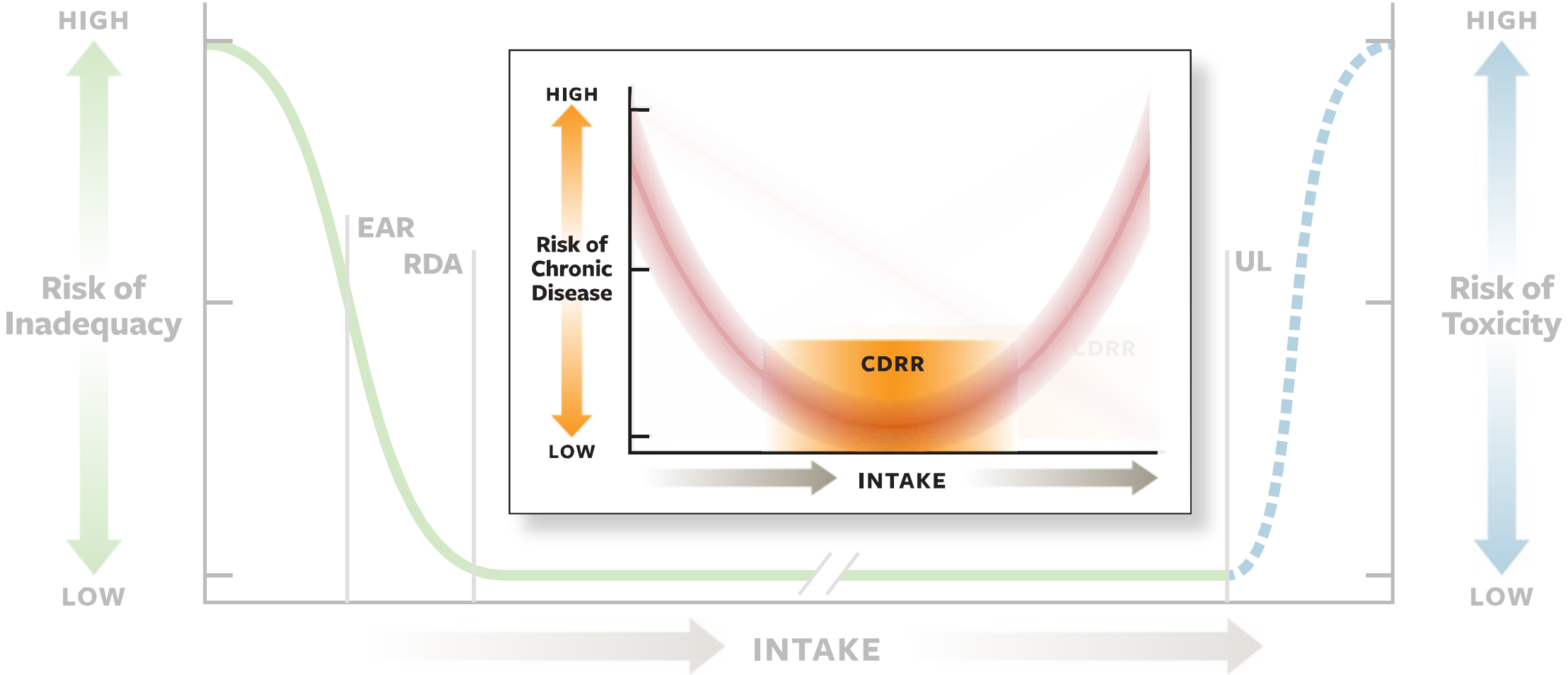
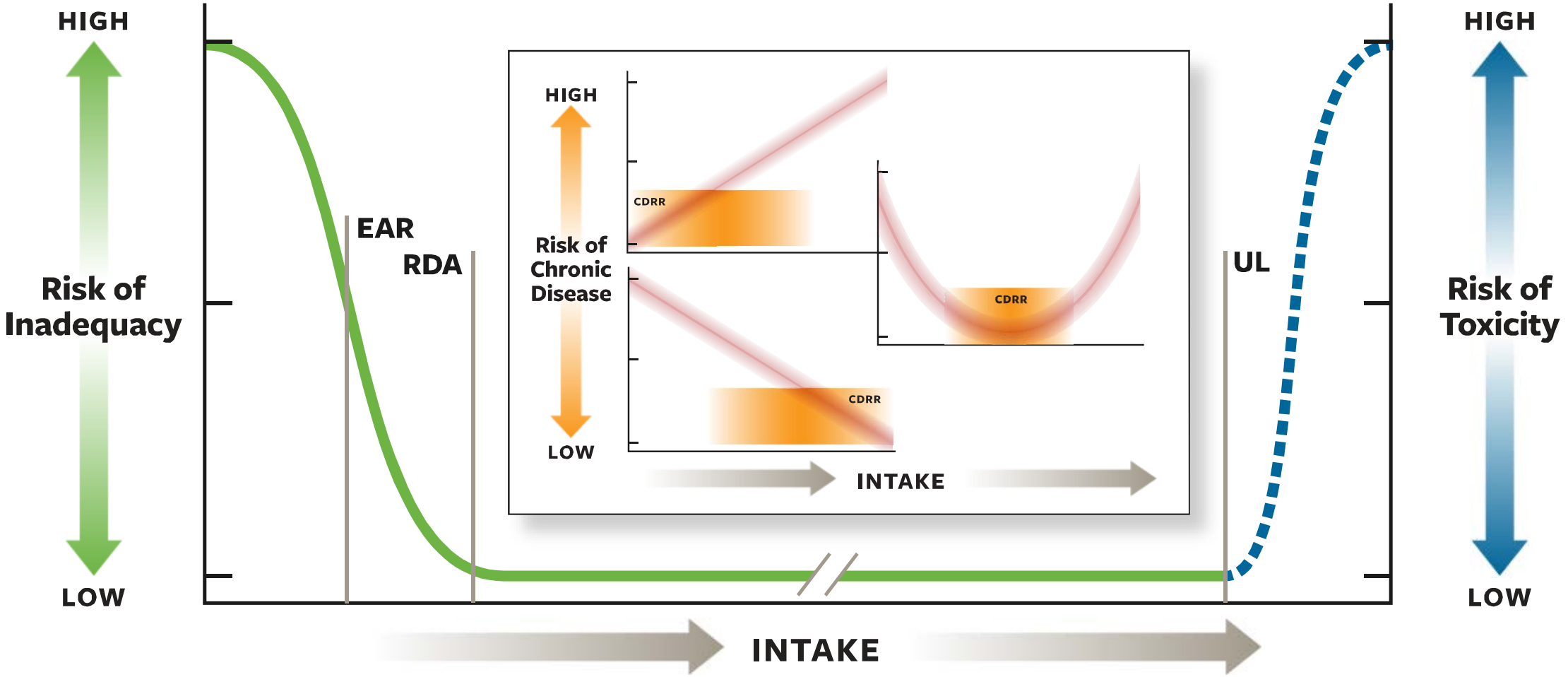
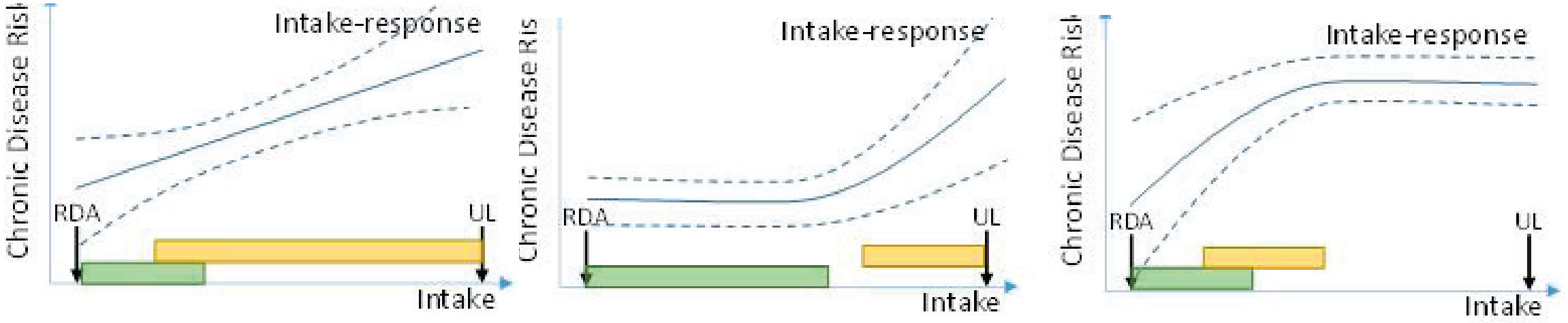


Expanded Dietary Reference Intakes with CDRR and Chronic Disease Outcomes



DRI and Possible Intake Relationships for Increased Risk with Increased Intakes



Possible Dietary Reference Intake Ranges for a Single Chronic Disease

= Acceptable Range of Intakes

= Range of Beneficial Decreased Intakes

CDRR →

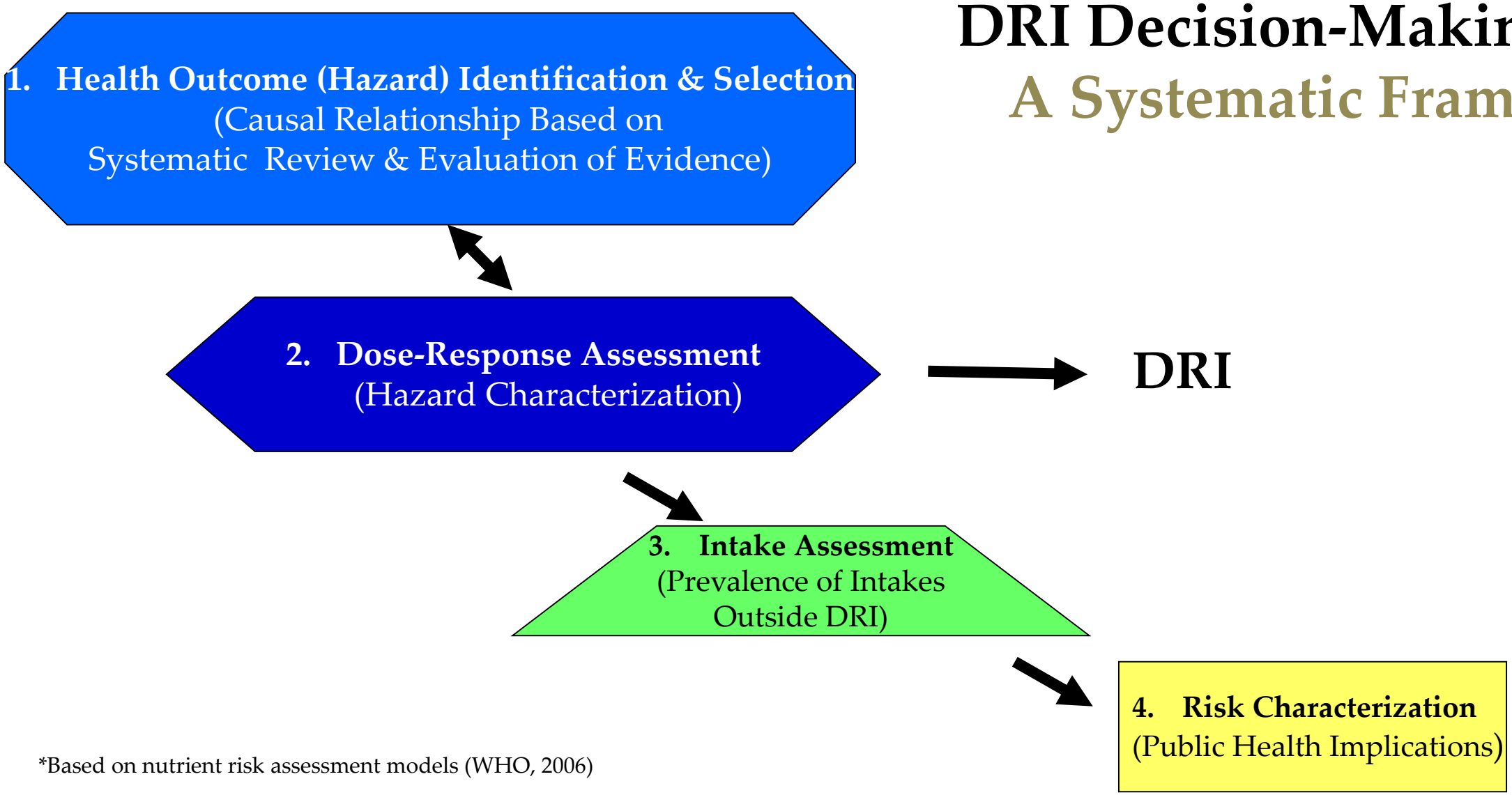
Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease Outcomes. 2017, National Academies Press

Distinctions Between DRI for Adequacy/Toxicity and Chronic Disease

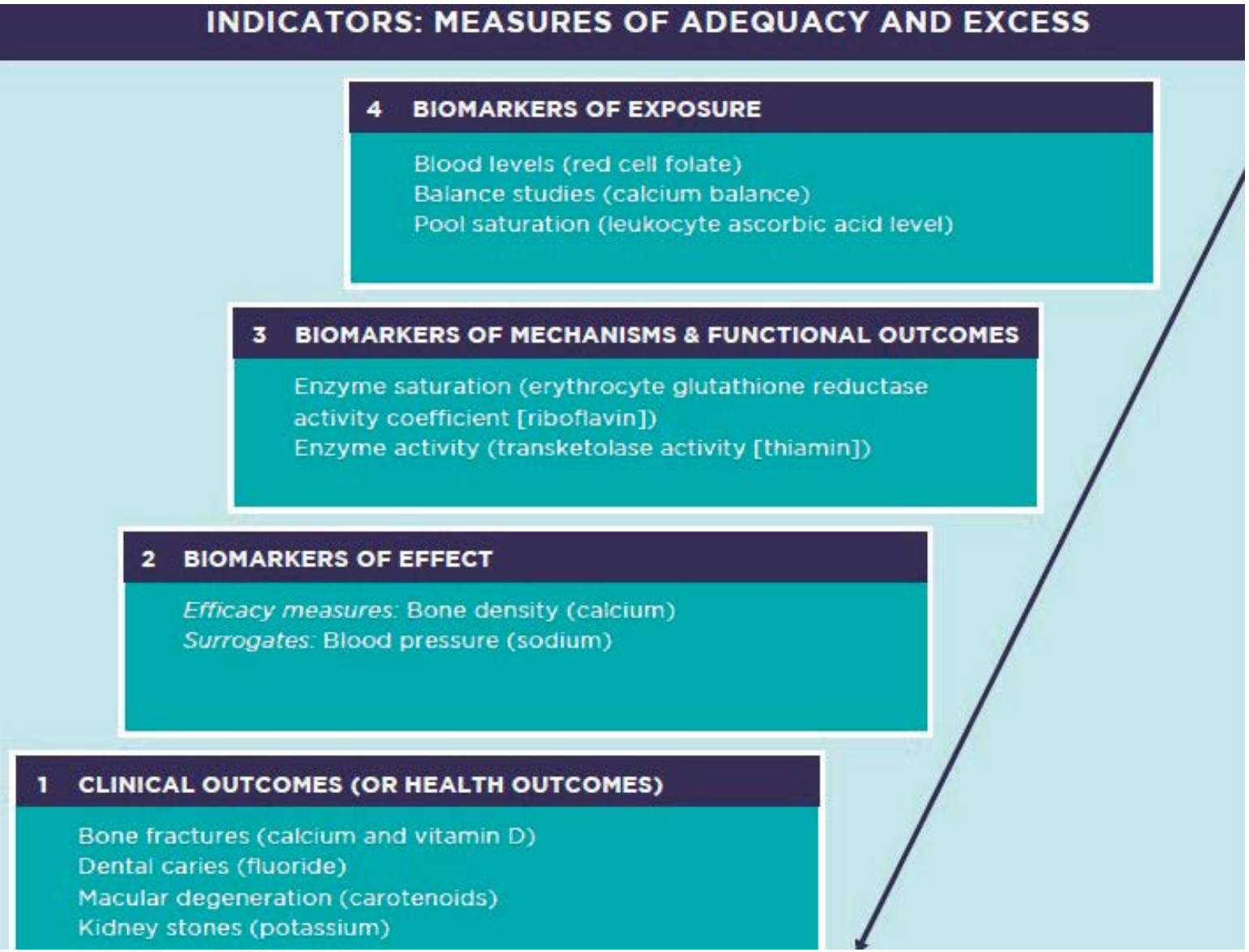
DRI for Adequacy/Toxicity	DRI for Chronic Disease
Needed because of deficiency (essential) or toxicity of a **nutrient**:	Not warranted unless sufficient evidence exists for **nutrient or naturally-occurring food substance (NOFS)** because risk of chronic disease:
• Affects everyone if intake is inadequate or excessive	• Varies by individual, age and lifestage • Is relative and can be small
• Is caused by single nutrient	• Related often to many factors (individual and environmental)
• Is prevented by nutritional interventions	• Is only partly ameliorated by nutritional intervention

Adapted from *Dietary Reference Intakes for Sodium and Potassium*. 2019, National Academies Press

DRI Decision-Making Steps:
A Systematic Framework

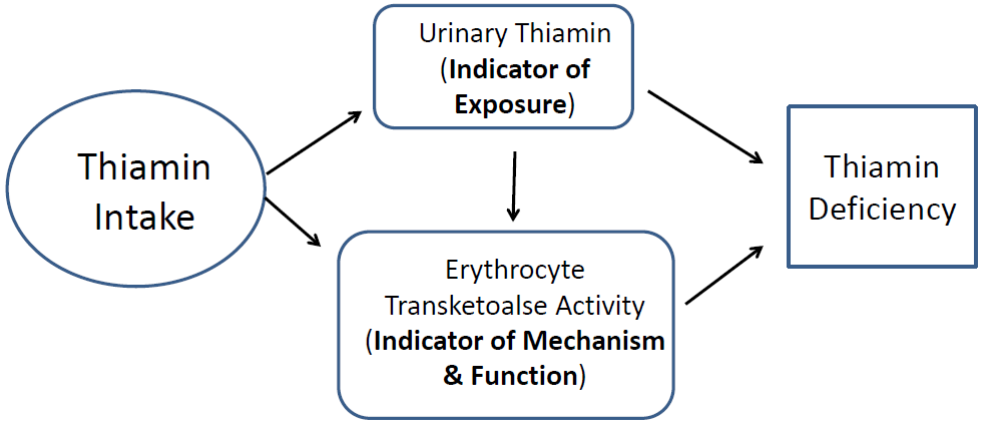


*Based on nutrient risk assessment models (WHO, 2006)



Evidence for Selection of Adequacy/Toxicity Outcomes

- **Indicator of status (biomarkers), on the causal pathway for disease of deficiency**



Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease Outcomes. 2017, National Academies Press

Yetley et al. Am J Clin Nutr 2017; 105(Suppl):249S.

INDICATORS: MEASURES OF ADEQUACY AND EXCESS

4 BIOMARKERS OF EXPOSURE

Blood levels (red cell folate)
Balance studies (calcium balance)
Pool saturation (leukocyte ascorbic acid level)

3 BIOMARKERS OF MECHANISMS & FUNCTIONAL OUTCOMES

Enzyme saturation (erythrocyte glutathione reductase activity coefficient [riboflavin])
Enzyme activity (transketolase activity [thiamin])

2 BIOMARKERS OF EFFECT

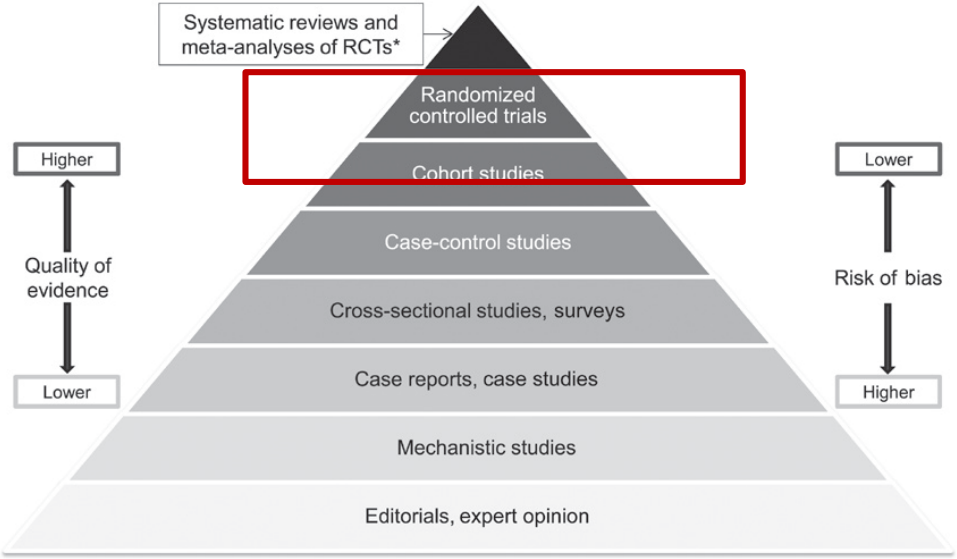
Efficacy measures: Bone density (calcium)
Surrogates: Blood pressure (sodium)

1 CLINICAL OUTCOMES (OR HEALTH OUTCOMES)

Bone fractures (calcium and vitamin D)
Dental caries (fluoride)
Macular degeneration (carotenoids)
Kidney stones (potassium)

Evidence for Selection of Adequacy/Toxicity Outcomes

- **Indicator of status (biomarkers), on the causal pathway for disease of deficiency**
- **Direct evidence of disease of deficiency or adverse effect**
- **High certainty of causal & intake-response relationships (RCT, metabolic/balance, depletion/repletion studies)**



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Insufficient Evidence to Support Selection of Adequacy Indicator for Sodium or Potassium: Approach to AI Differed

Potassium

Median intakes of healthy US/CN populations appropriate for AI (No CDRR)

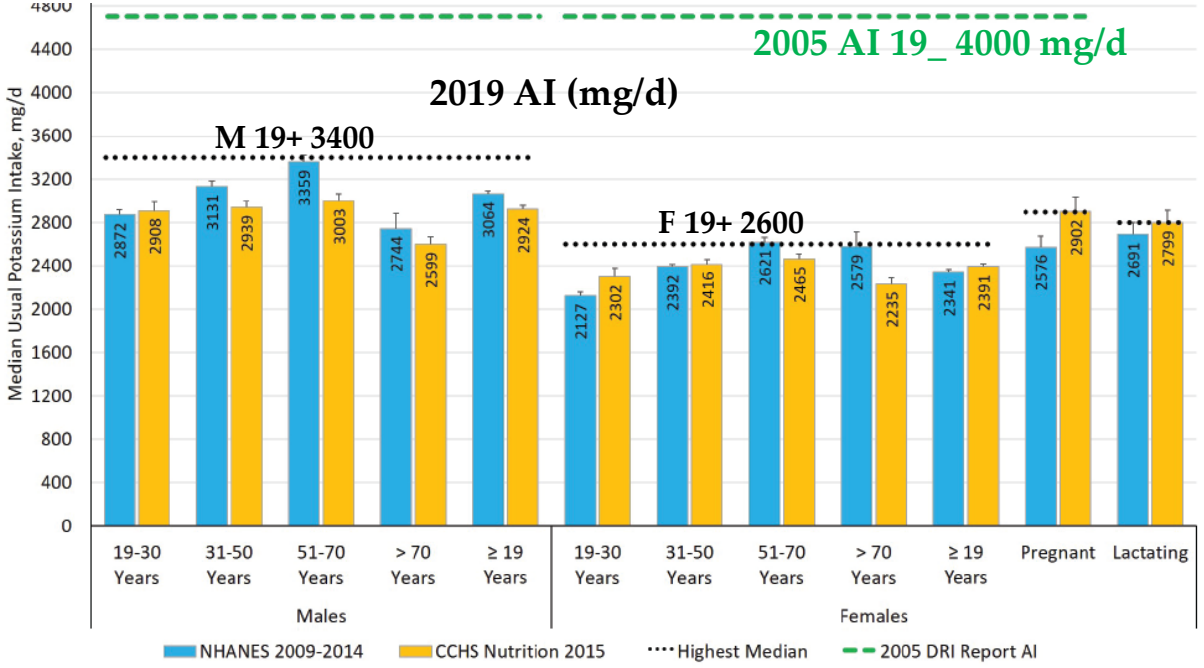


FIGURE 4-2 Median usual potassium intake of U.S. and Canadian normotensive adults 19 years of age and older.

Sodium

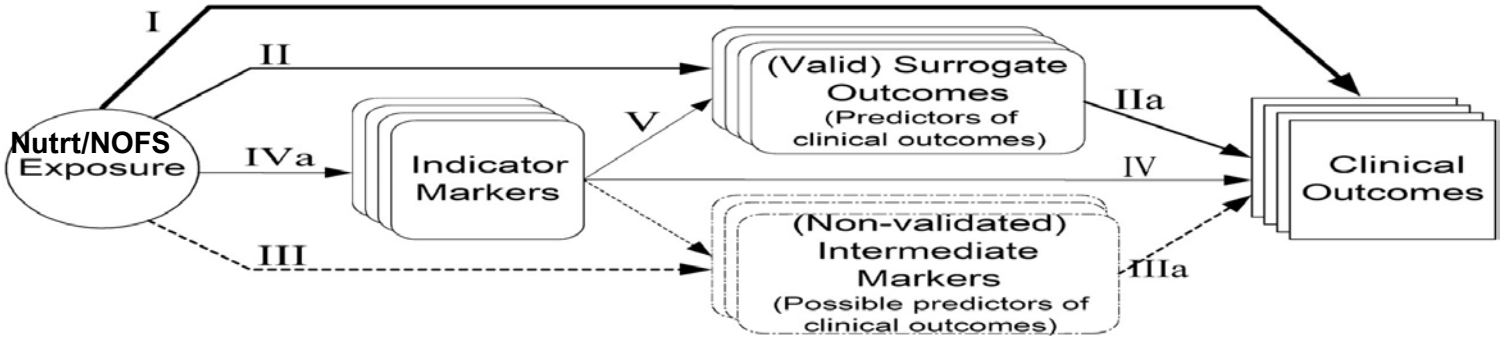
Median sodium intakes > CDRR so median intake of 'healthy' US/CN population not appropriate for AI

- **Committee concluded lowest levels of sodium intake evaluated in best designed RCT and evidence from best designed balance studies (limited in number) congruent in adults and used to set AI.**
- **Extrapolated to children 1-18 yr based on sedentary EER.**
- **AI for 19+ yr 1500 mg/d**

Evidence for Selection of Chronic Disease Outcome

- **At least moderate strength of evidence (GRADE) for causal association of nutrient or NOFS with chronic disease outcomes**
  - **Assess strength of evidence for single chronic disease outcome (IDEAL) or single qualified surrogate outcome individually (no aggregate of outcomes)**
  - **Nature of evidence may vary from that for adequacy**
    - **More evidence may be from observational studies than RCTs**
    - **Lower certainty of causal relation**
      - **Inherently higher risk of bias**
        - **Selection, confounding, etc.)**
        - **Methodologic (*intake assessment*, exposure-disease continuum across lifespan, outcome assessment)**
          - **More use of qualified surrogate outcomes**
        - **Publication**

Evidence for Selection of Chronic Disease Outcomes: Qualifying a Surrogate Outcome



For reproducible, analytically-validated surrogate outcomes, evidentiary process requires that the surrogate outcome:

- **Is on causal pathway (observational and small intervention studies)**
- **Is concordant with changes in health outcome with specific nutritional intervention (rigorous clinical trials)**
  - **Explains a clinically significant proportion of response to nutritional intervention**
- **Predicts accurately (prognostic value) effect of nutritional intervention on clinical outcome (rigorous clinical trials**

Adapted from Russell et al. Opportunities and challenges in conducting systematic reviews to support the development of nutrient reference values: vitamin A as an example. American Journal of Clinical Nutrition. 2009; 89:728–33
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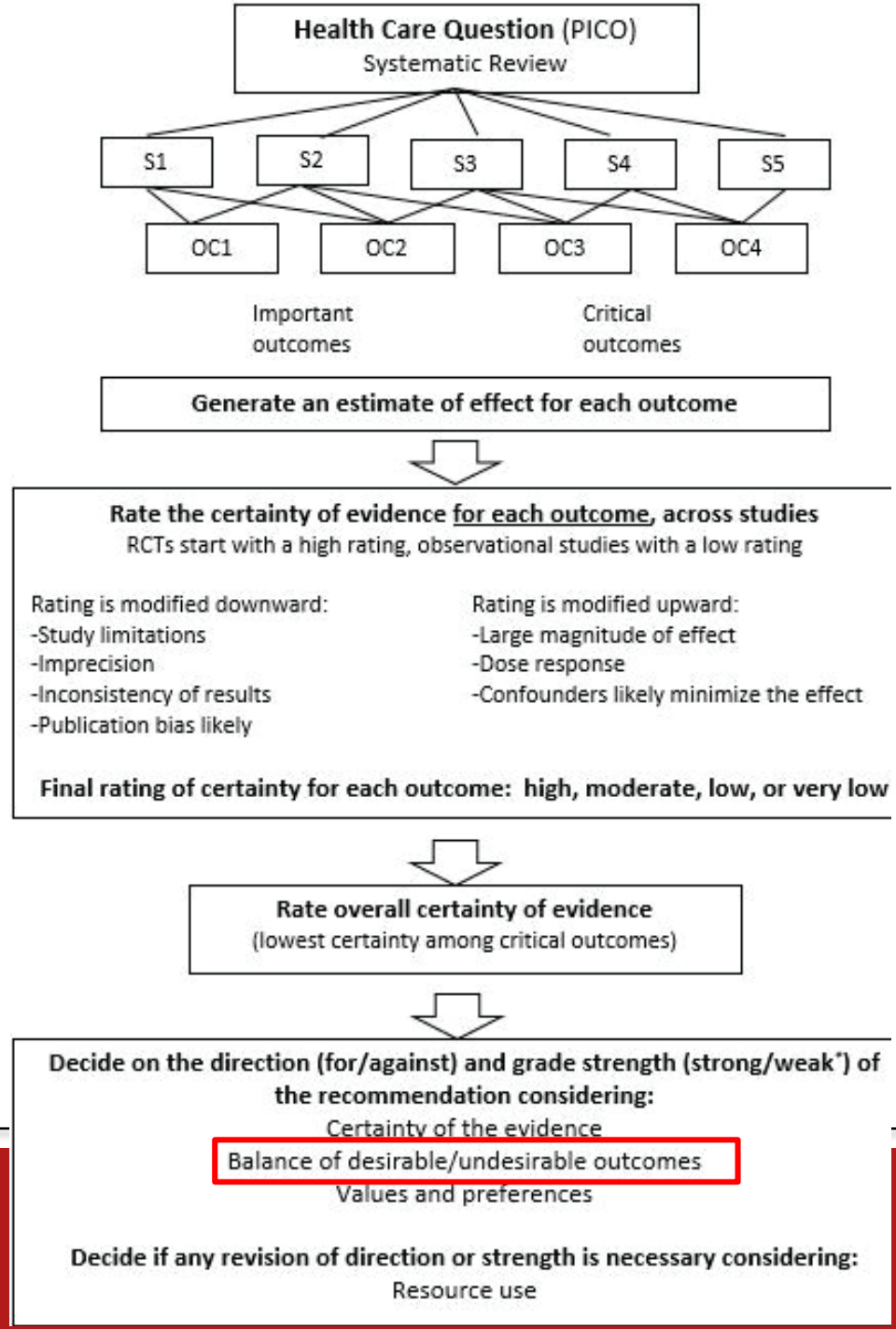
Use GRADE to Evaluate Strength of the Evidence

GRADE = Grading of Recommendations: Assessment, Development and Evaluation



Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease Outcomes. 2017, National Academies Press

Evidence for Selection of Chronic Disease Outcome

- **Moderate strength of evidence (GRADE) for intake does-response of nutrient or NOFS with chronic disease outcomes**

Potassium – a case study

- ❖ Moderate evidence for causal relationship of potassium supplementation with reductions in blood pressure (a qualified surrogate outcome)
- ❖ Lack of evidence for intake-response relationship
  - Heterogeneity across studies
  - Lack of supportive evidence for benefit of potassium on CVD prevention
- ❖ No CDRR specified

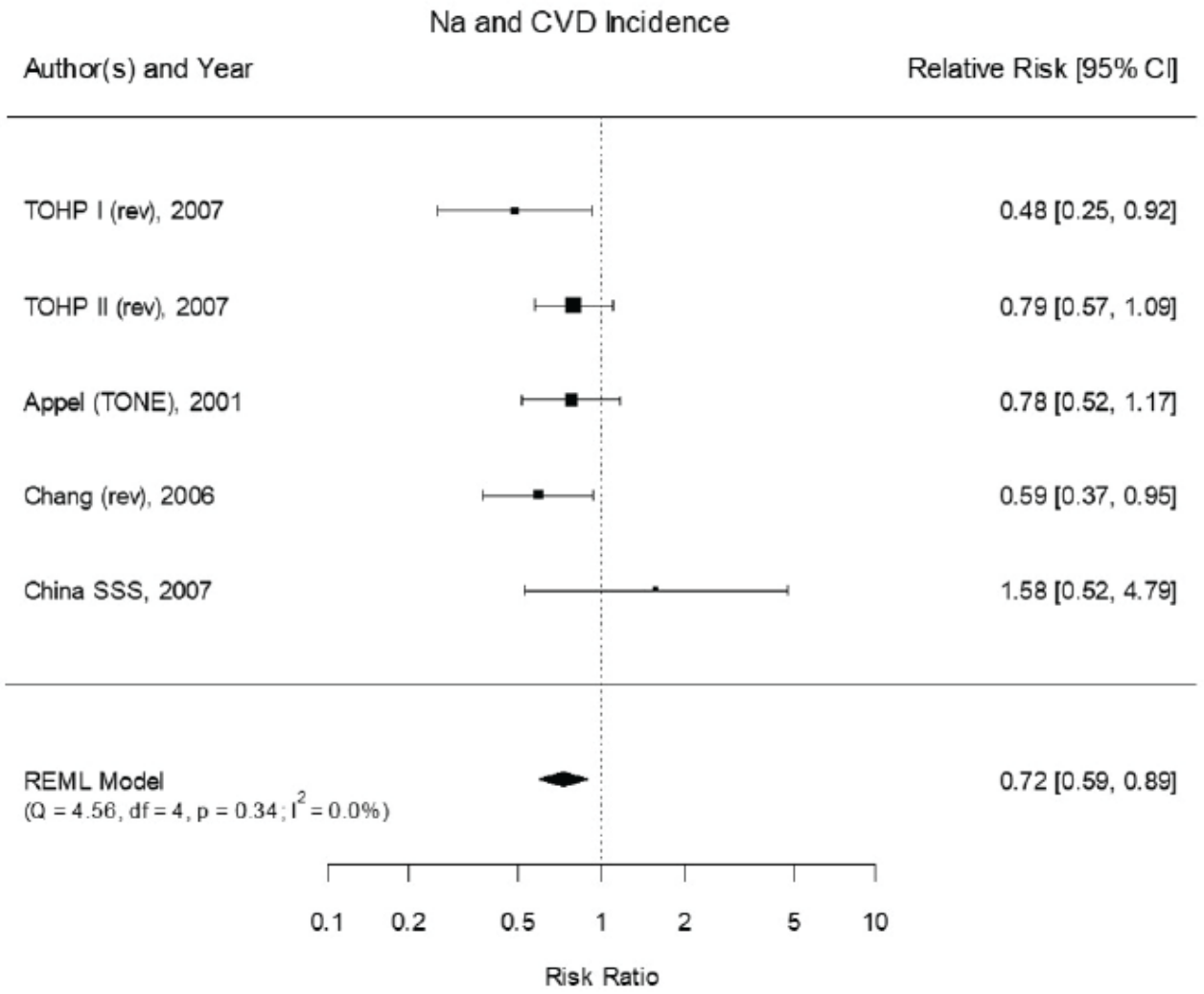


FIGURE 10-1 Random-effects meta-analysis of trials of effects of sodium reduction on cardiovascular disease incidence.

Sodium: Assessing the Evidence for Chronic Disease (CVD)

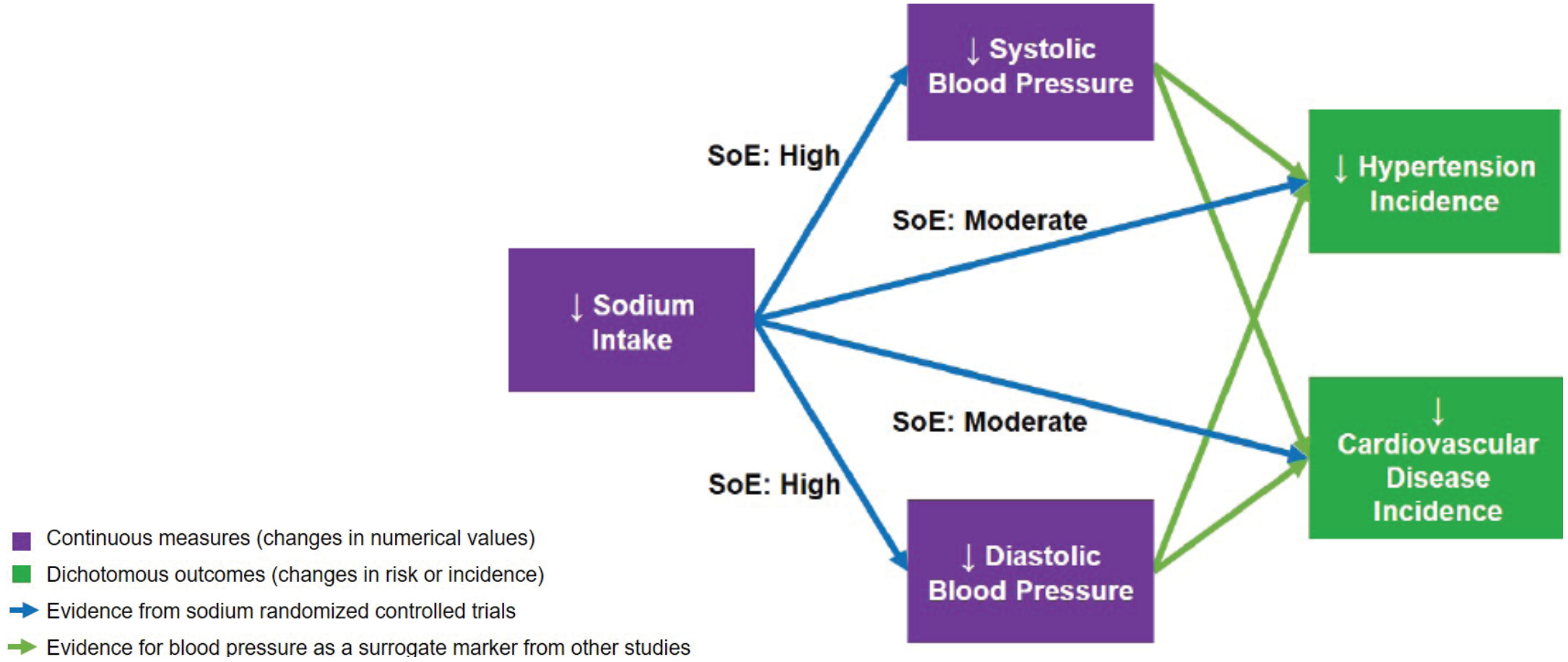
Sodium: Summary of Evidence for Causal Association with Chronic Disease

TABLE 10-8 GRADE Summary of Findings Used to Determine the Causal Relationship Between Reduction in Sodium Intake and Chronic Disease Risk

Indicator	Duration of Study or Follow-Up	Study Results and Measurements	Strength of Evidence
Cardiovascular disease event incidence	2.5 to 12 years	Relative risk: 0.74 [95% CI: 0.58, 0.93]	Moderate, due to imprecision
Hypertension incidence	2.5 to 4 years	Relative risk: 0.79 [95% CI: 0.67, 0.93]	Moderate, due to imprecision
Systolic blood pressure	4 weeks to 4 years	See Table 10-6	High
Diastolic blood pressure	4 weeks to 4 years	See Table 10-7	High

Dietary Reference Intakes for Sodium and Potassium. 2019, National Academies Press

Analytic Framework for the Relationship of Sodium Intake and Chronic Disease and Qualified Surrogate Outcomes (Fig. 10-13)



Sodium: Summary of Evidence for Intake-Response and Reduction of Chronic Disease Risk

Sodium Intake Range (mg/d)	Chronic Disease Indicator	Nature of Evidence	Strength of Evidence
>8000	CVD, HTN, SBP, DBP	N o RCT/low risk bias observational studies	Insufficient
5000-8000	CVD, HTN, SBP, DBP	No RCT/ 1 low risk bias CVD observational study	Insufficient
4100-5000	CVD, HTN SBP, DBP	No RCT/1 low risk bias CVD observational study 11(SBP)-10(DBP) RCT	Moderate (indirectness)
2300-4100	CVD, HTN SBP, DBP	3 RCT/1 low risk bias CVD observational study 21 RCT	High
1000-2300	CVD, HTN SBP, DBP	No RCT/ 1 low risk bias CVD observational study 19 RCT	Low, (inconsistency & indirectness)
<1000	CVD, HTN, SBP, DB_	No RCT or low risk bias observational studies	Insufficient

Dietary Reference Intakes for Sodium and Potassium. 2019, National Academies Press

Specifying Sodium CDRR Evidence for Causal and Intake Response Relationship for Reduction of Chronic Disease Risk

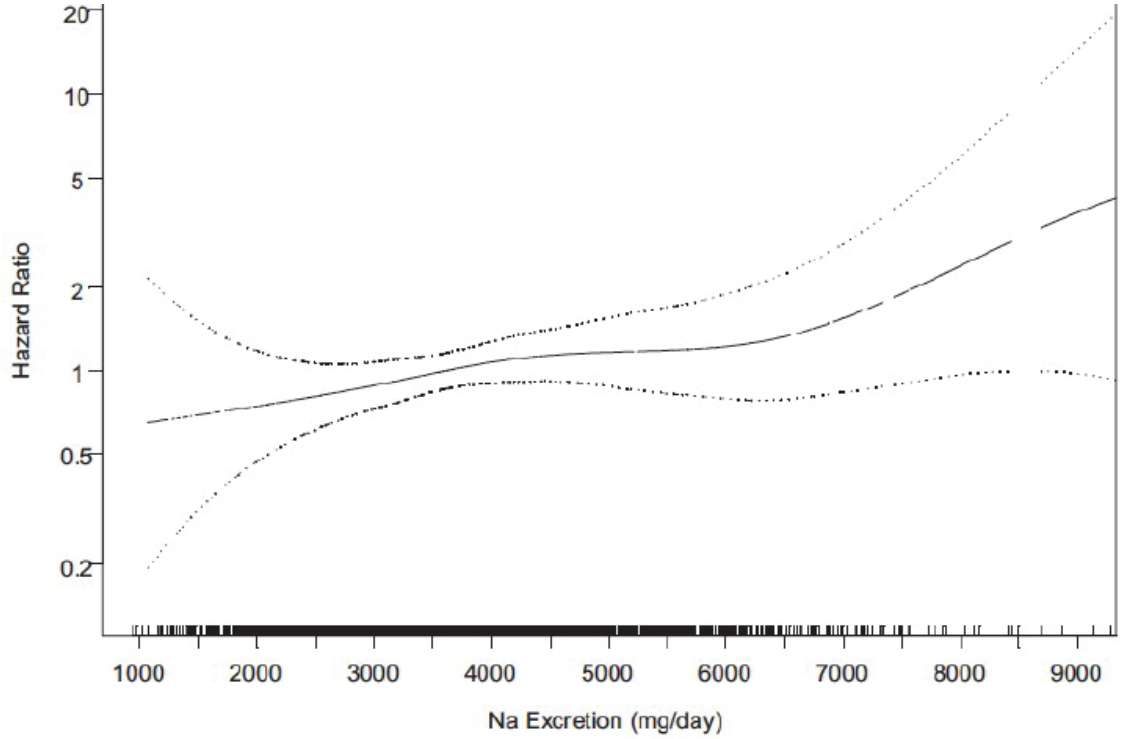


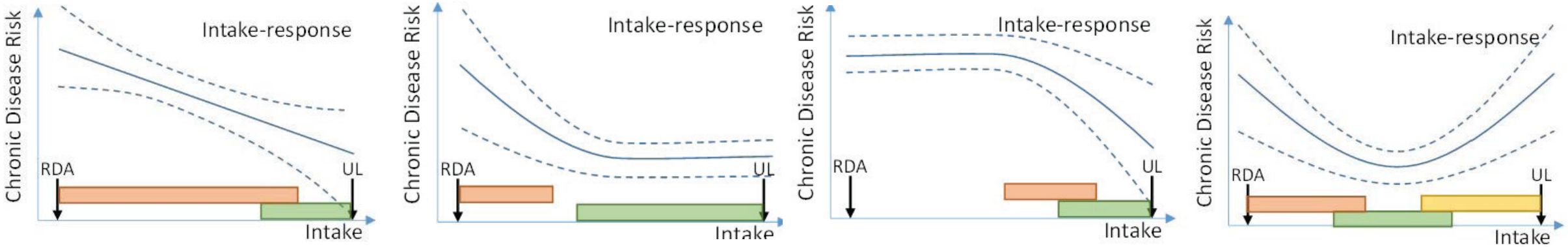
FIGURE 10-27 Spline plot of the hazard ratio for cardiovascular disease by mean sodium excretion from observational follow-up of Trials of Hypertension Prevention studies.

CDRR set at lowest sodium intake level 2300 mg/d in range of 2300-5000 mg/d, with high to moderate evidence of reduction of cardiovascular disease based on several interrelated indicators

Benefit of reducing intakes above 2300 up to 5000 mg/d

Implications for Omega 3 FA and Chronic Disease

- **Is there at least moderate evidence for causal association AND intake response needed for CDRR ?**
  - **What is the analytic framework for intake of omega 3 FA and chronic disease?**
  - **Are surrogate markers qualified?**
  - **Is there sufficient intake-response data to determine the nature of the relationship**

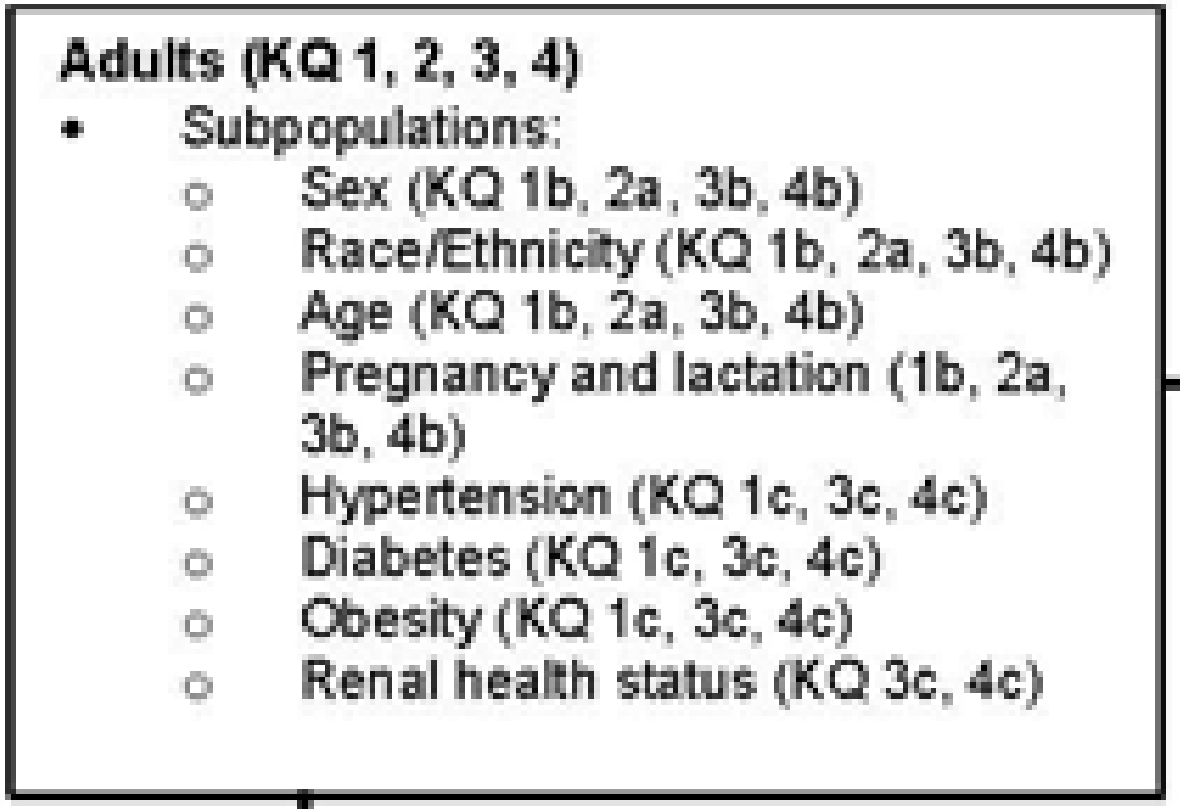


Recent MetaAnalyses & Evidence Summaries Relative to Evidence Requirements for CDRR

Issue	Hu, et al.	Kris-Etherton et al.
Relevant Population	Includes in some studies those with prior history of CHD, stroke, diabetes	Includes in some studies those with prior history CHD/CVD, diabetes,
Relevant intervention	Y	Y
Multiple outcomes each analyzed individually	Y (except aggregate major vascular events)	Y (except some composite endpoints)
Indicators on causal pathway (analytic framework)	NR	NR
Surrogate markers qualified	NR	NR
GRADE used to evaluate strength of evidence	N	N
Moderate to High evidence for causal relationship	?	?
Moderate to High evidence for intake-response relationship	?	?
Sufficient evidence to determine nature of intake-response relationship	Y (if moderate to high strength evidence)	Y?

Implications for Omega 3 FA and Chronic Disease

- **Is there at least moderate evidence for causal association AND intake response needed for CDRR ?**
  - **Unclear as evidence has not been evaluated with GRADE**
- ***What is level of evidence for primary prevention in those who are apparently healthy with no prior history of CVD, CHD or relevant outcomes?***
  - ***Will need to address question of inclusion of diabetes given its medical nutrition therapy and recognizing the increased risk for CVD?***



Included populations for ***AHRQ Systematic Review of Sodium and Potassium Intake: Effects on Chronic Disease Outcomes*** (Newberry et al., 2018)

Implications for Omega 3 FA and Chronic Disease:

- **Is there at least moderate evidence for causal association AND intake response needed for CDRR ?**
  - **Unclear as evidence has not been evaluated with GRADE**
- ***What is level of evidence for primary prevention in those who are apparently healthy with no prior history of CVD, CHD or relevant outcomes?***
  - *Will need to address question of inclusion of diabetes given its medical nutrition therapy and recognizing the increased risk for CVD?*
- **What is the analytic framework for intake of omega 3 FA and chronic disease?**
  - **Unclear**
- **Is there sufficient intake-response data to determine the nature of the relationship**
  - **Likely based on metaanalayses (Hu et al.) if strength of evidence is moderate to high**

Summary

- Expanded Dietary Reference Intakes include CDRR and chronic disease outcomes
- Moderate to high strength of evidence (GRADE) needed for nutrient/NOFS intake for chronic disease for both
  - Causality of Relationship
  - Intake-Response Relationship
- Key Implications for Omega 3 Fatty Acids
  - Strength of evidence using GRADE
  - Relevance of inclusion in some studies of participants with existing CVD/CHD decreases in some studies to apparently healthy population needed for DRI