Methods to Study Health: Using Meta-analysis to Study Health Across the Lifespan

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How Nutrition and Health Change Over a Person's Life Course

NASEM Standing Committee on Evidence Synthesis and Communications in Diet and Chronic Disease Relationships

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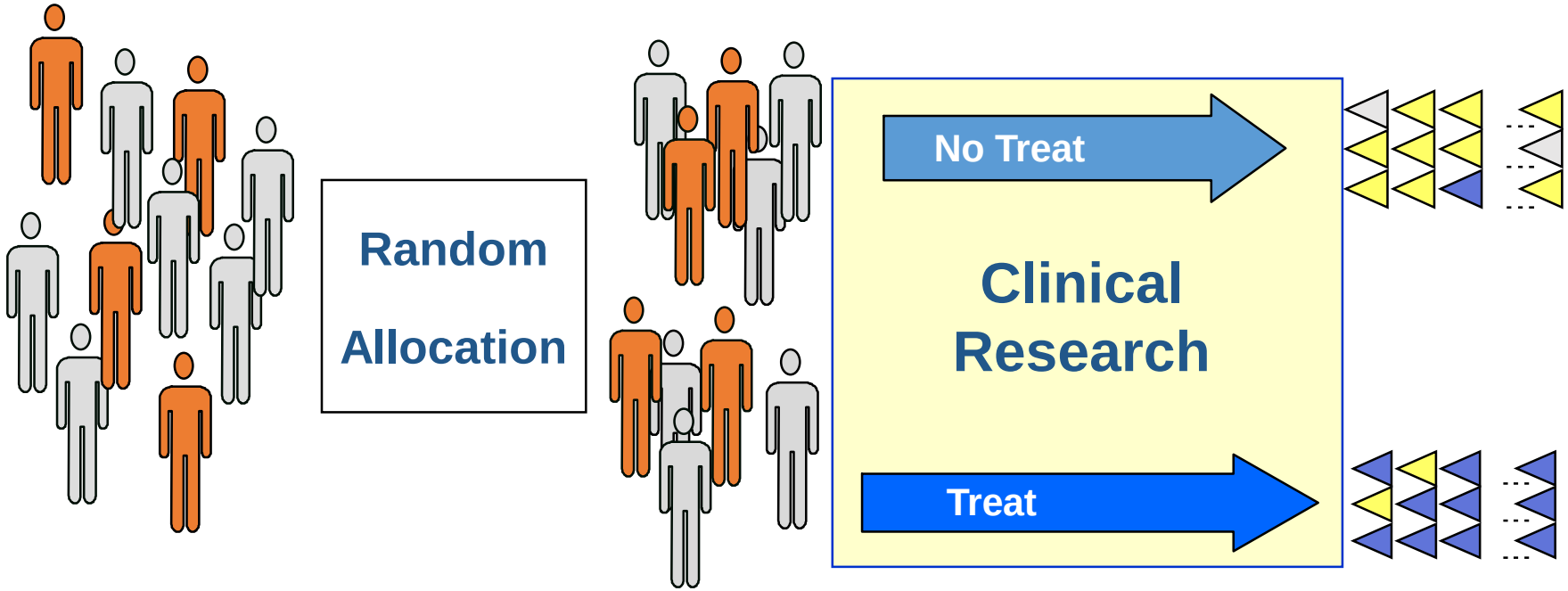
Randomized Controlled Trial (RCT) Evidence Generation

- RCTs gold standard: Does treatment work?



- Pinnacle of Evidence → guidelines and quality of care measures

Treating Acute Myocardial Infarction

	Dead	Alive	Total
Streptokinase	18	138	156
Control	30	128	158

Mortality: SK = 11.5% Controls = 18.9%

Relative Risk (RR) = 0.61

RR = 0.61 95% CI 0.35-1.04 or P-value = 0.07

European Cooperative Study Group N Engl J Med 1979;301:797-802

Errors of Hypothesis Testing

		Truth	
		Drug Beneficial	Drug Not Beneficial
Study Result	Drug Beneficial		$\alpha = 0.05$ Type I error
	Not Beneficial		$1 - \alpha = 0.95$

Errors of Hypothesis Testing

		Truth	
		Drug Beneficial	Drug Not Beneficial
Study Result	Drug Beneficial	$1 - \beta = 0.80$ Power	$\alpha = 0.05$ Type I error
	Not Beneficial	**$\beta = 0.20$** **Type II error**	$1 - \alpha = 0.95$

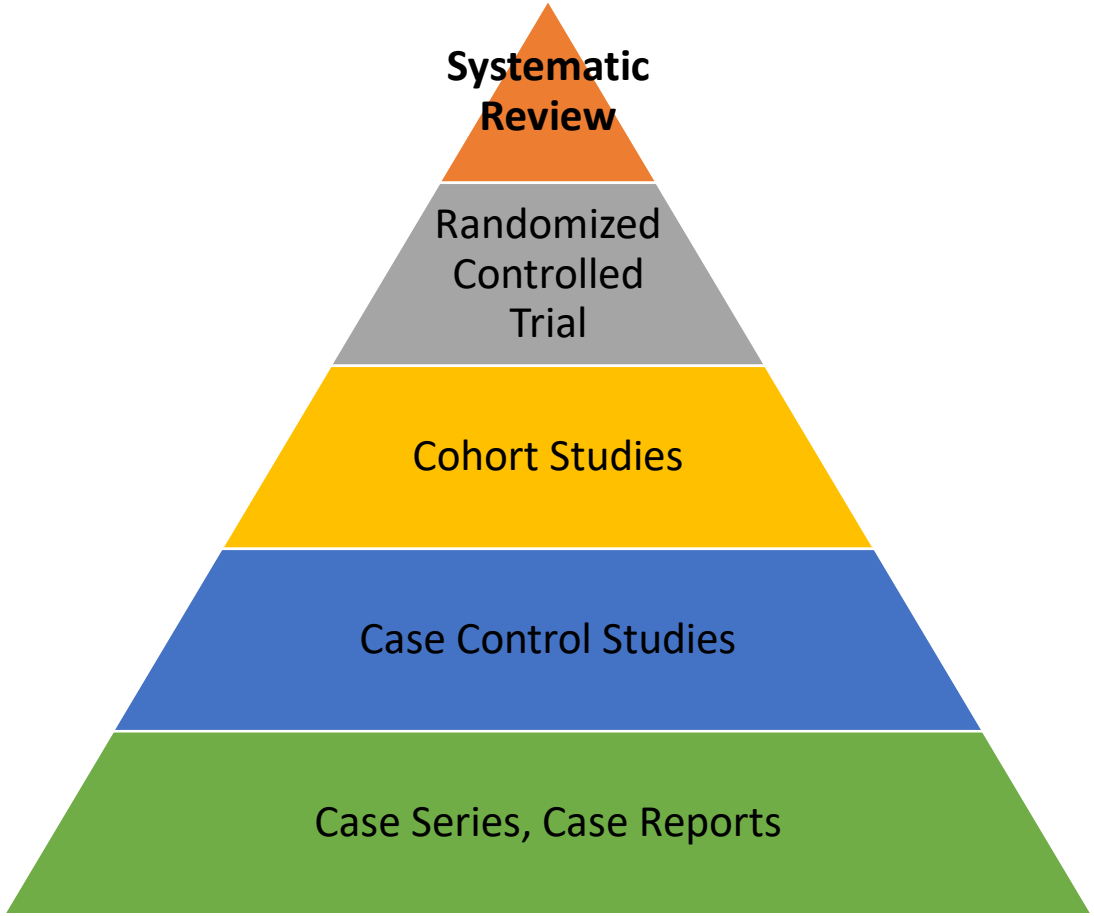
Cumulative Meta-analysis

- Some randomized trials have found benefit from intravenous streptokinase (SK) and others have found harm
- What happens if update the randomized trial evidence every time a new trial appears?
- 33 trials from 1959 to 1988 involving nearly 37,000 patients
  - P<0.01 1959-73 (8 RCTs n=2432)
  - P<0.001 1959-77 (15 RCTs n=4314)
- Yet no routine recommendation until 1986 when P<0.000001 and only 5 out of 9 textbooks or reviews even then recommended SK

Lau J et al. N Engl J Med 1992;327:248-54; Antman EM et al. JAMA 1992;268:240-8

Finding What Works in Health Care: Standards for Systematic Reviews

- "**Knowing what works in health care [nutrition] is of highest importance for patients, healthcare providers, and other decision makers**.
- The *most reliable way to identify benefits and harms associated with various treatment [nutrition] options is a systematic review of comparative effectiveness research*." –Harvey Fineberg, MD, PhD



Institute of Medicine 2011. Finding What Works in Health Care: Standards for Systematic Reviews. Washington, DC: The National Academies Press. p *ix*

Finding What Works in Health Care: Standards for Systematic Reviews

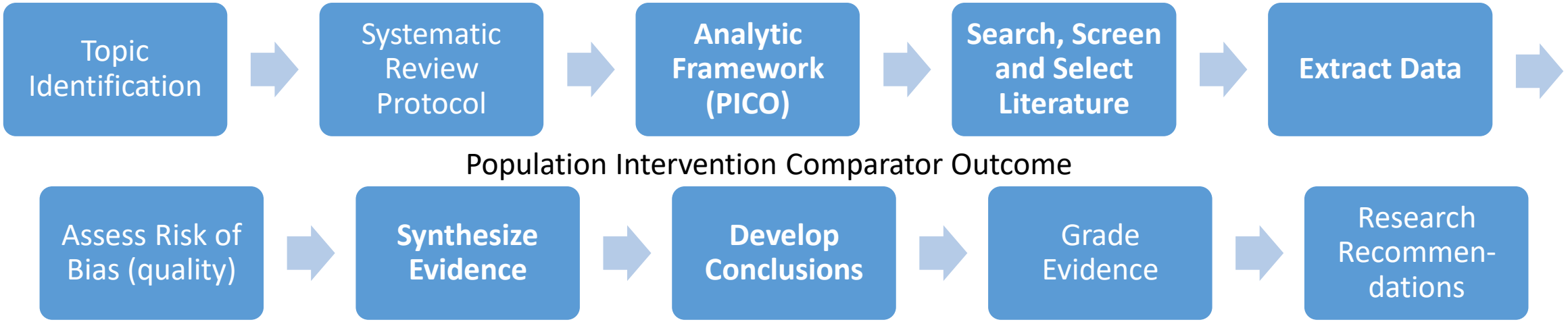
- **Systematic review** (SR): A *scientific investigation asking a specific question* and answered with "explicit, planned scientific methods to identify, select, assess, and summarize the findings of similar but separate studies"

- **Meta-analysis** "is an SR that uses statistical methods to combine…the results of similar studies… to allow inferences to be made from the sample of studies and be applied to the population of interest"

- 21 standards recommending 82 elements

Institute of Medicine 2011. Finding What Works in Health Care: Standards for Systematic Reviews. Washington, DC: The National Academies Press. pp 21

2020 Dietary Guidelines Advisory Committee: Nutrition Evidence Systematic Review (NESR) Process for Conducting Systematic Reviews



RoB: risk of bias
ROBINS-I: non-randomized studies of interventions
NESR modified ROBINS-I for nutrition: **RoB-NObs**

1. Risk of Bias
2. Consistency
3. Directness
4. Precision
5. Generalizability

Dietary Guidelines Advisory Committee. 2020. Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC. Part C.

Dietary Patterns and Risk of Cardiovascular Disease: A Systematic Review

- *Conclusion and Grade*: Adults "**Strong and consistent evidence**… dietary patterns associated with **decreased risk of cardiovascular disease"**
  - **↑ vegetables, fruits, whole grains, low-fat dairy,** and **seafood**
  - **↓ red and processed meat, refined grains,** and **sugar-sweetened foods and beverages**
  - Regular **nuts and legumes** and **moderate alcohol**
- "(2015 Dietary Guidelines Advisory Committee Grade: Strong)"

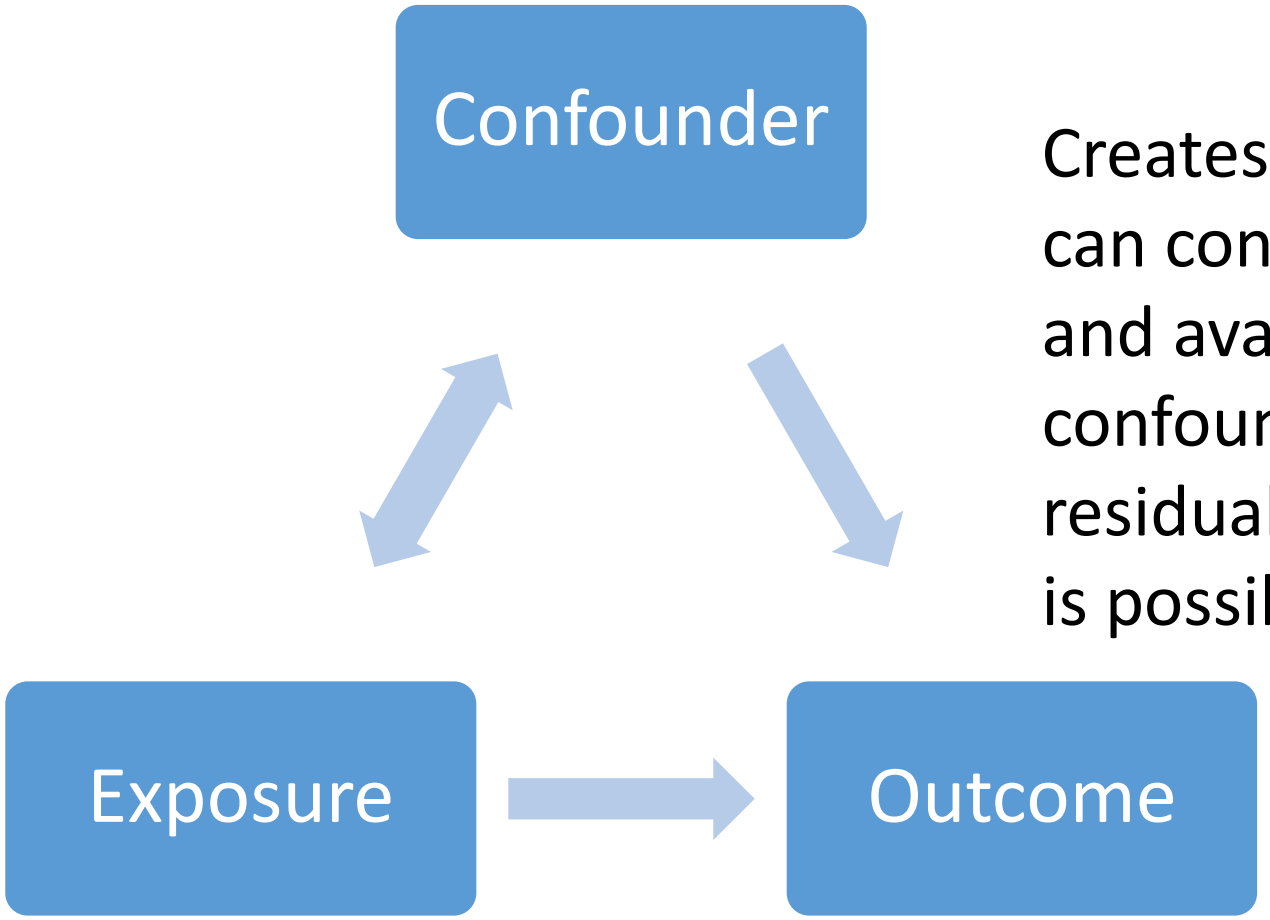
2020 Dietary Guidelines Advisory Committee and Nutrition Evidence Systematic Review Team. Dietary Patterns and Risk of Cardiovascular Disease: A Systematic Review. 2020 Dietary Guidelines Advisory Committee Project. Alexandria, VA: U.S. Department of Agriculture, Food and Nutrition Service, Center for Nutrition Policy and Promotion, July 2020.

Added Sugars Consumption and Risk of Cardiovascular Disease: A Systematic Review

- *Conclusion and Grade*: "Limited evidence from prospective cohort studies that were based primarily on sugar-sweetened beverages suggests that **higher consumption of added sugars in adulthood is associated with increased risk of cardiovascular disease mortality**. (Grade: Limited)"
- Insufficient evidence for 6 other PICO questions
- Limitations: **studies not designed for this question, less generalizable to younger, older, and non-white, multiple areas with potential risk of bias**

2020 Dietary Guidelines Advisory Committee and Nutrition Evidence Systematic Review Team. Added Sugars Consumption and Risk of Cardiovascular Disease: A Systematic Review. 2020 Dietary Guidelines Advisory Committee Project. Alexandria, VA: U.S. Department of Agriculture, Food and Nutrition Service, Center for Nutrition Policy and Promotion, July 2020.

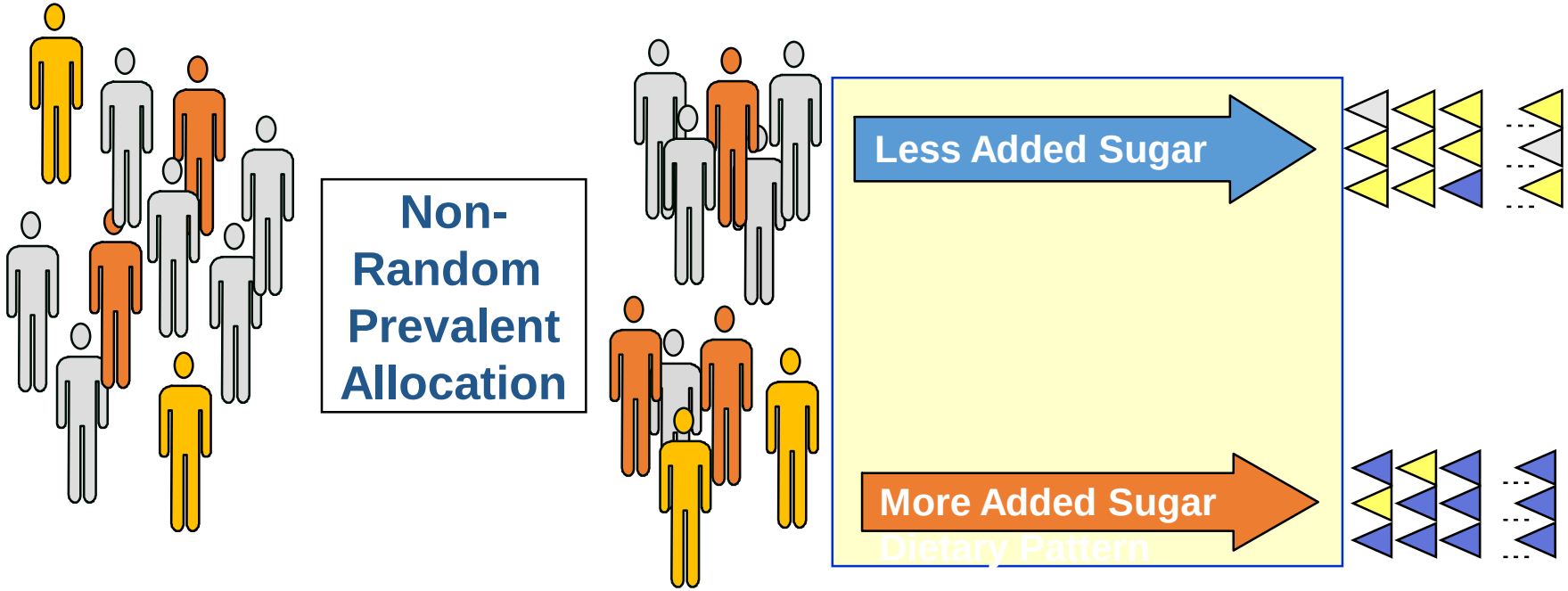
Undiagnosed Confounding Creates Bias in Observational Studies



Creates bias however can control for known and available confounders but residual confounding is possible

Verbeek JH, et al.; GRADE Working Group. An approach to quantifying the potential importance of residual confounding in systematic reviews of observational studies: A GRADE concept paper. Environ Int. 2021 Dec;157:106868.

Non-randomized Observational Evidence Generation



- Patients with ↑ risk factors (race/ethnicity, SES, naturally occurring sugar, physical activity, smoking) may lead ↑ **cardiovascular disease**
- **Residual Confounding**: not all of the studies controlled for these known risk factors associated with outcome

Dietary Evidence

Randomized Controlled Trials

- Robust evidence for efficacy and causal inference
- Better inference if one-time intervention & short follow-up
- But not possible to control for dietary regimen (except supplement)
- Low adherence to specific dietary regimens

Cohort Studies

- External validity
- Long-term association of lifestyle behaviors and patient outcomes
- But risk for bias and residual confounding, e.g., prevalent-user design
- Inappropriate comparators
- Measurement errors

Schwingshackl L, et al. An Empirical Evaluation of the Impact Scenario of Pooling Bodies of Evidence from Randomized Controlled Trials and Cohort Studies in Nutrition Research. Adv Nutr. 2022 Oct 2;13(5):1774-1786.

Systematic Scoping of Recommendations to Systematic Review and Meta-analyze Observational Studies

- 2461 articles → 93 eligible for identifying 10 key methodological items
- Only 1 of 93 addressed all 10 key items with 10% to 56% making recommendations for any 1 key item
- "A comprehensive guidance document on how to conduct evidence synthesis of observational studies is lacking."
- Most important areas: "**width of research questions, considering randomized trials and non-randomized studies in one assessment pooling, and assessment of quality of observational studies using summary scores**"

Mueller M, et al. Methods to systematically review and meta-analyse observational studies: a systematic scoping review of recommendations. BMC Med Res Methodol. 2018 May 21;18(1):44.

Pooling Bodies of Evidence from Randomized Controlled Trials RCTs and Cohort Studies (CSs) in Nutrition Research

- 10% of Cochrane reviews nutrition and 2% with observational studies
- 33 systematic reviews (SR) of RCTs and 46 matching SRs of CSs with 160 effect estimates from 773 RCTs and 720 CSs
  - 56 diet-disease associations "similar but not identical" & 24 "broadly similar"
- Of the 80, # excluding no effect by 95% CI
  - 17 (21%) from RCTs I^2=0%
  - 43 (54%) from CSs I^2=55%
  - 7 (9%) for both

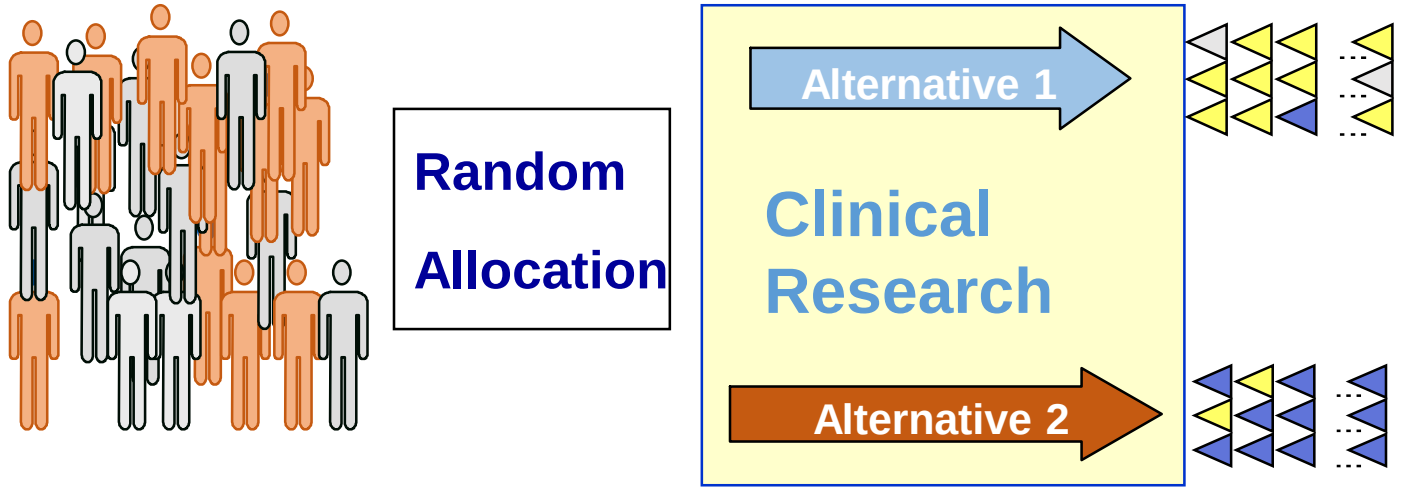
} Pool RCT+CSs changed 35 RCTs (44%) diet-disease association w/ 66% of evidence CSs I^2 = 46% (vs 0% RCT & 55% CSs)

Recommend "analyzing RCTs and CSs in separate MAs, or, if combined together, with a subgroup analysis, a random effects model, and excluding CSs with a critical RoB"

Schwingshackl L, et al. An Empirical Evaluation of the Impact Scenario of Pooling Bodies of Evidence from Randomized Controlled Trials and Cohort Studies in Nutrition Research. Adv Nutr. 2022 Oct 2;13(5):1774-1786.

Analysis and Interpretation of Subgroups

"The dilemma articulated by Bernard in 1865 still haunts the clinician: the **response of the 'average' patient to therapy is not necessarily the response of the patient being treated**."



Yusuf S *et al JAMA* 1991;266:93-8

Analysis and Interpretation of Subgroups

- International Study of Infarct Survival (ISIS-2) trial found mortality benefit for aspirin over placebo when given for suspected heart attack ($P < 0.00001$)
- Divide 17,000 patients into 12 subgroups
  - Two had no benefit for aspirin (G & L)
  - One had one-half of benefit from aspirin (C)
- "When clinicians believe such subgroup analyses, there is a real danger of harm to the individual patient"

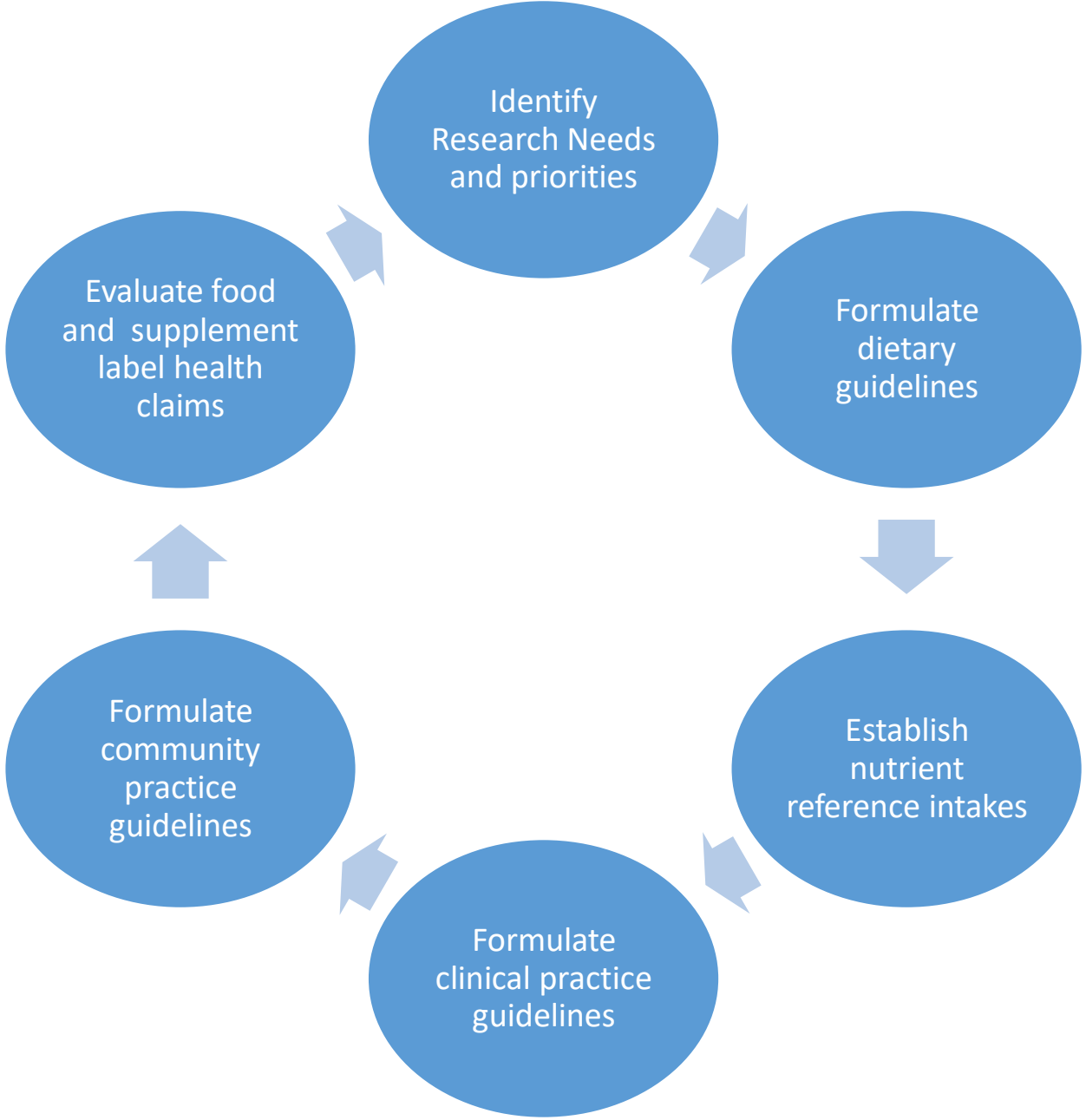
Peto R *Br J Cancer* 2011;104:1057-8; Sleight P *Curr Control Trials Cardiovasc Med* 2000;1:25–7

Heterogeneity of Treatment Effect

- **Average benefit driven by subset at greatest risk for outcome**
- Risk stratified analysis of Diabetes Prevention Program trial: 3060 impaired glucose randomized to placebo, metformin or lifestyle
- Lowest risk quartile
  - Metformin: non-significant ↑diabetes (9.6% vs 8.3% control)
  - Lifestyle: 4.9% absolute risk ↓ (NNT=20)
- Highest risk quartile
  - Metformin: 21% absolute risk ↓ (NNT=4.6)
  - Lifestyle: 28% absolute risk ↓ (NNT=3.5)
- Precision nutrition for prevention and management of type 2 diabetes nutrigenomics, metabolomics, and gut microbiome

Sussman JB, et al. Improving diabetes prevention with benefit based tailored treatment: risk based reanalysis of Diabetes Prevention Program. BMJ. 2015 Feb 19;350:h454; Wang DD, Hu FB. Precision nutrition for prevention and management of type 2 diabetes. Lancet Diabetes Endocrinol. 2018 May;6(5):416-426.

Applications of Systematic Review Methodology to the Field of Nutrition: Learning Healthcare System



Lichtenstein AH, Yetley EA, Lau J. Application of systematic review methodology to the field of nutrition. J Nutr. 2008 Dec;138(12):2297-306. doi: 10.3945/jn.108.097154. PMID: 19022948; PMCID: PMC3415860.

Backup Slides

Unique Considerations for Nutrition-related Systematic Reviews

- **Baseline exposure**: background dietary food, supplement or endogenous synthesis
- **Nutrient status**: nutrient-specific tissue and homeostatic mechanism
- **Bioequivalence** of different chemical forms of nutrients: folate, folic acid
- **Bioavailability**: iron and pregnancy
- **Multiple & interrelated biological functions of a nutrient**: Vit D, calcium
- **Undefined nature of nutrient intervention**: food-based vs supplement
- **Uncertainties in assessing dose response relationships**: dietary or recall

Lichtenstein AH, Yetley EA, Lau J. Application of Systematic Review Methodology to the Field of Nutrition. (Prepared by the Tufts Evidence-based Practice Center under Contract No. 290-020022). AHRQ Publication No. 09-0025. Rockville, MD: Agency for Healthcare Research and Quality. January 2009. Chapter 3.

Issues and Challenges in Systematic Reviews for Nutrient Reference Values

- **Multiple bioactive forms**: nutrient conversation factors
- **Baseline exposure**: background or habitual diet & deletion or supplement
- **Nutrient status**: baseline prior to intervention, body store status, and bioavailability across cultures through coingestion or non-food
- **Body weight changes**: weight loss on hormone and iron release or weight gain on increasing nutrient reservoirs
- **Bioequivalence**: natural/fortified, food processing, added synthetic form
- **Food supplement**: calcium-fortified orange juice

Russell R, Chung M, Balk EM, et al. Issues and Challenges in Conducting Systematic Reviews to Support Development of Nutrient Reference Values: Workshop Summary. (Prepared by the Tufts Evidence-based Practice Center under Contract No. 290-02-0022). AHRQ Publication No. 09-0026-2. Rockville, MD: Agency for Healthcare Research and Quality. March 2009. p8.

A Proposed Framework for Identifying Nutrients and Food Components of Public Health Relevance in the Dietary Guidelines for Americans

- Define terminology
- Establish quantitative thresholds to identify “nutrients or food components” (NFCs) of public health concern by life stage
- Examine national data
  1. Dietary intakes
  2. Biological endpoints
  3. Clinical health consequences such as prevalence of health conditions, directly or indirectly through validated surrogate markers
- Multiple limitations: Biomarkers of nutrient status based on NHANES 2003-2006, DRI may not be up to date, nonexistent nutritional biomarkers

Bailey RL et al. J Nutr 2021;151:1197-1204

Frequency of Eating during Pregnancy and Gestational Weight Gain: A Systematic Review

- *Conclusion and Grade*: **No evidence** is available to determine the relationship between the frequency of eating during pregnancy and gestational weight gain. (Grade: Grade not assignable)

2020 Dietary Guidelines Advisory Committee and Nutrition Evidence Systematic Review Team. Frequency of Eating during Pregnancy and Gestational Weight Gain: A Systematic Review. 2020 Dietary Guidelines Advisory Committee Project. Alexandria, VA: U.S. Department of Agriculture, Food and Nutrition Service, Center for Nutrition Policy and Promotion, July 2020.

Dietary Patterns during Pregnancy and Gestational Weight Gain: A Systematic Review

- *Conclusion and Grade*: **Limited evidence** suggests that dietary patterns during pregnancy higher in vegetables, fruits, nuts, legumes, fish, and lower in added sugar, and red and processed meat are associated with a lower risk of excessive gestational weight gain during pregnancy. (Grade: Limited)
- Limitations: few RCTs so primarily observational with inconsistent control of key confounders and risk-of-bias issues

2020 Dietary Guidelines Advisory Committee and Nutrition Evidence Systematic Review Team. Dietary Patterns during Pregnancy and Gestational Weight Gain: A Systematic Review. 2020 Dietary Guidelines Advisory Committee Project. Alexandria, VA: U.S. Department of Agriculture, Food and Nutrition Service, Center for Nutrition Policy and Promotion, July 2020.