PRECISION FOR DIETARY REFERENCE INTAKE RECOMMENDATIONS

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2014-20 **NASEM food and nutrition board** member
2016-17 **committee** to develop guiding principles for the inclusion of chronic disease endpoints in future DRI

UMASS LOWELL
Learning with Purpose

THE DRI PROCESS, HISTORY OF THE RDA

DRI Development Timeline

1943 The first RDAs

Concepts

- Relief of starvation due to war or economic depression
- Standards for public health programs

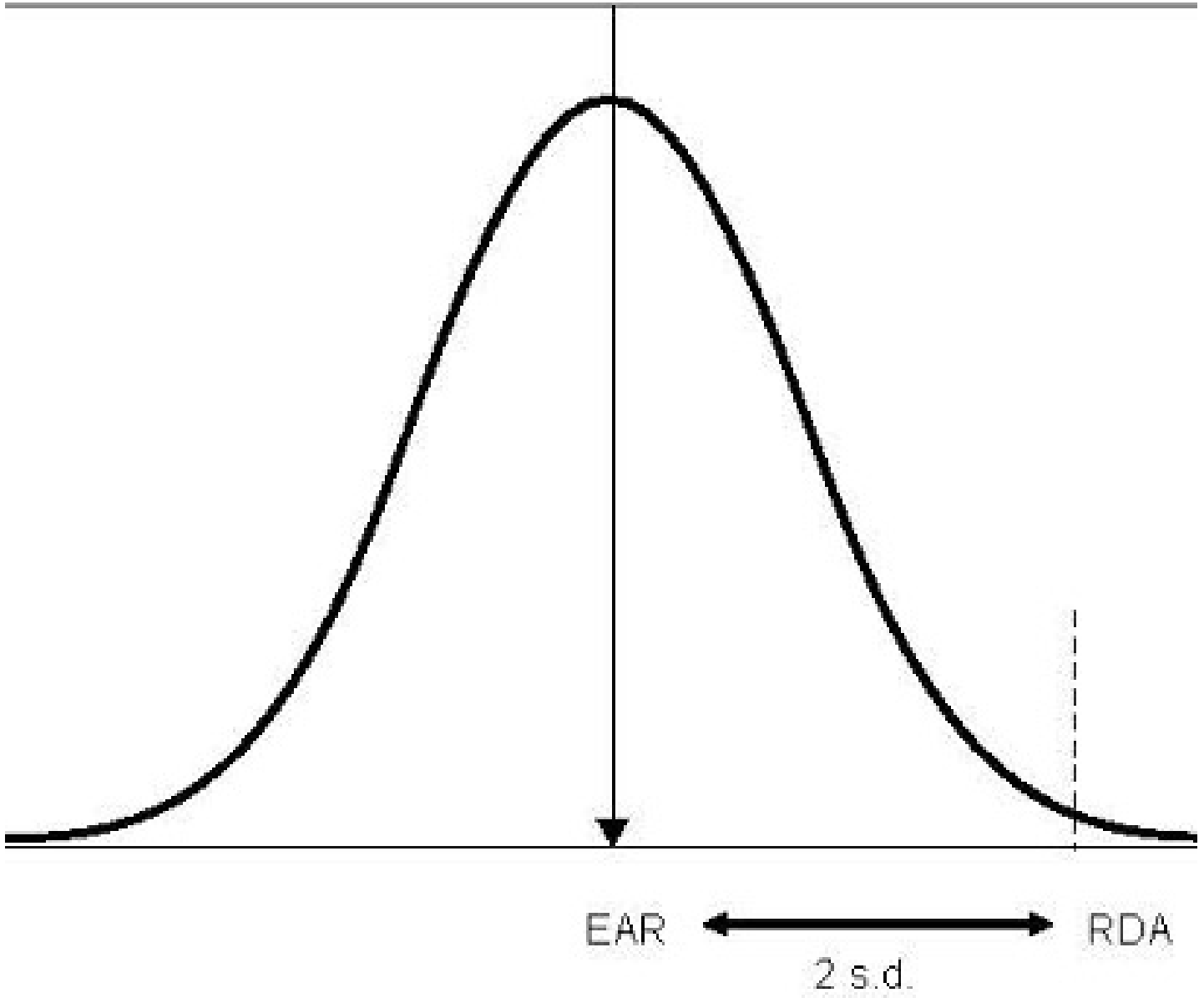
Science Base

- Observations of usual food patterns
- Experimentally determined nutrient requirements

- recommended nutrient intakes were based on physiologic requirements and biological activity of nutrients to determine the amount that would cover the needs of most people in defined age and sex groups
  - Designed to apply to apparently healthy persons
  - Focused on preventing deficiency
  - RDAs were determined if sufficient data
  - Ais were set based on observed median intakes of populations without inadequacy
- Used widely to inform food policy, nutrition education, labeling, feeding programs and more

. POPULATION INTAKE DISTRIBUTION CURVE

The 50th percentile (average) represents the point at which half the population has intakes are at or above the estimated average requirement (EAR), and half of the population intakes are less than the average requirement. The Recommended Dietary Allowance is 2 standard deviations (SD) from the EAR.



IOM. Dietary Reference Intakes research synthesis: Workshop summary 2006

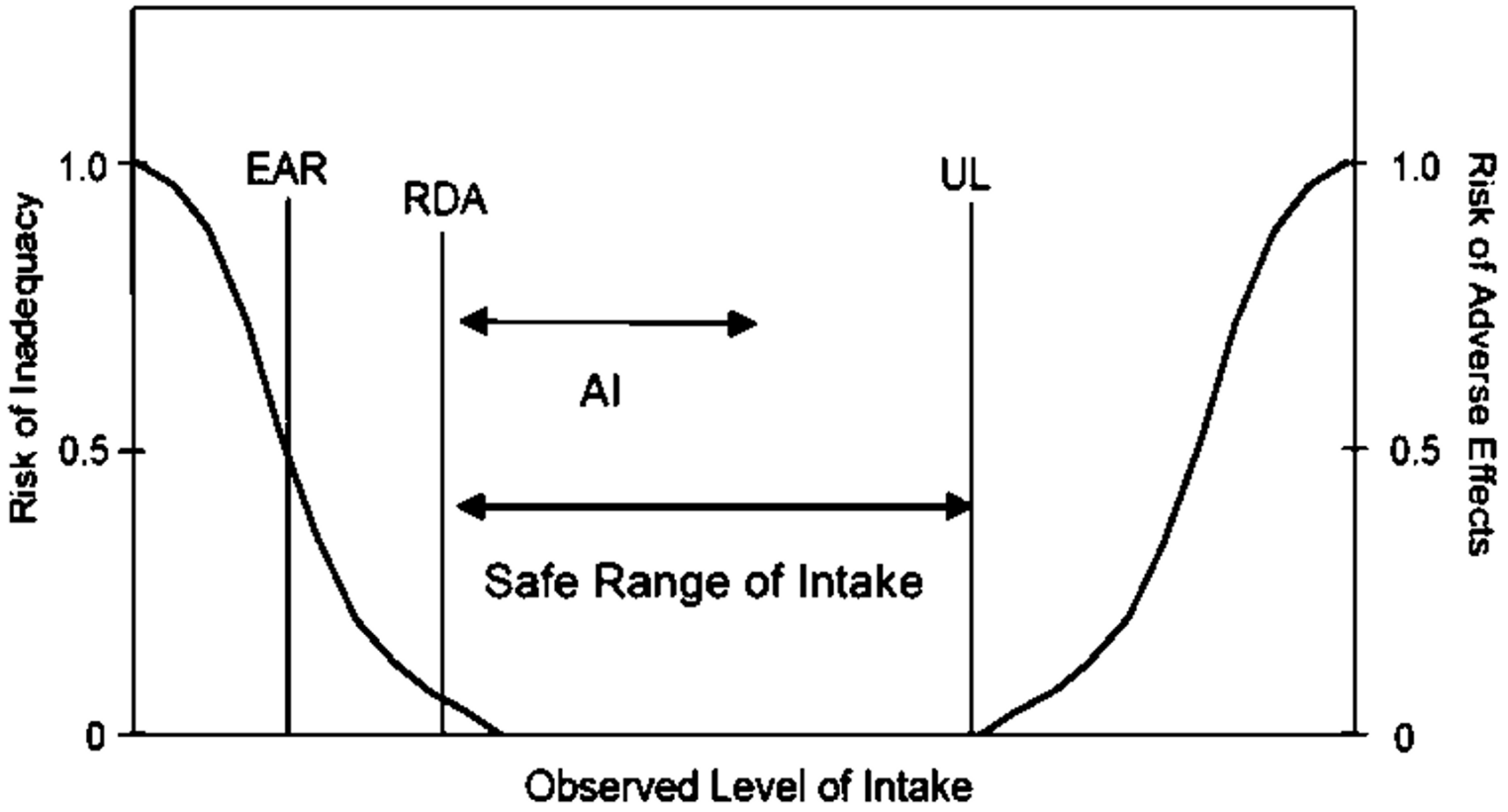
BEGINNING IN THE 1990S, THE RDAS WERE EXPANDED TO THE DRI INTRODUCED MULTIPLE REFERENCE POINTS, THE EAR, RDA/AI, UL

DRI Value	Acronym	Definition
Estimated Average Requirement	EAR	The average daily nutrient intake estimated to meet the requirement of half the individuals in a particular sex and life stage group.
Recommended Dietary Allowance	RDA	The average daily dietary nutrient intake sufficient to meet the nutrient requirements of nearly all (97–98 percent) individuals in a particular sex and life stage group.
Adequate Intake	AI	The recommended average daily intake based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of individuals that are assumed to be adequate – used when an RDA cannot be determined.
Acceptable Macronutrient Distribution Range	AMDR	A range of usual intakes for a macronutrient that is associated with reduced risk of chronic disease while providing adequate intakes of essential nutrients. An AMDR is expressed as a percentage of total energy intake.
Estimated Energy Requirement	EER	The average dietary energy intake that is predicted to maintain energy balance in a healthy adult of a defined age, sex, weight, height, and level of physical activity.

IOM. How should the Recommended Dietary Allowances be revised? 1994.
IOM. Dietary reference values. A risk assessment model for establishing upper intake levels for nutrients 1998.

DERIVATION OF THE DRI VALUES

The reference points are bounded by the estimated average requirement (EAR) and the tolerable upper intake level (UL)



IOM. Dietary reference values. A risk assessment model for establishing upper intake levels for nutrients. 1998

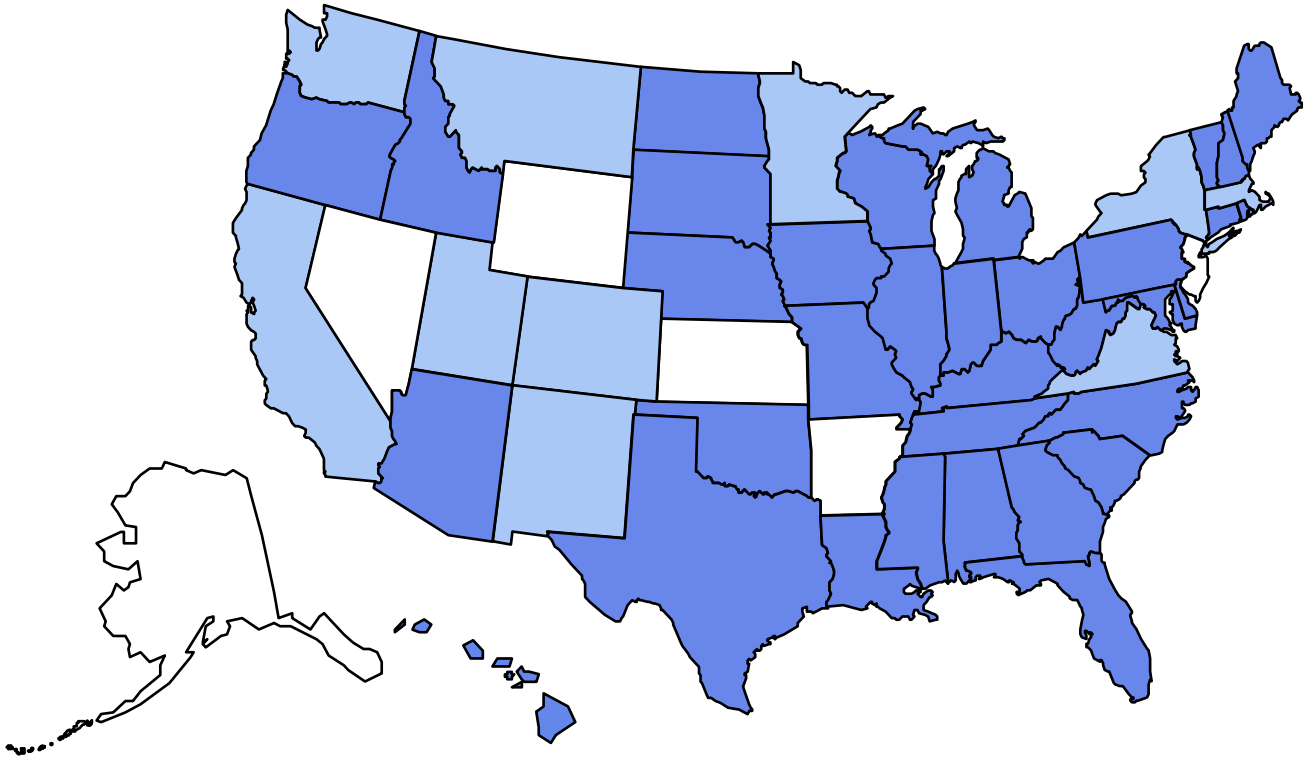
CONSIDERATION OF CHRONIC DISEASE

- RDAs were designed for the non-institutionalized healthy population
- With the epidemic of obesity, diabetes and chronic disease, how many does that represent?
- Considering disease burden, medications, etc, it was recognized that intakes greater than the RDA, in many cases, may be protective against these chronic conditions.

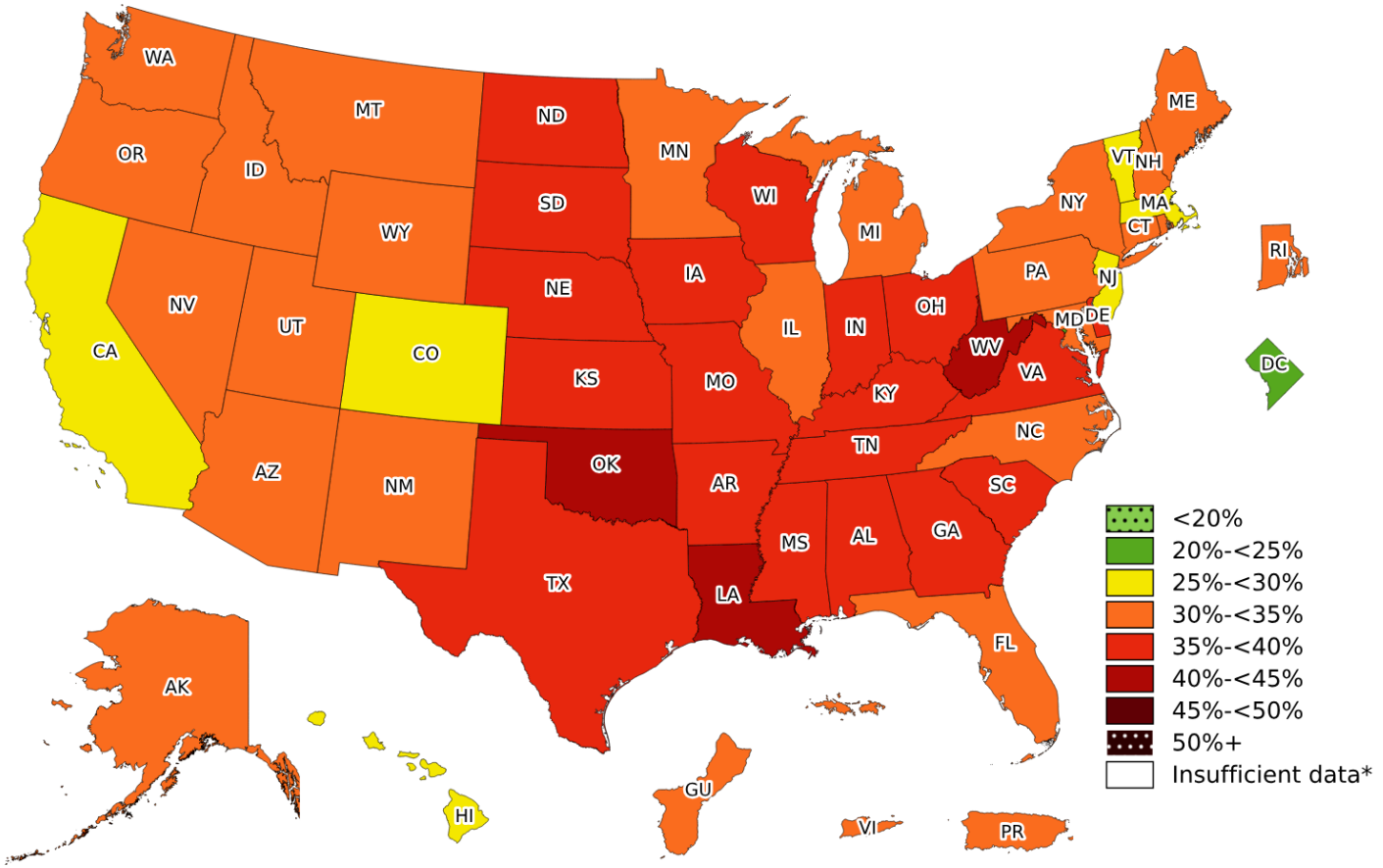
OBESITY TRENDS* AMONG U.S. ADULTS

BRFSS, 1990

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



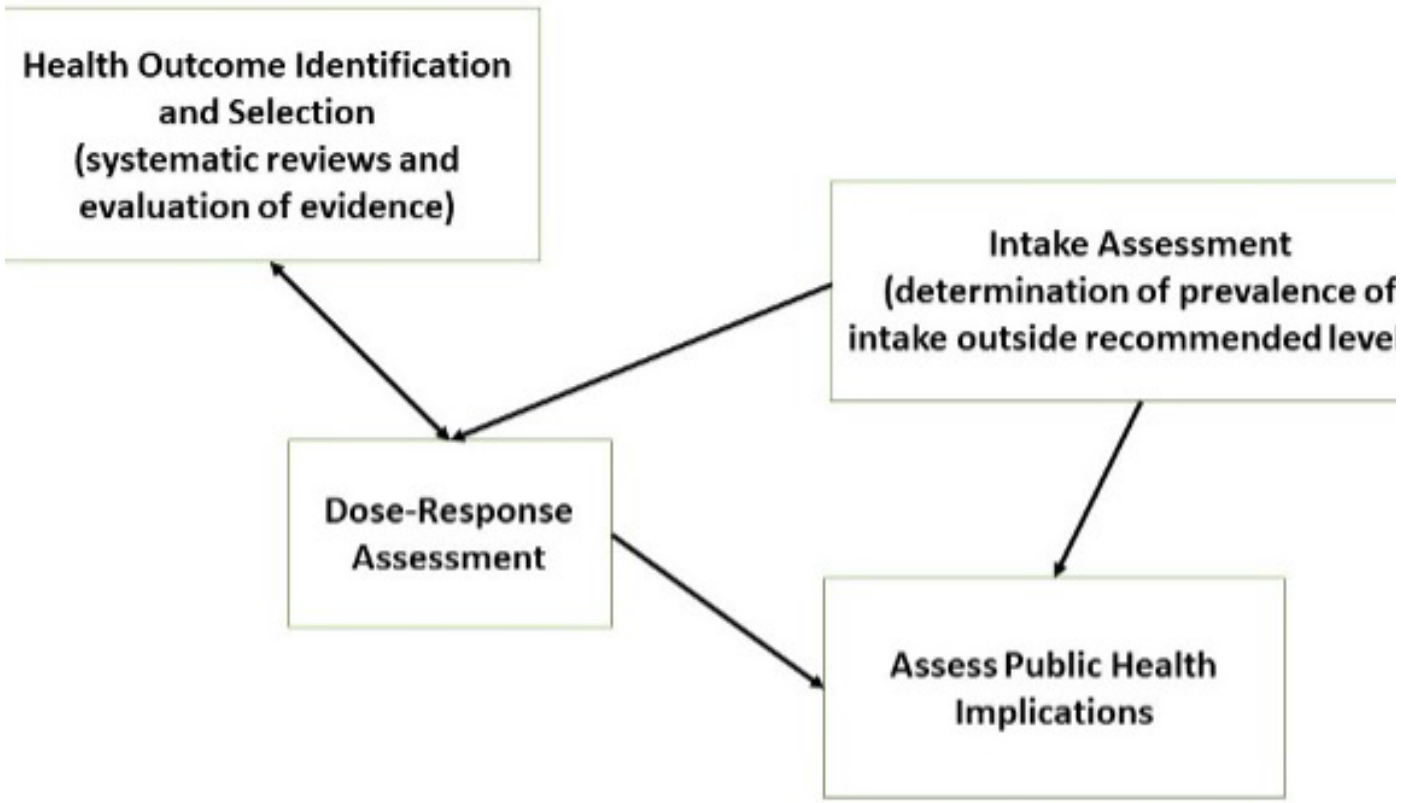
PREVALENCE¶ OF SELF-REPORTED OBESITY AMONG U.S. ADULTS BY STATE AND TERRITORY, BRFSS, 2023



RISK ASSESSMENT FRAMEWORK

Three main concepts
- No decision is not an option
- Uncertainties must be dealt with by documentation and scientific judgement
- User needs must guide the process

Requires data on
- Existing intake distributions
- Evidence of association and dose response by systematic review



IOM. The Development of DRIs 1994-2004: Lessons Learned and New Challenges: Workshop Summary 2008
NRC. Risk assessment in the federal government: Managing the process. 1983

OPTIONS REPORT

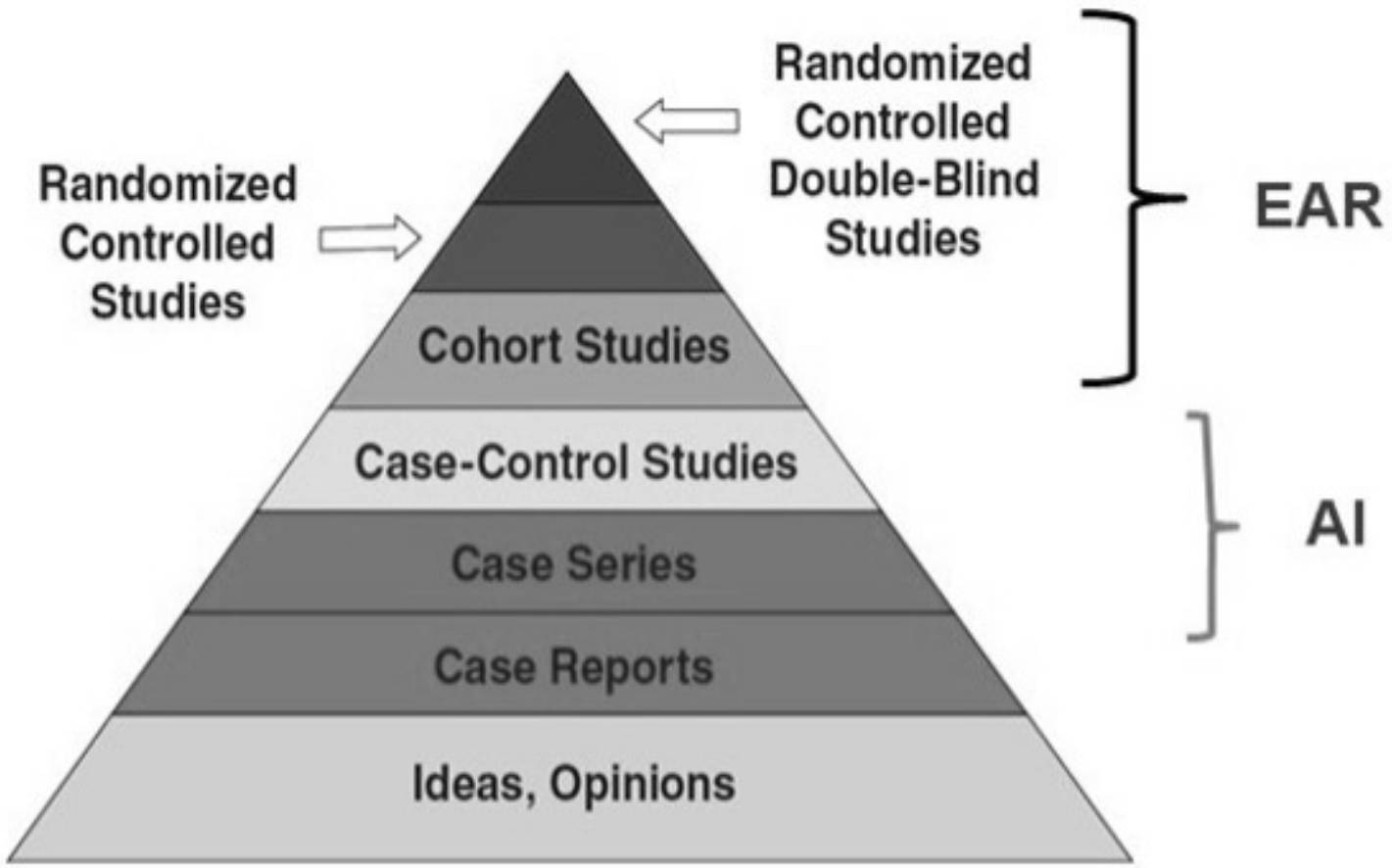
- 2008 DRI for calcium and vitamin D was the first to explicitly consider chronic disease using the risk assessment model
  - First to include this risk assessment model
  - Able to define RDA for vitamin D based on bone health
  - Still missing data to define risk of chronic disease, particularly for dose response and to define causality

- OPTIONS REPORT to consider approaches to a process to define a chronic disease DRI value
  - Systematic review; Consideration of the totality of the evidence
  - Range of outcomes for each chronic disease

Yetley Am J Clin Nutr 2017
NASEM. 2017

HIERARCHY OF EVIDENCE TO SUPPORT A DRI REVIEW

Began commissioning systematic reviews to evaluate the evidence for. Recommendations to prevent chronic disease, in addition to the original goal of avoiding inadequacy



IOM. The Development of DRIs 1994-2004: Lessons Learned and New Challenges: Workshop Summary 2008

GRADING OF RECOMMENDATIONS ASSESSMENT, DEVELOPMENT AND EVALUATION (GRADE) SYSTEM— DOMAINS USED TO RATE THE STRENGTH OF THE EVIDENCE

- **Domains That May Reduce the Strength of Evidence***
  - **Risk of bias** is systematic error attributable to limitations in the study design or execution.
  - **Imprecision** is random error that occurs when studies have a small sample size and the number of events is also small.
  - **Inconsistency** is unexplained heterogeneity or variability of study results.
  - **Indirectness** occurs when a study does not compare the interventions of interest, apply the intervention to the population of interest, or measure the outcomes that are important to patients.
  - **Publication bias** is a systematic underestimation or overestimation of the underlying beneficial or harmful effect caused by the selective publication of studies.

1. **Domains That May Increase the Strength of Evidence**
   - Large magnitude of effect, with consideration for both the magnitude and precision of the estimate.
   - Intake–response gradient.
   - Plausible residual confounding, which under certain circumstances can increase confidence in an estimate

GUIDING PRINCIPLES FOR DEVELOPING DRIS BASED ON CHRONIC DISEASE

- Recommendations
  - that DRI committees use Grading of Recommendations Assessment, Development and Evaluation (GRADE) in assessing the certainty of the evidence related to the causal association between nutrients and chronic disease
  - extrapolation of intake-response data for chronic disease DRIs only to populations that are similar to studied populations in the underlying factors related to the chronic disease of interest.
  - that DRIs for chronic disease risk take the form of a range, rather than a single number.
    - Intake–response relationships should be defined as different ranges where risk is at minimum, is decreasing, and/or is increasing

NASEM 2017

TABLE 2-2 Conceptual Distinction Between DRIs for Adequacy and Toxicity and DRIs Based on Chronic Disease

DRIs for Adequacy and Toxicity	DRIs Based on Chronic Disease
Needed because deficiencies (of essential nutrients) and toxicities:	Are not warranted unless sufficient evidence exists because:
• Will affect everyone, if intake is inadequate or excessive • Are caused by a single nutrient • Are prevented by nutritional interventions	• Risk to acquire chronic diseases varies by individual • Chronic diseases are often related to many risk factors (e.g., genetic, environmental) • Nutritional interventions will only partly ameliorate the risk of chronic disease

SOURCE: Adapted from NASEM, 2017b.

CHRONIC DISEASE REDUCTION RANGE

- CDRR take the form of a range, rather than a single number.
  - Intake–response relationships should be defined as ranges where risk is at minimum, is decreasing, and/or is increasing
  - The magnitude of risk slope necessary to set a CDRR should be based on clear public health goals
- If the increase in risk only occurs at intakes > UL, no CDRR is required
- level of certainty in the intake–response relationship should generally be at least "moderate," using GRADE.
  - in some cases of disease risk, the level of certainty acceptable might be lower
- If possible, health risk/ benefit analyses should consider the certainty of evidence for harms and benefits of changing intake, based on clearly articulated public health goals

SODIUM AND POTASSIUM DRI, FIRST TO INCLUDE CDRR

- Using the recommendations from the Guiding Principles Report
  - Strengthen the rigor and transparency of the process
  - Applied GRADE to assessment
  - Added a new DRI for chronic disease risk reduction intake (CDRR)
    - Only for sodium
    - Set as a range defined by moderate evidence of reduction in risk of CVD

POTASSIUM (K) DRI

- Data from the Canadian Community Health Survey–Nutrition 2015 and the NHANES 2009–2014 were used to derive the potassium AIs.
  - intake data from apparently healthy participants, whose usual K intake would not be affected by illness, medications, or medical nutrition management.
  - normotensive males and females without self-reported history of cardiovascular disease.
  - highest median K intake across surveys was selected as the AI for each age and sex group
- Despite moderate strength of evidence that potassium supplementation reduces blood pressure, a potassium CDRR cannot be established because of
  - heterogeneity across studies
  - lack of intake–response relationship
  - low or insufficient strength of evidence for related chronic disease endpoints

SODIUM (NA) DRI

- AI based on range of sodium intakes assessed in sodium reduction trials included in the *AHRQ Systematic Review*.
  - In a controlled feeding trial, the lowest sodium intake ranged from 949 to 2,452 mg/d /d
  - low sodium intake group in 8 sodium reduction trials was < 1,800 mg/d; no deficiency symptoms
  - insufficient evidence that low sodium intakes are associated with other potential harmful health effects.
  - balance study, ~ neutral balance achieved at sodium intake of 1,525 mg/d
- Sodium AI for adults 19 years of age and older established at 1,500 mg/d
- CDRR based on synthesis of evidence from sodium-reduction trials and outcomes of incident CVD, hypertension, and blood pressure.
  - sodium CDRR is the lowest level of intake with sufficient strength of evidence for chronic disease risk reduction.
  - Further reduction below the CDRR may have a lowering effect on blood pressure, but the effect on chronic disease risk could not be characterized.
  - For adults the CDRR states: reduce intake if > 2300 mg/d
- There is insufficient evidence of toxicological risk from high levels of sodium intake, separate from chronic disease risk.
  - no sodium Tolerable Upper Intake Level is established.

CDRR RECOMMENDATIONS

Until better intake assessment methodologies are developed and applied widely, DRI committees should ensure that random and systematic errors and biases of nutrient or other food substance exposure assessment methodologies are considered in their evidence review.

- **Need to improve nutrient / food substance exposure assessments for application in CDRR**
- Ideal outcome to establish CDRR should be the chronic disease, defined by accepted diagnostic criteria.
- Surrogate markers may be considered as supporting information of results based on the chronic disease of interest.

GRADE should be used in assessing the certainty of the evidence related to the causal association between nutrient or food substance and chronic disease.

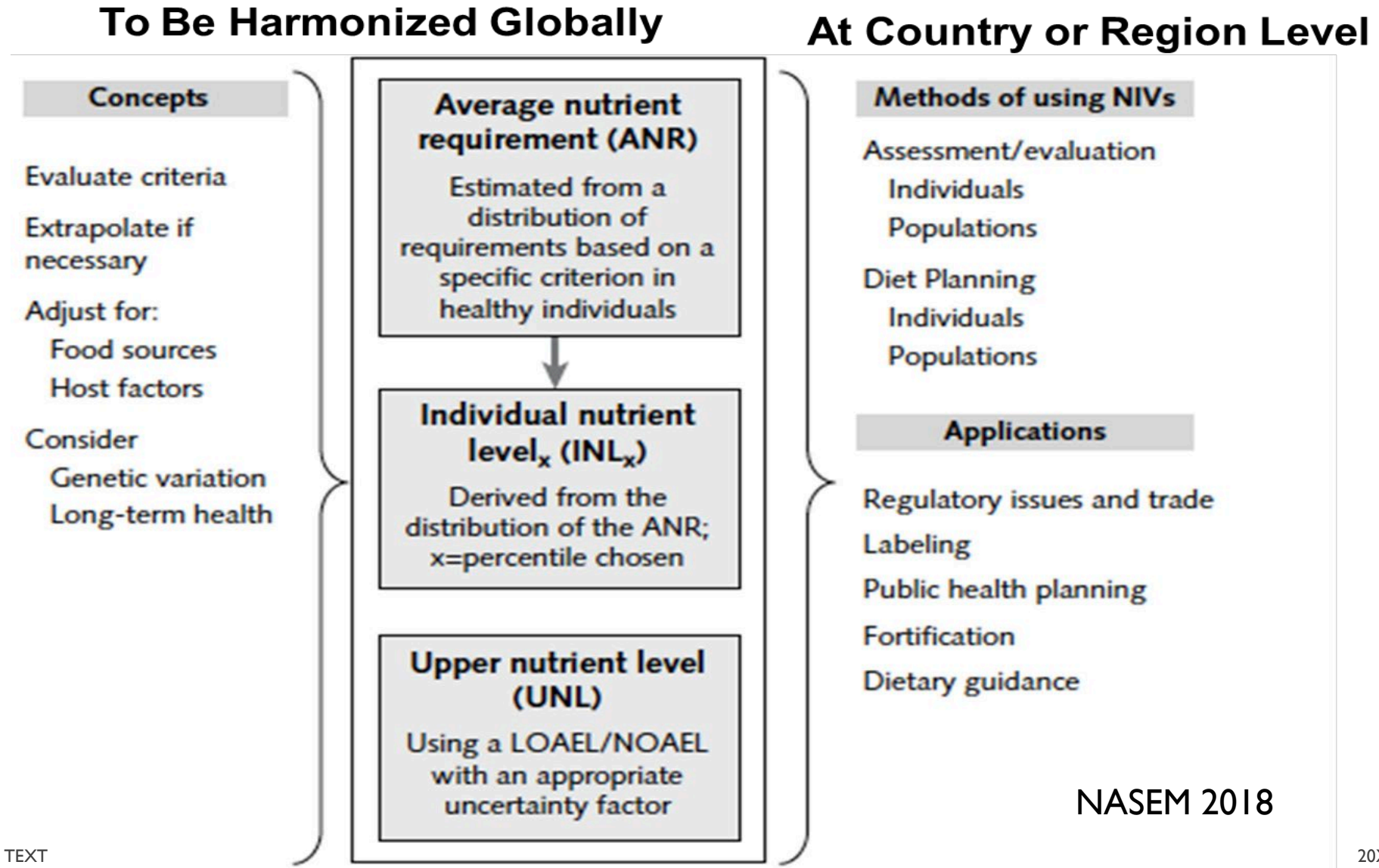
- CDRR should be based on **at least moderate certainty of a causal relationship**, with existence of an intake–response relationship.

Ideal to use a single outcome indicator on the causal pathway.

- when a nutrient / food substance reduces risk of > one chronic disease, develop for each chronic disease.

Extrapolate intake–response data for CDRR only to populations like studied populations in the underlying factors related to the chronic disease of interest.

HARMONIZATION OF DRI



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GLOBAL HARMONIZATION AND PERSONALIZED NUTRITION

- **Genetics** is one of several modifiers that can change physiological processes in ways that affect nutrient requirements.
- Because **baseline measurements of habitual intake, nutrient status, and body composition are critically important in RCTs** for nutrient requirements, it is essential that subjects be "adapted" before collecting these measurements.
- **Infections** can impair nutrient metabolism and, consequently, nutrient requirements in several ways. Two sets of nutrient intake recommendations could be considered: one for developed countries, the other for developing countries with allowance for infections
- By **70 years of age**, people have lost, on average, 40 percent of muscle mass and strength and bone mass. It is important not just for physiological and metabolic responses to nutrient intakes, but also functional (e.g., risk of falls) and chronic disease outcomes
- **Medications** affect nutrient requirements
- There are many host-condition, dietary, and environmental factors that can affect **bioavailability,** thereby changing physiological and dietary requirements.
  - It is not the values themselves that need to be harmonized, rather the approaches used to estimate these values. Each country still uses its own methods, despite a 2005 harmonization report on how to estimate bioavailability.

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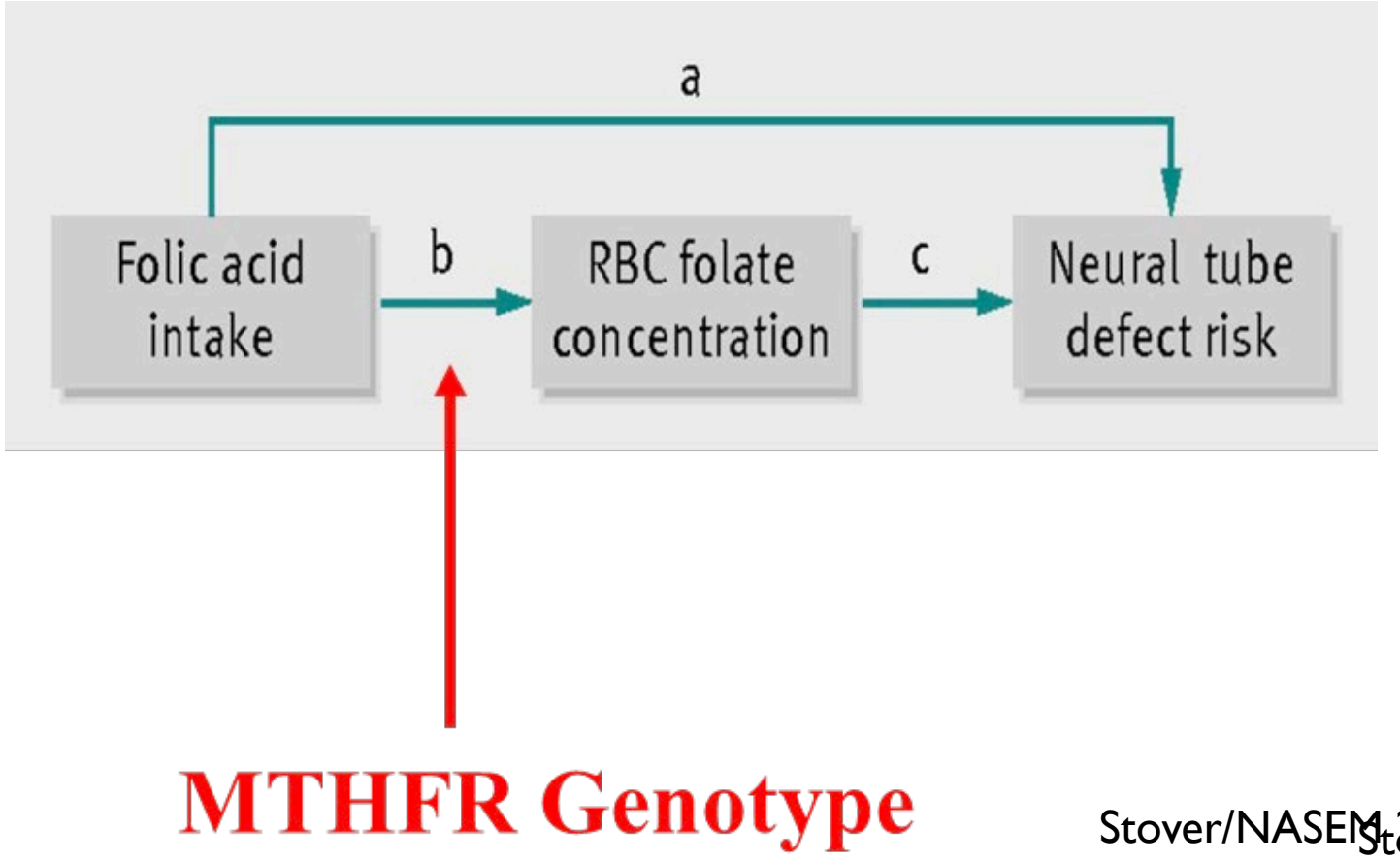
GENETICS



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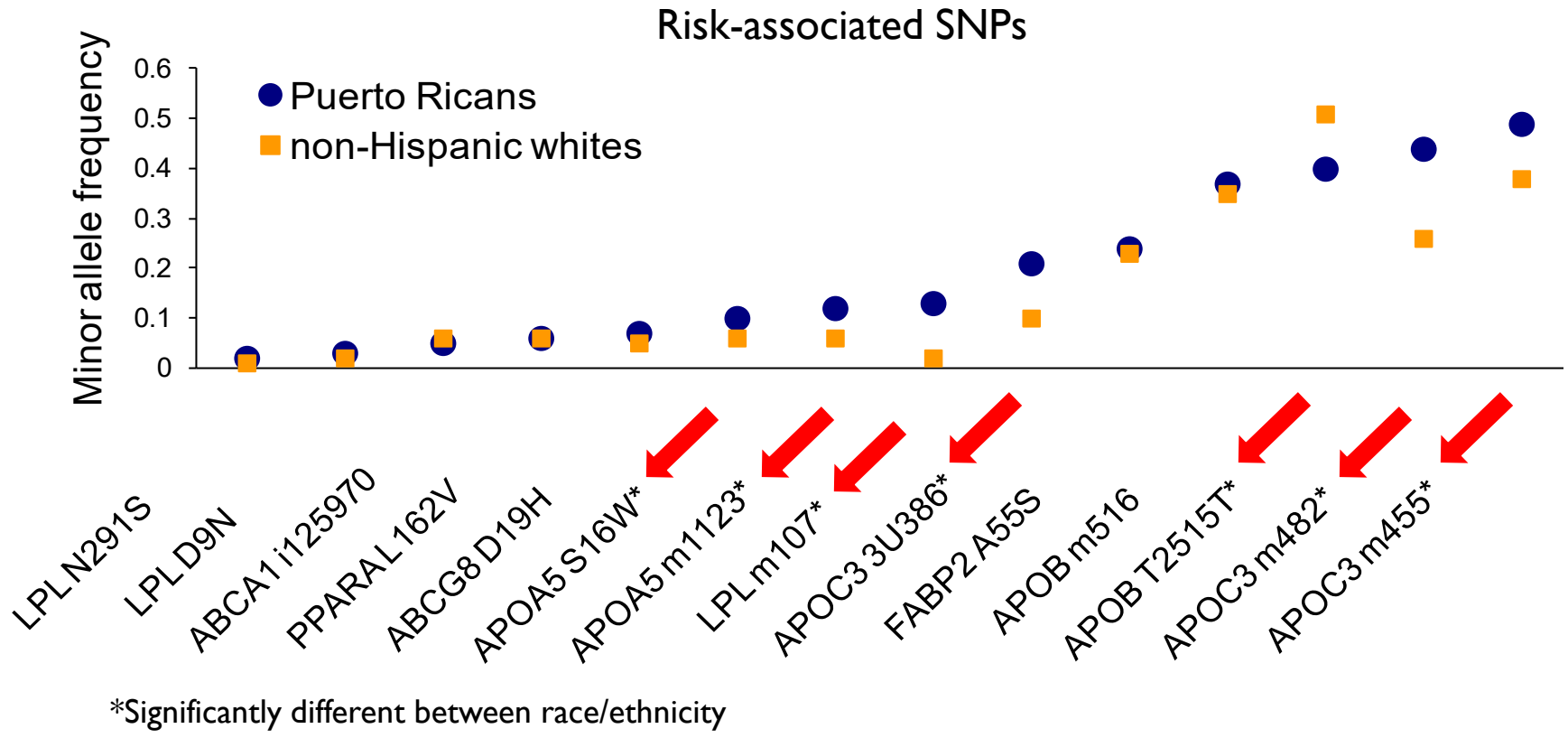
RISK ALLELES IN PUERTO RICANS

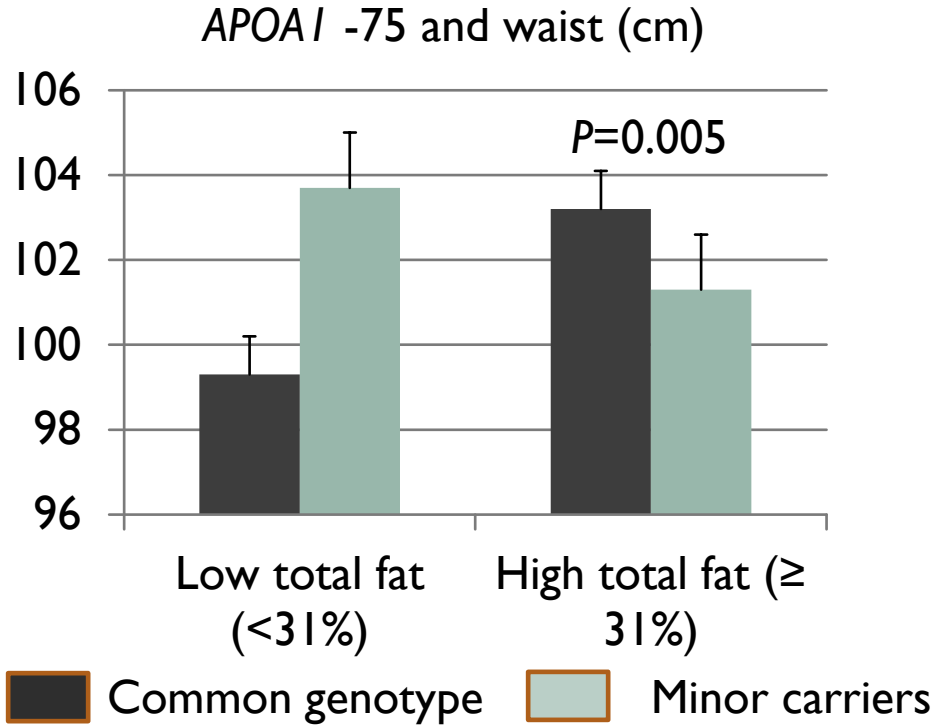
Puerto Ricans have higher frequency of risk-associated alleles than non-Hispanic whites; mostly in lipid metabolism SNPs.

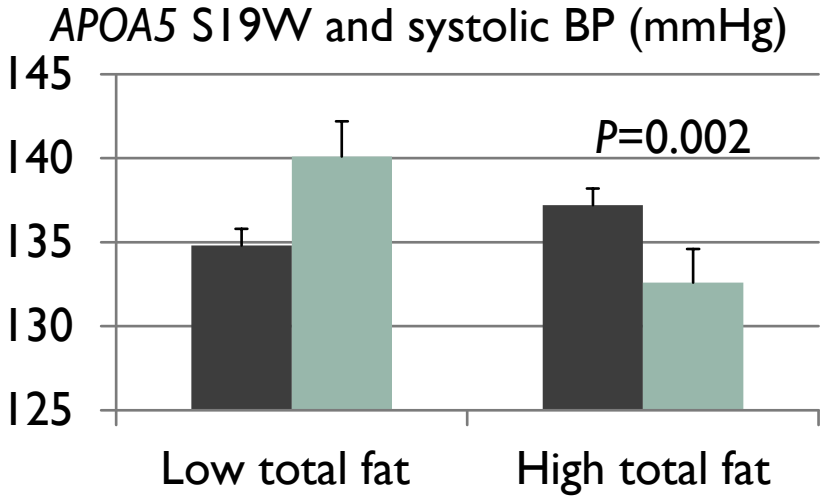


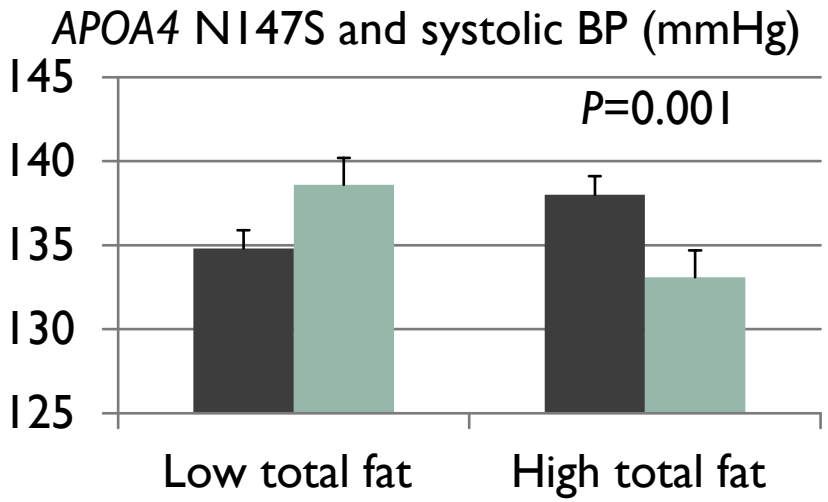
*Significantly different between race/ethnicity

Mattei *et al.* BMC Genetics, 2009.

APOLIPOPROTEIN GENES AND DIETARY FAT INTAKE







70% carry common genotypes.
Observing a diet lower in fat may maintain lower BP and WC.

Mattei *et al.* Nutr Metab Cardiovasc Dis 2010.
Mattei *et al.* J Nutr. 2009.

NEXT STEPS

- A standing committee has been convened to consider how to define the DRI population
  - Individuals with chronic diseases or risk factors should be included
  - Exclude conditions which alter nutrient metabolism/requirements
  - Support a globally unified approach to resolve dissimilarities and promote consistency in population health objectives