Diet and Cancer: Evaluating the Quality of the Evidence

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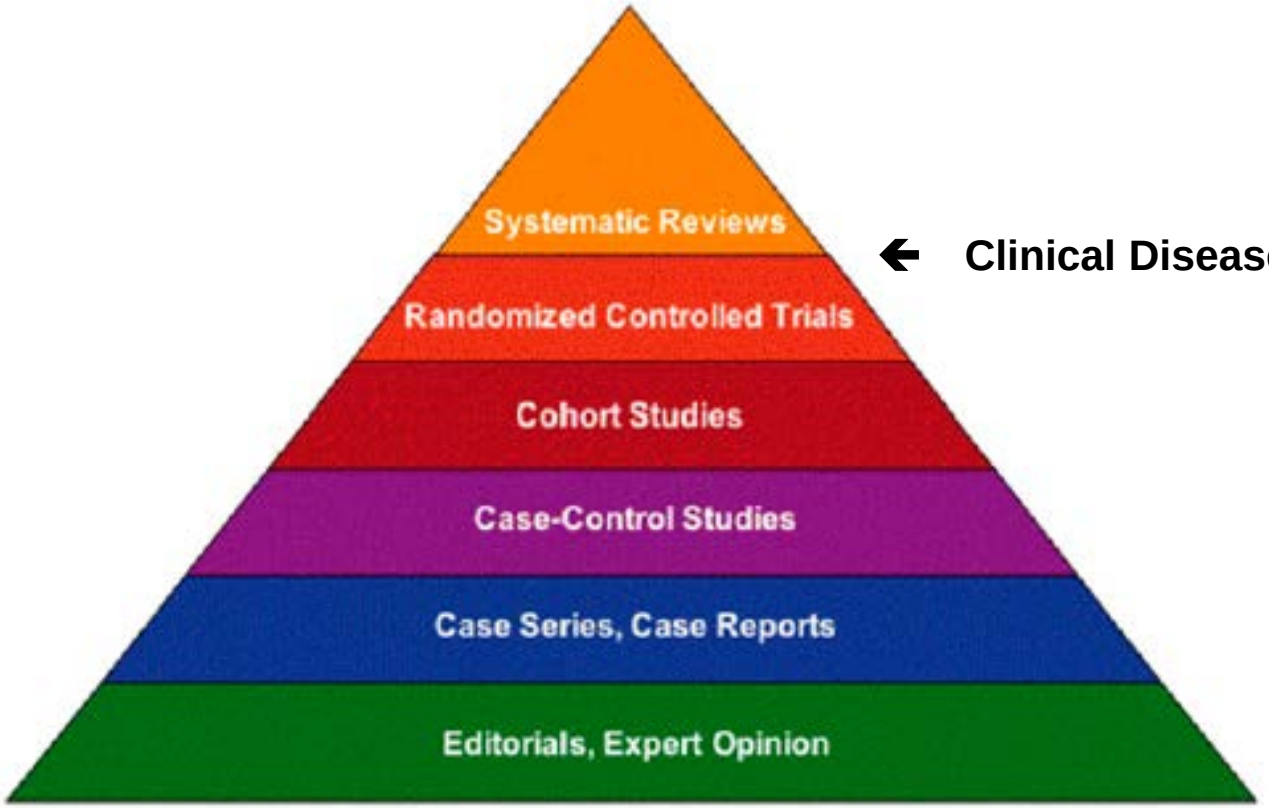
Evidence-based Medicine

- **An approach to the development of clinical guidelines and health policy recommendations**
  - Example: Dietary Guidelines for Americans
- **Considers all available evidence on benefits and risks; weighs the evidence according to a hierarchy based on the type of study design and study quality**
  - All study designs have strengths and limitations
  - A study higher on the hierarchy will not provide a more reliable answer if it is poorly designed
  - Most clinical trials (top of hierarchy) answer a narrow question in a select, and often non-representative sample

EBM Hierarchy of Study Design



← **Clinical Disease Event RCTs**

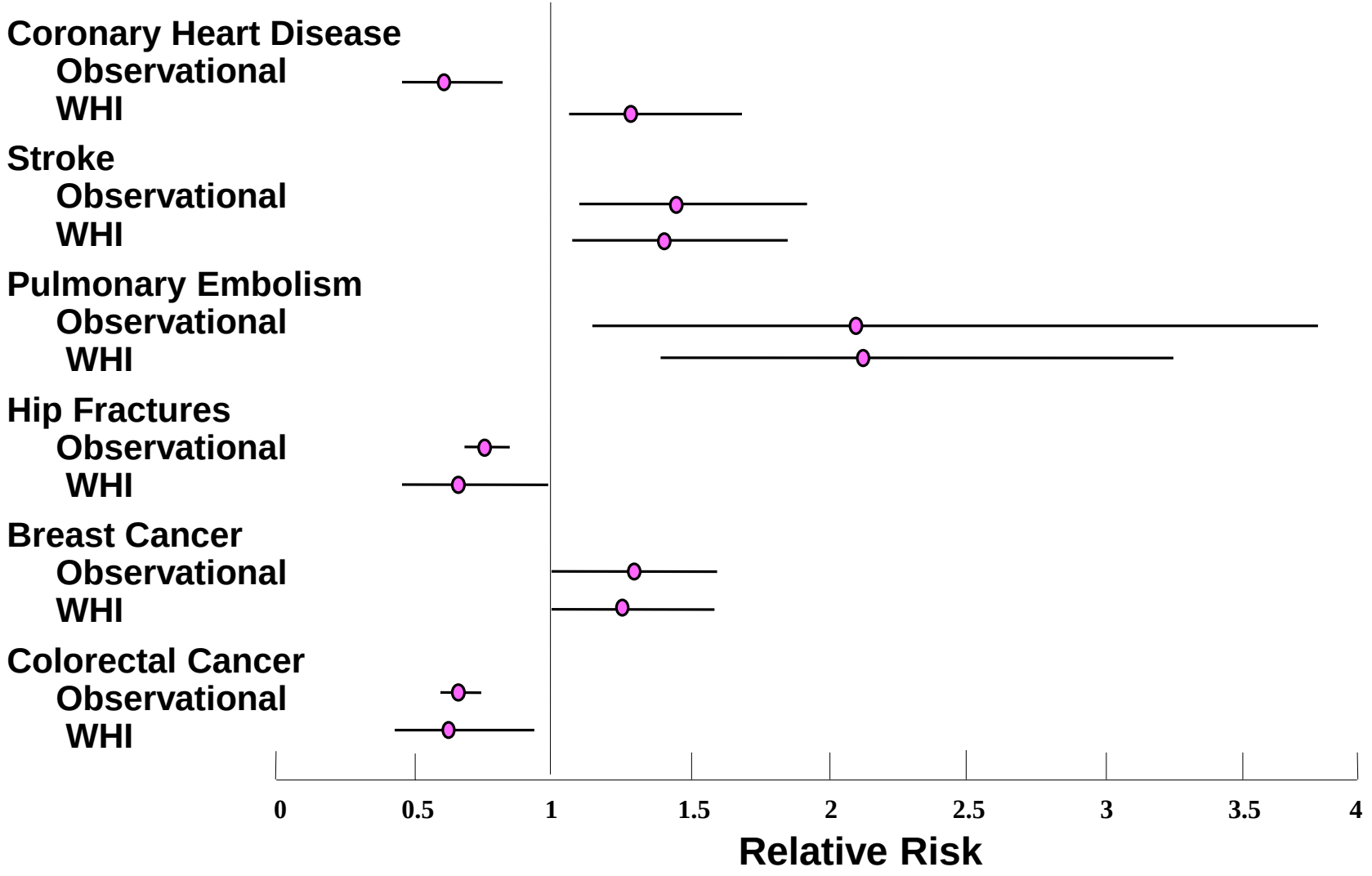
Available from: http://ebp.lib.uic.edu/nursing/node/12

Strengths and Weaknesses of Lines of Evidence

RCTs	Observational Studies
Strengths • Gold standard for testing clinical interventions with least susceptibility to certain types of bias (e.g., selection bias) **Weaknesses** • Mainly used in the evaluation of drugs – few reliable RCTs of lifestyle interventions • Concerns about generalizability – results may be of uncertain clinical relevance to those with characteristics that differ from RCT participants • Expensive and often answer a very narrow question	**Strengths** • Simpler and less expensive than large-scale RCTs to evaluate clinical outcomes • Many research questions that cannot be easily addressed in RCTs can be investigated using observational study designs **Weakness** • Generally have greater risk of bias and confounding than RCTs

IAS Panel. J Clin Lipidol. 2014;8:29-60.

Postmenopausal Hormone Therapy and Health Outcomes



Manson JE, et al. N Engl J Med. 2003;349:523-534.

Reduced CHD Risk Associated with Higher Vitamin E Intake in the US Health Professionals Prospective Cohort

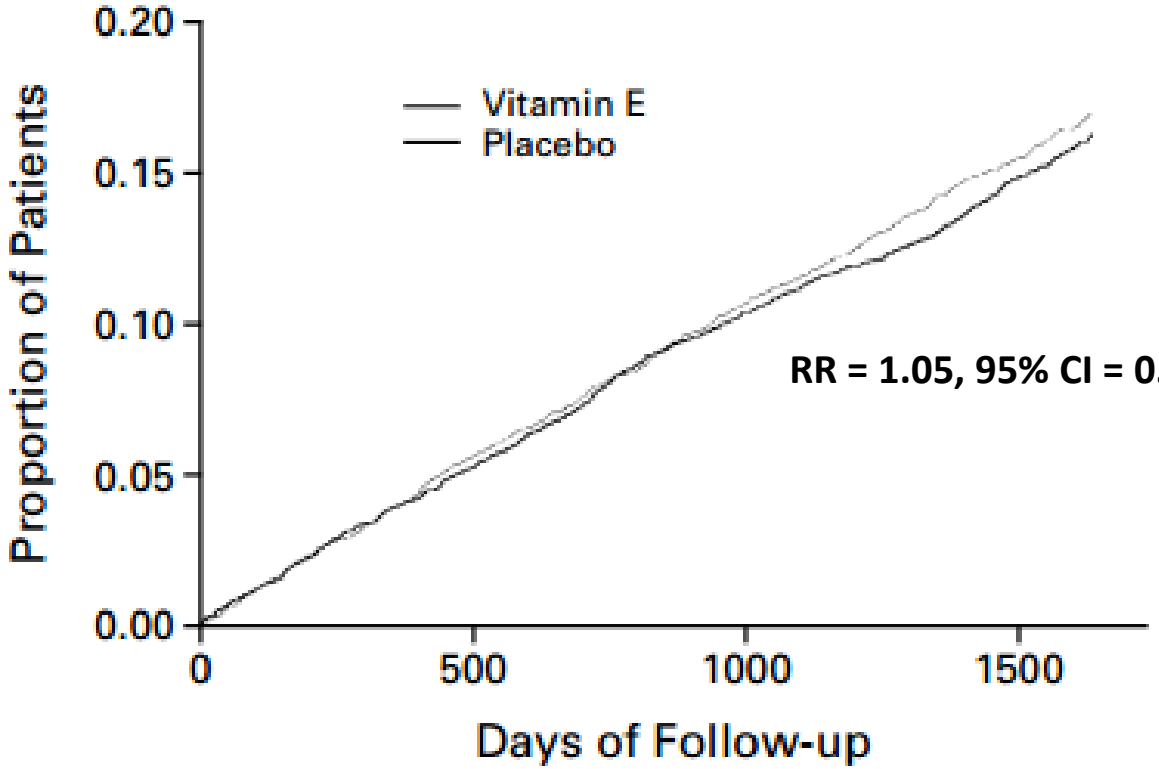
Variable*	Quintile Group					P Value for Trend
	1	2	3	4	5	
Vitamin E — median intake (IU/day)	**6.4**	**8.5**	**11.2**	**25.2**	**419**	
Coronary disease — no. of cases	155	140	130	127	115	
Relative risk						
Age-adjusted	1.0	0.88	0.77	0.74	0.59	0.001
95% CI	—	0.70–1.10	0.61–0.98	0.59–0.93	0.47–0.75	
Multivariate	1.0	0.90	0.82	0.77	0.64	0.003
95% CI	—	0.71–1.14	0.64–1.07	0.60–0.98	0.49–0.83	
Multivariate with anti-oxidants	1.0	0.89	0.81	0.71	0.60	0.01
95% CI	—	0.70–1.14	0.62–1.05	0.54–0.92	0.44–0.81	

Most in the top quintile group used vitamin E supplements

Rimm EB, et al. N Engl J Med. 1993;328:1450-1456.

RCTs Have Failed to Show Reduced CVD Events with Vitamin E Supplementation

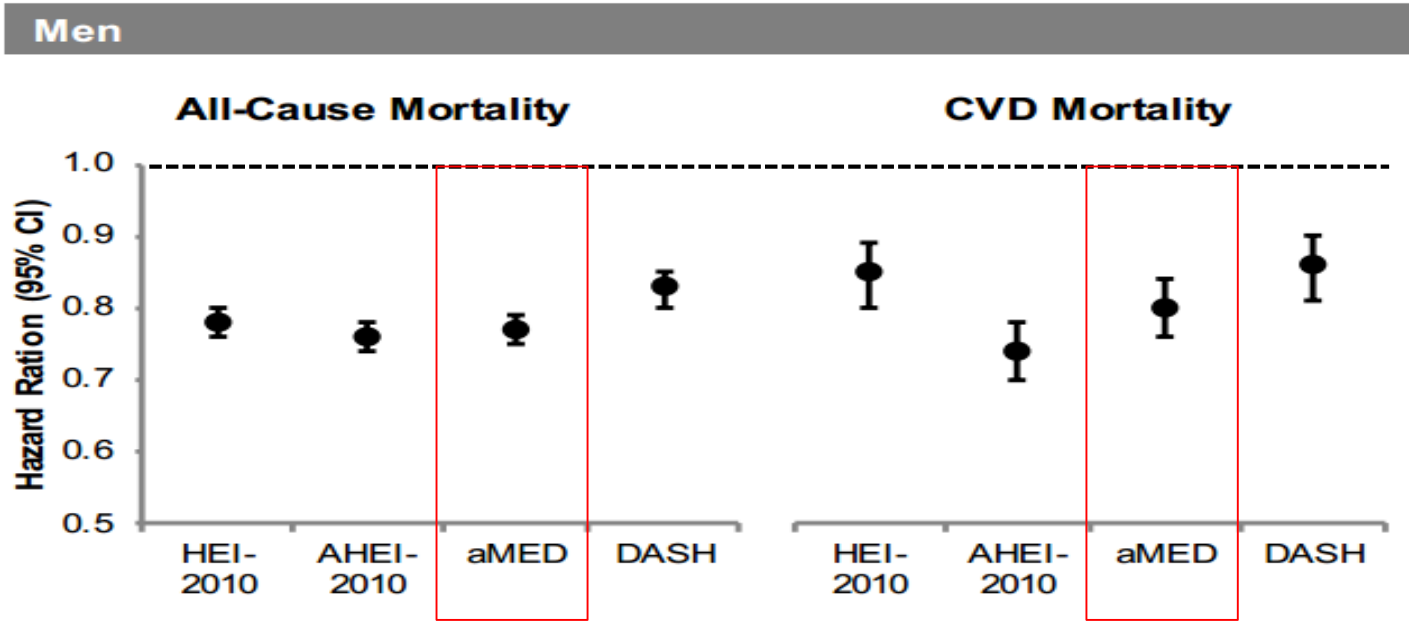
Effect of Vitamin E on the Composite Outcome of Nonfatal MI, Stroke, or Death from CV Causes in the HOPE Study



RR = 1.05, 95% CI = 0.95 to 1.16, p = 0.33

Yusuf S, et al. N Engl J Med. 2000;342:154-160.

Observational Evidence Supports Association Between Mediterranean Diet Pattern and Reduced CVD and Mortality Risks



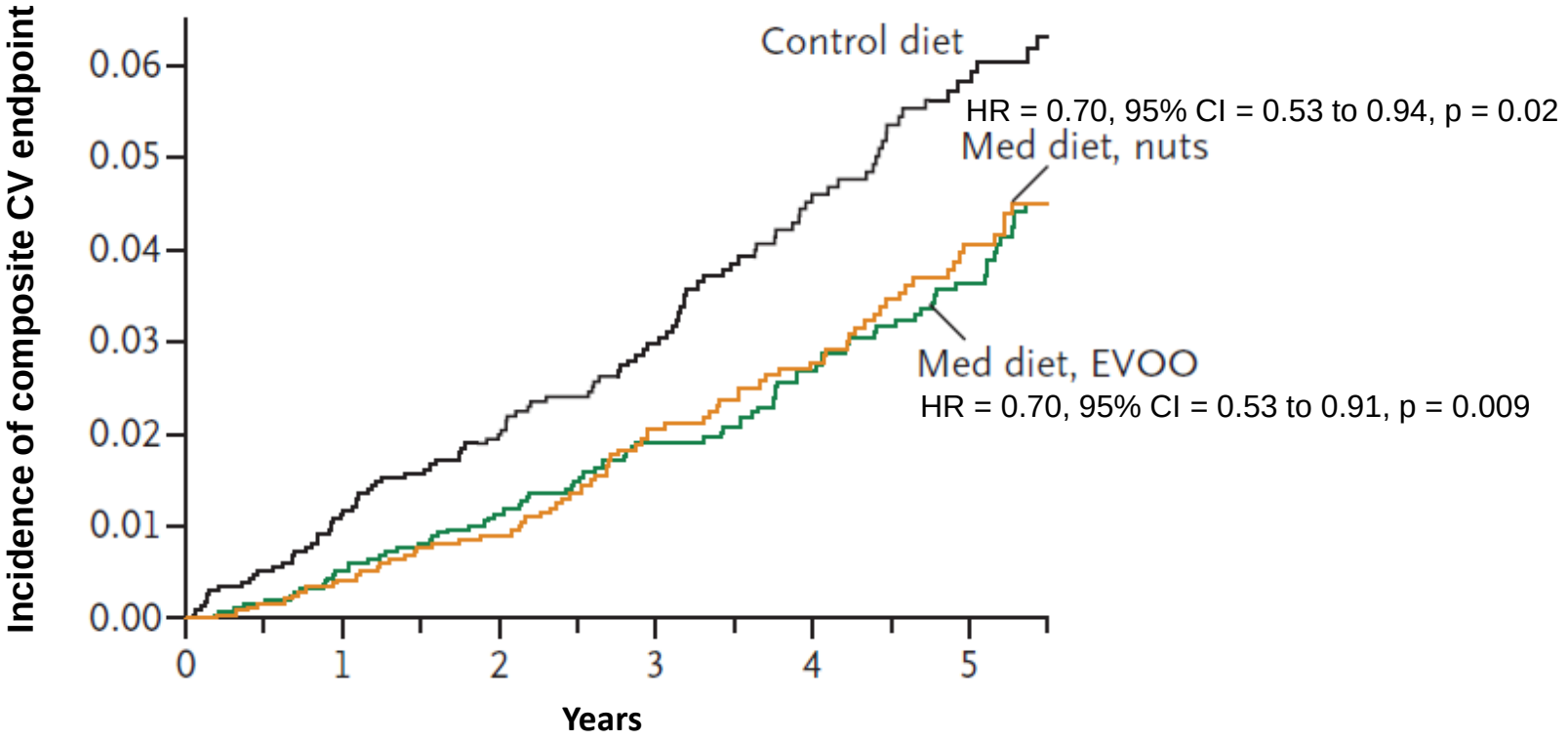
Multivariate HRs and 95% CIs for all cause mortality and CVD, comparing highest (Q5) to lowest quintile index scores (Q1) for the Healthy Eating Index-2010 (HEI-2010), Alternative Healthy Eating Index-2010 (AHEI-2010), Alternate Mediterranean Diet (aMED), and Dietary Approaches to Stop Hypertension (DASH) Score among 242,321 men

Mediterranean Diet characteristics include high consumption of non-refined grains, legumes, nuts, fruits, vegetables, olive oil, fish and red wine.

Reedy J, et al. J Nutr. 2014;144:881-889.

Alignment of RCTs with Observational Findings for Mediterranean Diet and Reduced CVD Risk

Effect of supplemented Mediterranean diets on acute MI, stroke, or death from CV causes in the Prevención con Dieta Mediterránea (PREDIMED) Trial



Estruch R, et al. N Engl J Med. 2013;368:1279-1290.

Evidence-based Public Health Nutrition

"…conducting RCTs [of dietary interventions] under real-world conditions is very challenging and often impossible because of enormous logistical, ethical, and political challenges. In addition, even when feasible, RCTs have serious external validity (generalizability) limitations because it is commonly found that not all population subgroups respond in the same way ..."

– R Pérez-Escamilla, et al.

Perez-Escamilla R, King J. J Nutr. 2007;137:478-479.

Evidence-based Dietary Recommendations

- **For most diet-disease relationships, policy recommendations are based mainly on observational studies and RCTs of surrogate markers (risk factors or measures of subclinical disease) due to the absence of RCTs examining disease incidence**
  - As a result, prospective cohort studies are often the strongest evidence available
    - Limitations of such data are frequently underappreciated among nutrition scientists and other policymakers

Review Paper

Limitations of Observational Evidence: Implications for Evidence-Based Dietary Recommendations[1,2]

Kevin C. Maki,[3]* Joanne L. Slavin,[4] Tia M. Rains,[3] and Penny M. Kris-Etherton[5]

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©2014 American Society for Nutrition. Adv. Nutr. 5: 7–15, 2014; doi:10.3945/an.113.004929.

Methodological Limitations of Observational Data

Several issues inherent to the study of dietary exposures warrant highlighting:

1) Measurement error
2) Co-linearity
3) Displacement/substitution effects
4) Healthy or unhealthy consumer bias
5) Confounding and effect modification
6) Modest associations with diet-disease relationships

Measurement Error

- **Dietary intake tools are imperfect measures of exposure**
  - Random error
    - Biases diet exposure-disease relationship toward the null
  - Systematic error
    - Can bias a relationship in either direction
    - Ex: under-reporting of energy intake (greater underestimation with higher BMI); over-reporting of “healthy” foods, under-reporting of “unhealthy” foods
- **Changes in the food supply and dietary habits over time**
  - Incomplete information in food and nutrient databases
  - Dietary exposures measured long before onset of disease

Co-linearity

- **Highly correlated nature of nutrients and dietary components adds complexity to the interpretation of results**

- **Example: dietary fiber**
  - Commonly found in foods also high in magnesium and B vitamins
  - Therefore, it is difficult to establish independence of associations between fiber intake and disease risk

Displacement and Substitution Effects

- **An association between the intake of a food or nutrient and a disease outcome could be an indication of a harmful or protective effect of the dietary exposure under study *or* it could reflect a harmful or protective effect of the displacement of other foods and/or nutrients from the diet**

Healthy or Unhealthy Consumer Bias

- **Intake of a food, or category of food, may be associated with other variables that may be difficult or impossible to fully adjust for in statistical modeling**
  - This likely accounts for the association between use of postmenopausal estrogen-progestin therapy and lower CHD risk (e.g., Nurses' Health Study) that was not confirmed in RCTs (e.g., Women's Health Initiative)

Confounding and Effect Modification

- **Some non-dietary risk factors may not be measured, or may be measured imprecisely, resulting in residual <u>confounding</u>**
  - Example: physical activity is related to risks for heart disease and some cancers
  - Most large-scale cohorts have assessed physical activity with questionnaires that provide very crude estimates of daily activity

- **The influence of a dietary exposure may vary according to characteristics of the individual, producing different effects in subgroups of the population studied (<u>effect modification or interaction</u>)**
  - Example: a high-carbohydrate diet may have different effects in those with normal insulin sensitivity vs. insulin resistance (e.g., a lean marathon runner vs. an obese, sedentary individual).

Most Diet-Disease Associations are of Modest Strength

- **Most diet-disease associations are modest,**
  - Relative risk (RR) or hazard ratio (HR) estimates >0.75 (25% lower risk) and <1.5 (50% higher risk)
  - The closer a point estimate for an association is to the null (odds ratio, RR, or HR of 1.0), the greater is the likelihood that alternative explanations such as bias or residual confounding could account for the association

Hill's Criteria for Judging Causality

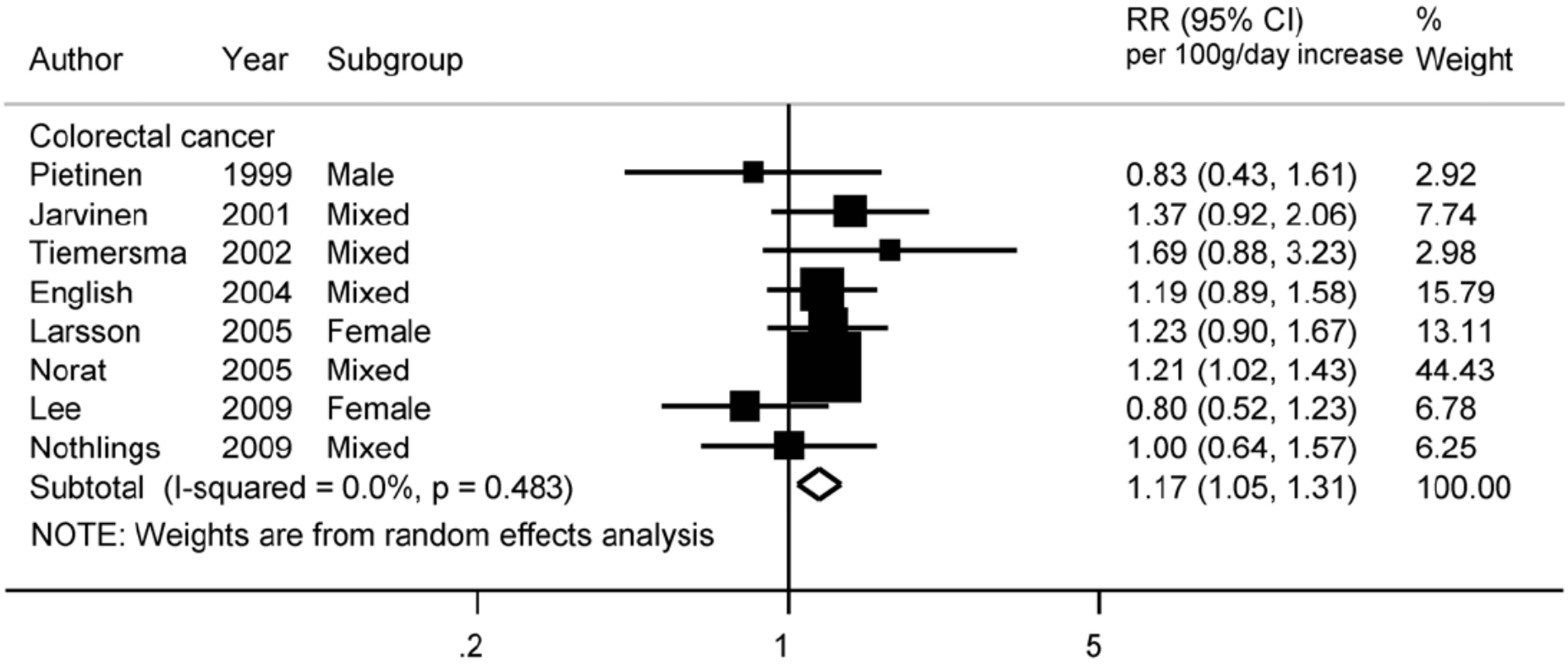
Sir Austin Bradford Hill proposed 9 criteria for judging causality between exposure and disease risk

The most important 6 criteria are:

1. ***Strength*** of association after adjustment for confounders
2. ***Consistency*** of association (different studies, populations, investigators)
3. ***Dose-response*** (biological gradient)
4. ***Biologic plausibility*** (mechanistic explanation)
5. ***Temporality*** (exposure precedes the disease)
6. ***Coherence*** with available data from other sources, including experimental evidence, especially from RCTs

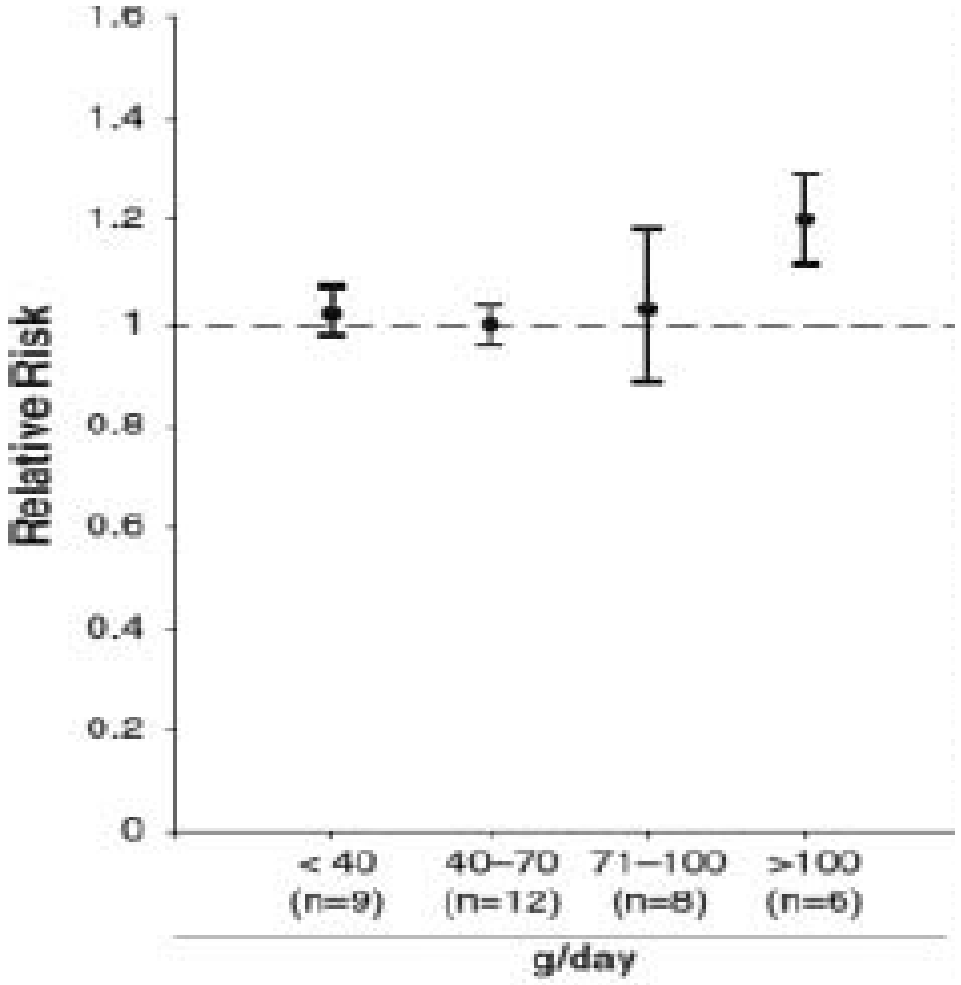
Hill AB, et al. Proc R Soc Med. 1965;58:295-300.

Red Meat Consumption and Colorectal Cancer Risk: Meta-analysis



Chan DSM, et al. PLoS One. 2011;6:e20456.

Red Meat Consumption and Colorectal Cancer Risk: Dose-response Analysis



Alexander DD, et al. J Am Coll Nutr. 2015;34:521-543.

Red Meat Consumption is Correlated with Other Factors

Parameter	Men Q1	Men Q5	% Difference Q5 vs. Q1
Red meat intake (g/1000 kcal)	12.0	67.0	+458%
BMI (kg/m^2)	26.1	28.4	+9%
Smoking: Never smoked (%)	34.3	25.8	-25%
Smoking: Current smoker (%)	6.7	17.5	+161%
Education, higher (%)	51.8	38.5	-26%
Physical activity (5+ times/wk) (%)	29.4	16.0	-46%
Energy intake (kcal/d)	1911	2127	+11%
Fruit intake (servings/1000 kcal)	2.2	1.1	-50%
Vegetable intake (servings/1000 kcal)	2.3	1.9	-17%

NIH-AARP Diet and Health Study.
Cross AJ, et al. PLoS Med. 2007;4:1973-1984.

Effect of a Low-fat, High-fiber Dietary Intervention on Risk of Colon Polyp Recurrence

TABLE 3. REPORTED DAILY DIETARY AND SUPPLEMENT INTAKES, BIOMARKERS, AND WEIGHT.*

VARIABLE	INTERVENTION GROUP		CONTROL GROUP		ABSOLUTE DIFFERENCE IN CHANGE BETWEEN GROUPS (95% CI)†
	AT RANDOMIZATION (N=958)	AT YEAR 4 (N=903)	AT RANDOMIZATION (N=947)	AT YEAR 4 (N=883)	
Fat (% of calories)	35.6±0.2	23.8±0.2	36.0±0.2	33.9±0.2	−9.7 (−10.3 to −9.0)
Fiber (g/1000 kcal)	10.0±0.1	17.4±0.2	9.5±0.1	10.0±0.1	6.9 (6.4 to 7.3)
Fruits and vegetables (servings/1000 kcal)	2.05±0.03	3.41±0.04	2.00±0.03	2.23±0.03	1.13 (1.04 to 1.21)
Calories (kcal/day)	1972±19	1870±16	1981±20	1910±18	−25 (−72 to 22)
Red and processed meat (g/day)	93.2±1.7	74.5±1.4	97.9±1.8	94.9±1.7	−15.8 (−20.2 to −11.5)

Schatzkin A, et al. N Engl J Med. 2000;342:1149-1155.

Effect of a Low-fat, High-fiber Dietary Intervention on Risk of Colon Polyp Recurrence

TABLE 4. RISK OF RECURRENCE OF ADENOMAS AMONG THE SUBJECTS WHO COMPLETED THE STUDY.

VARIABLE	INTERVENTION GROUP (N=958)	CONTROL GROUP (N=947)	RISK RATIO (95% CI)*	P VALUE
	no. of subjects (%)			
No. of adenomas				
⩾1†	380 (39.7)	374 (39.5)	1.00 (0.90–1.12)	0.98
1	219 (22.9)	217 (22.9)	1.00 (0.85–1.18)	1.00
2	88 (9.2)	82 (8.7)	1.06 (0.80–1.41)	0.75
⩾3	73 (7.6)	75 (7.9)	0.96 (0.71–1.31)	0.87

Schatzkin A, et al. N Engl J Med. 2000;342:1149-1155.

Effect of a Low-fat, High-fiber Dietary Intervention on Risk of Colorectal Cancer

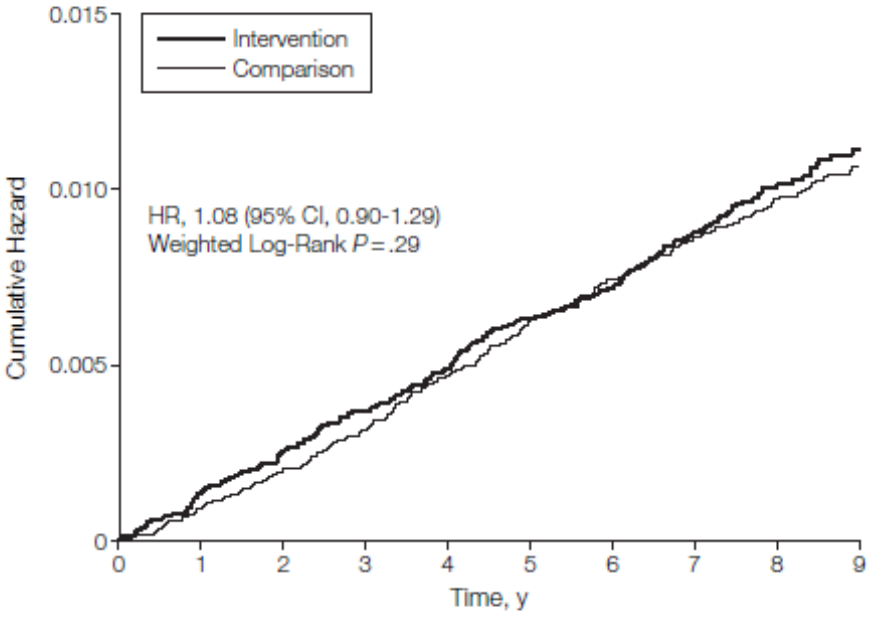
Table 2. Percentage Changes From Baseline to Year 3 for Dietary Factors and Selected Biomarkers Related to Colorectal Cancer Risk*

Risk Factors	Baseline, Mean (SD)		Year 3, Mean (SD)		Change at Year 3, %		
	Intervention	Comparison	Intervention	Comparison	Intervention, Mean (SD)	Comparison, Mean (SD)	Difference, Mean (95% Confidence Interval)
Dietary Factors							
Total energy, kcal/d	1790.2 (710.1)	1789.4 (703.0)	1495.9 (546.1)	1581.9 (647.5)	–10.0 (33.6)	–6.0 (35.1)	–4.1 (–5.6 to –2.5)†
Fiber, g/d	15.4 (6.4)	15.4 (6.4)	17.9 (7.7)	14.8 (6.5)	25.8 (60.7)	1.9 (44.4)	23.8 (21.6 to 26.1)†
Daily energy from fat, %	37.8 (5.1)	37.8 (5.0)	26.7 (7.9)	36.2 (7.1)	–28.6 (20.7)	–3.2 (18.5)	–25.4 (–26.3 to –24.5)†
Daily energy from saturated fat, %	12.7 (2.5)	12.7 (2.5)	8.8 (3.0)	12.1 (3.0)	–28.9 (24.8)	–2.4 (23.1)	–26.4 (–27.5 to –25.4)†
Servings/d							
Red meat	0.9 (0.6)	0.9 (0.6)	0.6 (0.4)	0.8 (0.6)	–9.7 (128.4)	10.5 (114.1)	–20.2 (–25.5 to –14.8)†
Fish	0.3 (0.3)	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)	39.3 (175.8)	43.2 (218.8)	–3.9 (–13.1 to 5.2)
Poultry	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)	25.6 (151.9)	23.3 (166.4)	2.3 (–4.9 to 9.5)
Vegetables and fruits	3.6 (1.8)	3.6 (1.8)	5.2 (2.5)	3.9 (2.0)	67.7 (134.1)	20.3 (89.2)	47.4 (42.5 to 52.2)†
Fruit	1.6 (1.0)	1.6 (1.1)	2.6 (1.5)	1.8 (1.2)	156.6 (542.9)	57.5 (295.7)	99.1 (80.8 to 117.5)†
Vegetables	2.0 (1.1)	2.0 (1.1)	2.6 (1.5)	2.1 (1.2)	60.1 (168.3)	22.7 (120.9)	37.4 (31.1 to 43.7)†
Grains	4.7 (2.5)	4.8 (2.5)	4.6 (2.5)	4.0 (2.2)	15.5 (80.6)	–2.0 (123.5)	17.6 (12.7 to 22.4)†
Vitamin E, mg/d	9.1 (5.7)	9.1 (5.5)	7.3 (5.4)	8.1 (5.0)	–9.1 (72.0)	2.0 (63.8)	–11.2 (–14.2 to –8.2)†
Dietary folate equivalent, µg/d	541.6 (421.1)	541.2 (423.4)	872.4 (480.8)	815.2 (492.7)	133.5 (210.0)	116.7 (192.4)	16.9 (7.8 to 25.9)†

Beresford SA, et al. JAMA. 2006;295:643-654.

Effect of a Low-fat, High-fiber Dietary Intervention on Risk of Colorectal Cancer

Figure 3. Kaplan-Meier Estimated Cumulative Hazards for Invasive Colorectal Cancer (N=48 835)



No. of Events									
Intervention	26	23	22	23	27	16	28	18	9
Comparison	27	32	32	43	44	33	33	22	11
No. at Risk									
Intervention	19541	19402	19218	19004	18784	18576	18290	15909	10507	5260
Comparison	29294	29070	28806	28554	28259	27916	27622	23991	15806	7913

HR indicates hazard ratio; CI, confidence interval.

Beresford SA, et al. JAMA. 2006;295:643-654.

Conclusions

- **Observational studies have value with regard to identifying diet-disease relationships, but their limitations are often underappreciated by nutrition scientists and policymakers.**
- **Given these limitations, it is not surprising that diet-disease relationships demonstrated in prospective cohort studies are not uniformly supported by RCT results.**
- ***The strongest dietary recommendations should be reserved for areas in which there is alignment between observational findings* and those from RCTs of clinical events*.**
  - *Considering strength, consistency, temporality, dose-response, biologic plausibility, coherence with other evidence (esp. RCTs)