Epidemiology of weak associations
The case of nutrition and cancer

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Causality in epidemiology

- Epidemiology can lead to the identification of specific components that explain the causes of cancer at the population level within a multi-causal framework
- Observational nature of most epidemiological investigations
  - potential role of systematic error (bias and confounding)
- Causal inference in epidemiology requires systematic error to be excluded
  - in addition to exclusion of random error and coherence with other lines of evidence

Sources of systematic error

- Bias
  - selection bias
    - groups of study subjects are not comparable
  - information bias
    - measurement error in exposure, outcome or covariates
  - reporting bias
    - published results represent a selected set
- Confounding
  - an extraneous factor explains the association between exposure and outcome

Hill's guidelines for causality

- In 1965 Hill proposed a set of guidelines, derived from those used in a 1964 US SG Report on Health Effects of Smoking to establish the causal nature of the association between tobacco smoking and lung cancer
- Hill's guidelines have become the paradigm of criteria to evaluate the causal nature of results of observational studies
  - several modifications have been proposed since

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Hill's guidelines

- Strength of Association
- Temporality
- Consistency
- Theoretical Plausibility
- Coherence
- Specificity in the Causes
- Dose Response Relationship
- Experimental Evidence
- Analogy

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Strength of association

- The association between a risk (or protective factor) and cancer is measured by comparing the occurrence of cancer in groups defined according to exposure to the risk factor
  - ratio of disease risk/odds/rate in exposed and unexposed
- The stronger the relationship between the independent variable and the dependent variable, the less likely it is that the relationship is due to an extraneous variable

Relative risk – Scenario 1

	Exposed	Non-exposed
Total	10,000	10,000
Cases	1,500	100
Non-cases	8,500	9,900
Risk	0.15	0.01

Relative risk 0.15/0.01 = 15
95% confidence interval 12.3, 18.3

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Relative risk – Scenario 2

	Exposed	Non-exposed
Total	10,000	10,000
Cases	150	100
Non-cases	9,850	9,900
Risk	0.015	0.01

Risk ratio 0.015/0.01 = 1.5
95% confidence interval 1.17, 1.93

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Weak associations

- Intuitively, we lend more credibility to 'strong' than to 'weak' associations
  - where is the boundary?
- Weak associations are more likely to be explained by chance, bias and confounding (and their combinations)

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Examples of 'old' carcinogens

Agent	Target organ	RR
Sunlight	Skin	3
Tobacco chewing	Oral cavity	4
Tobacco smoking	Lung	15
Alcohol drinking	Oral cavity	5
Aromatic amines	Bladder	8
Asbestos	Lung	5

WHO, 1964

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Examples of 'new' carcinogens

Agent	Target organ	Year	RR
Tobacco smoking	Liver	2004	1.6
Involuntary smk	Lung	2004	1.25
Formaldehyde	NPC	2007	1.3
Alcohol drinking	Breast	2007	~1.2
1,3 Butadiene	Lymphohem.	2008	1.15

Meta-analyses of lung cancer from involuntary smoking

Source of exposure	N studies	RR	95% CI
Spouse, women	44	1.24	1.14, 1.35
Case-control studies	39	1.23	1.13, 1.35
Cohort studies	5	1.28	1.07, 1.53
Spouse, men	9	1.36	1.02, 1.82
Workplace	20	1.17	1.04, 1.32

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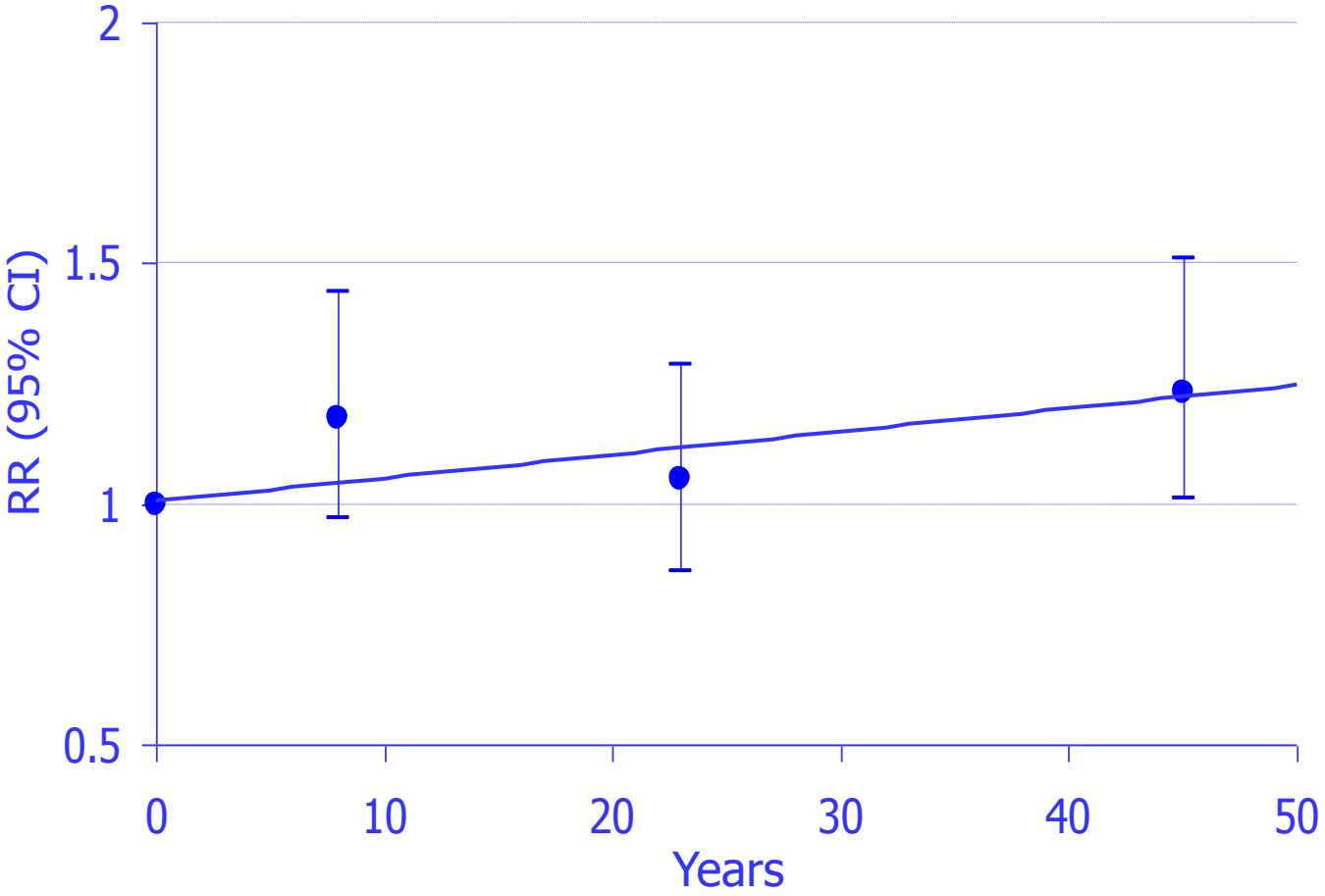
Effect of duration of spousal exposure

Pooled analysis of case-control studies



Brennan et al., 2004

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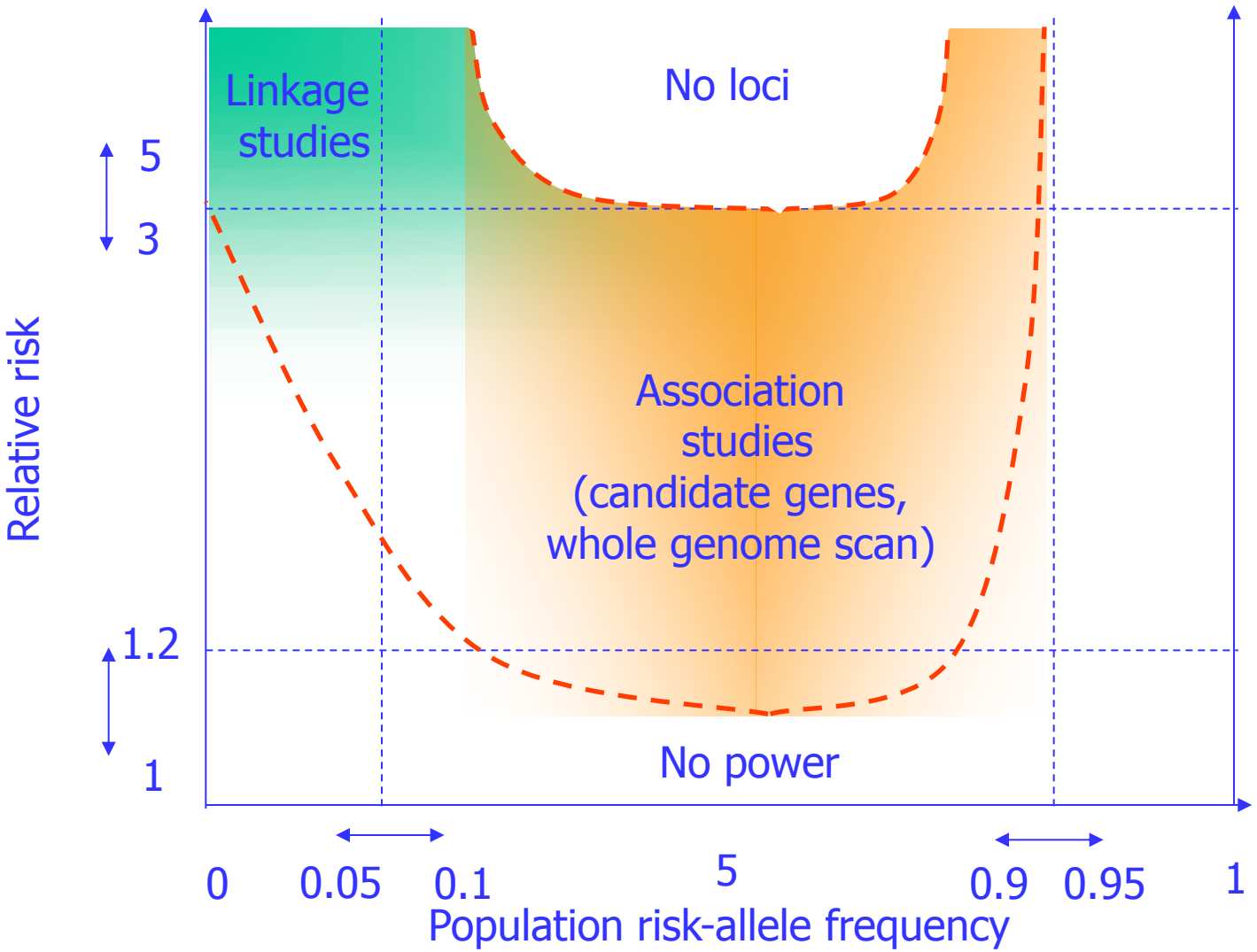
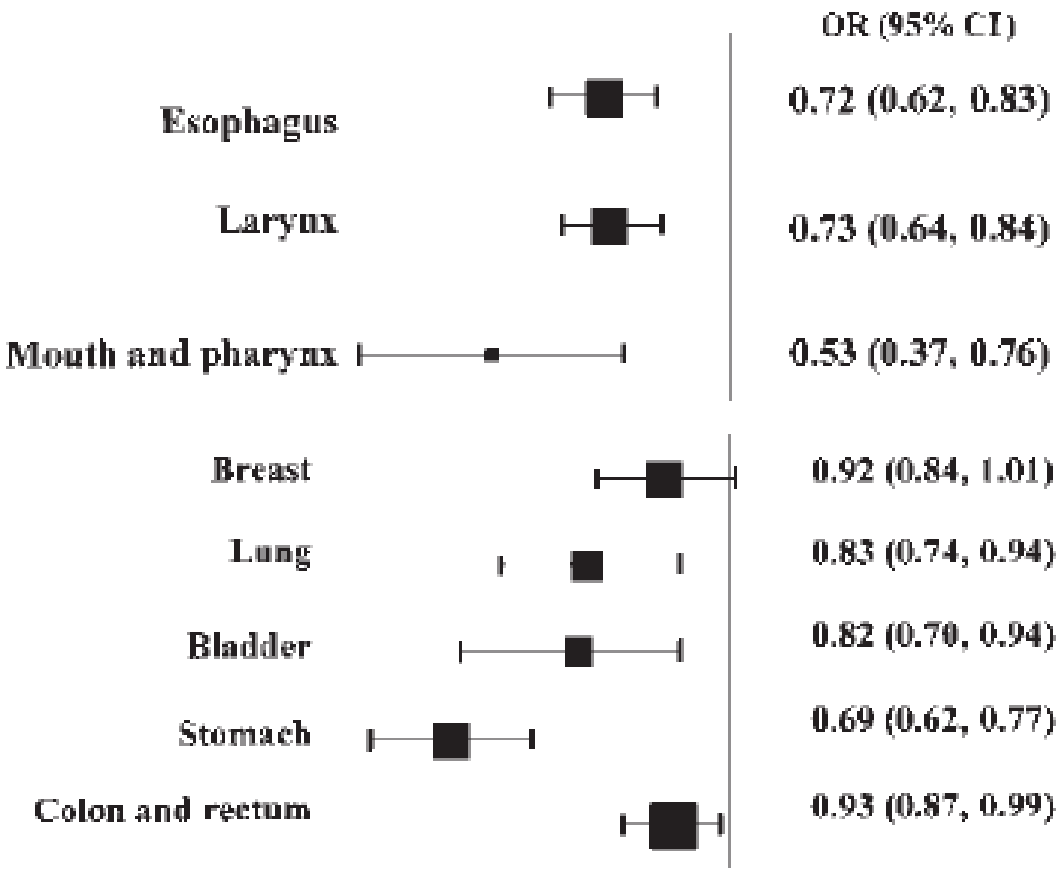
Weak associations in genetic cancer epidemiology



Meta-analysis of case-control studies of fruit intake and cancer risk



Riboli & Norat, 2003

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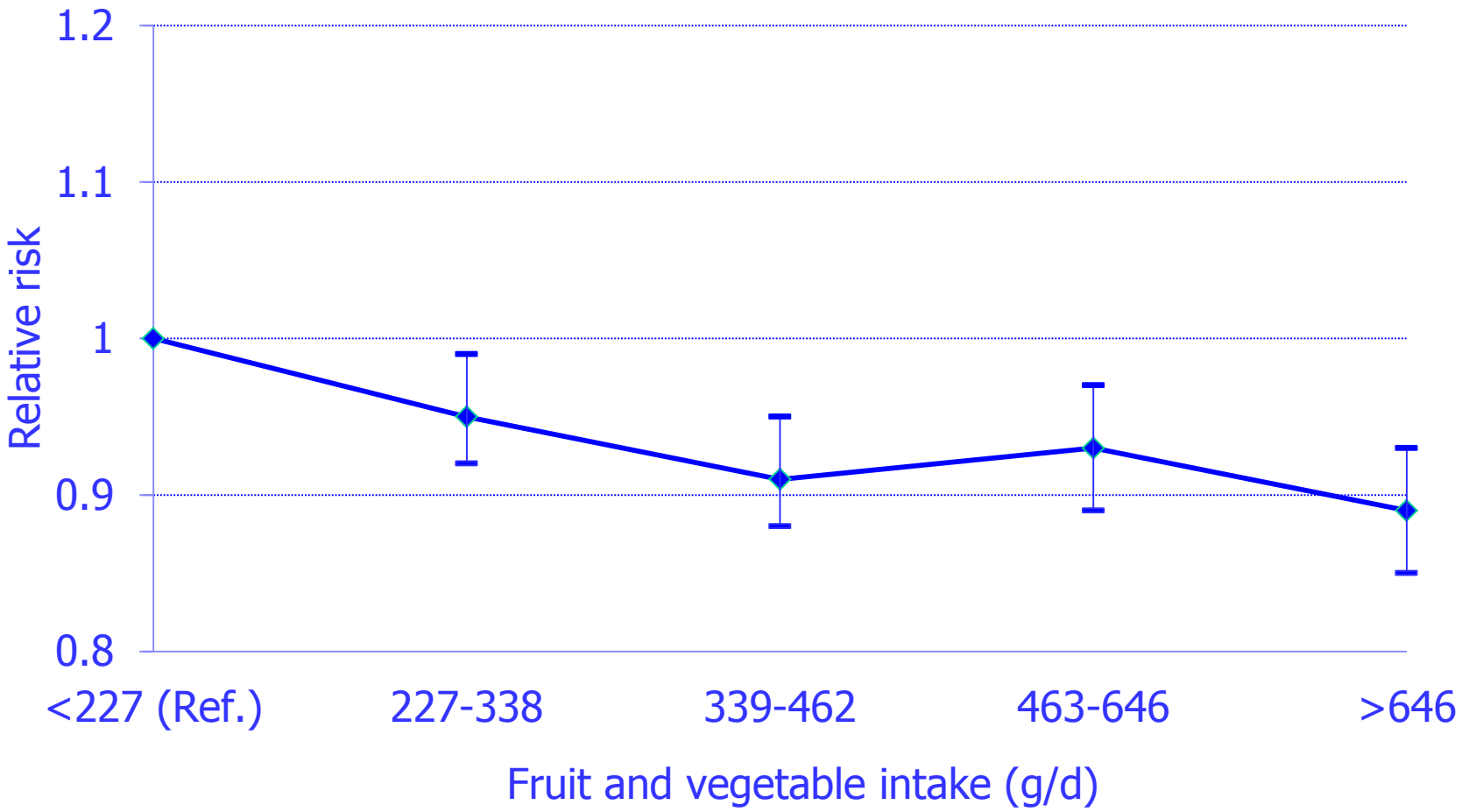
Fruit and vegetable intake and cancer risk - the EPIC study

	Men		Women		Overall	
Food group	**n**	**HR (95% CI)***	**n**	**HR (95% CI)***	**n**	**HR (95% CI)***
Vegetable intake						
Continuous (100 g/d, uncalibrated)	9604	0.98 (0.96 to 1.00)	21 000	0.98 (0.97 to 0.99)	30 604	0.98 (0.97 to 0.99)
Continuous (100 g/d, calibrated)	9604	1.02 (0.97 to 1.07)	21 000	0.95 (0.92 to 0.98)	30 604	0.97 (0.94 to 0.99)
Fruit intake						
Continuous (100 g/d, uncalibrated)	9604	0.98 (0.97 to 1.00)	21 000	1.00 (0.99 to 1.01)	30 604	0.99 (0.98 to 1.00)
Continuous (100 g/d, calibrated)	9604	0.98 (0.96 to 1.01)	21 000	0.99 (0.97 to 1.01)	30 604	0.99 (0.98 to 1.00)

Group of cancers	**Associated, HR (95% CI)***	**Not associated, HR (95% CI)***
Association with tobacco smoking†		
Number of cancer cases	5034	25 570
Fruits and vegetables (200 g/d, continuous)	0.92 (0.90 to 0.95)	0.98 (0.97 to 1.00)

Boffetta et al., 2010

Relative risk of cancer for fruit and vegetable intake (categorical analysis)



Boffetta et al., 2010

Strength of the evidence of a reduction in cancer risk from high vegetable and fruit intake

Evidence	*Vegetables*	*Fruits*
Convincing	Oral, oesophagus, lung, stomach, colon, rectum	Oral, oesophagus, lung, stomach
Probable	Larynx, pancreas, breast, bladder	Larynx, pancreas, breast, bladder
Possible	Liver, cervix, ovary, endometrium, prostate, kidney, thyroid	Cervix, ovary, endometrium, thyroid

WCRF, 1997

High vegetable and fruit intake and reduction in cancer risk – WCRF 2007

Evidence	*Vegetables*	*Fruits*
Convincing	-	-
Probable	Oral, larynx, esophagus, stomach	Oral, larynx, esophagus, lung, stomach
Possible	Lung, colorectum, ovary, endometrium	Pancreas, liver, colorectum

WCR., 2007

Meta-analysis of risk of stomach cancer from high intake of vegetables and fruits, by study design

	Case-control			Cohort		
	RR	95% CI	N	RR	95% CI	N
Vegetables	0.70	0.62-0.79	21	0.98	0.91-1.06	9
Fruits	0.67	0.59-0.76	29	0.95	0.89-1.02	9

WCRF, 2007

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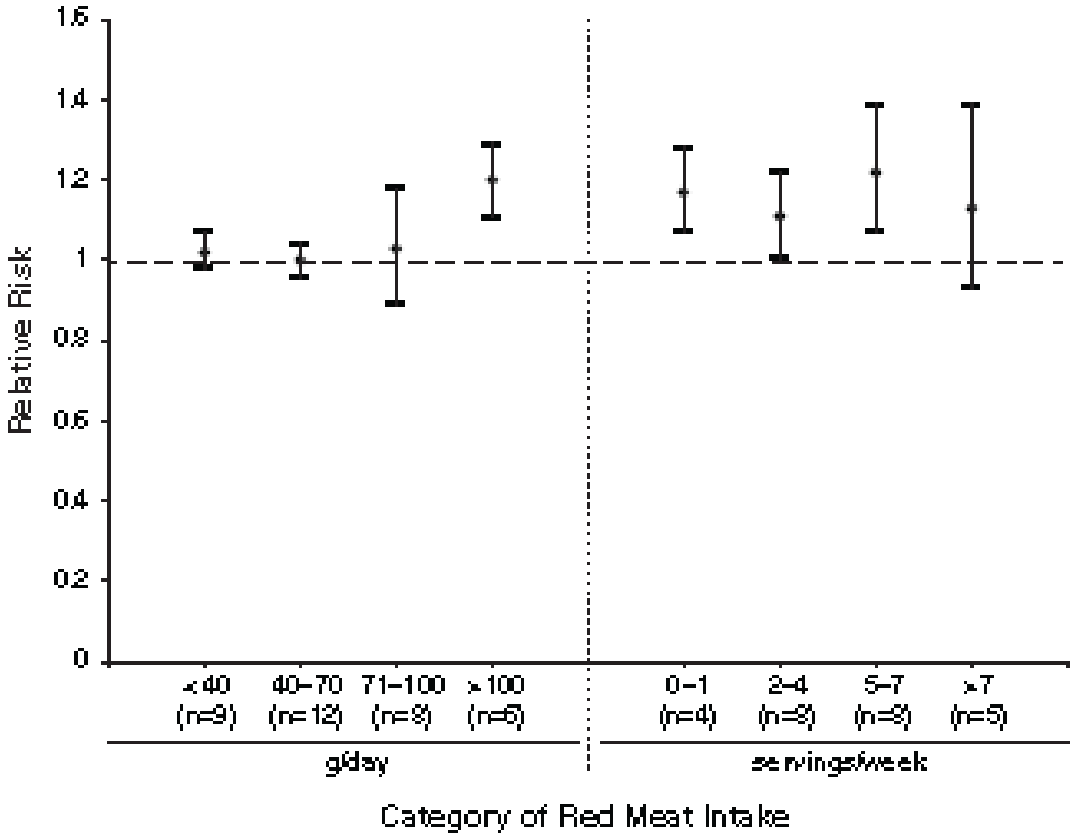
Meta-analysis of read meat intake and colorectal cancer risk



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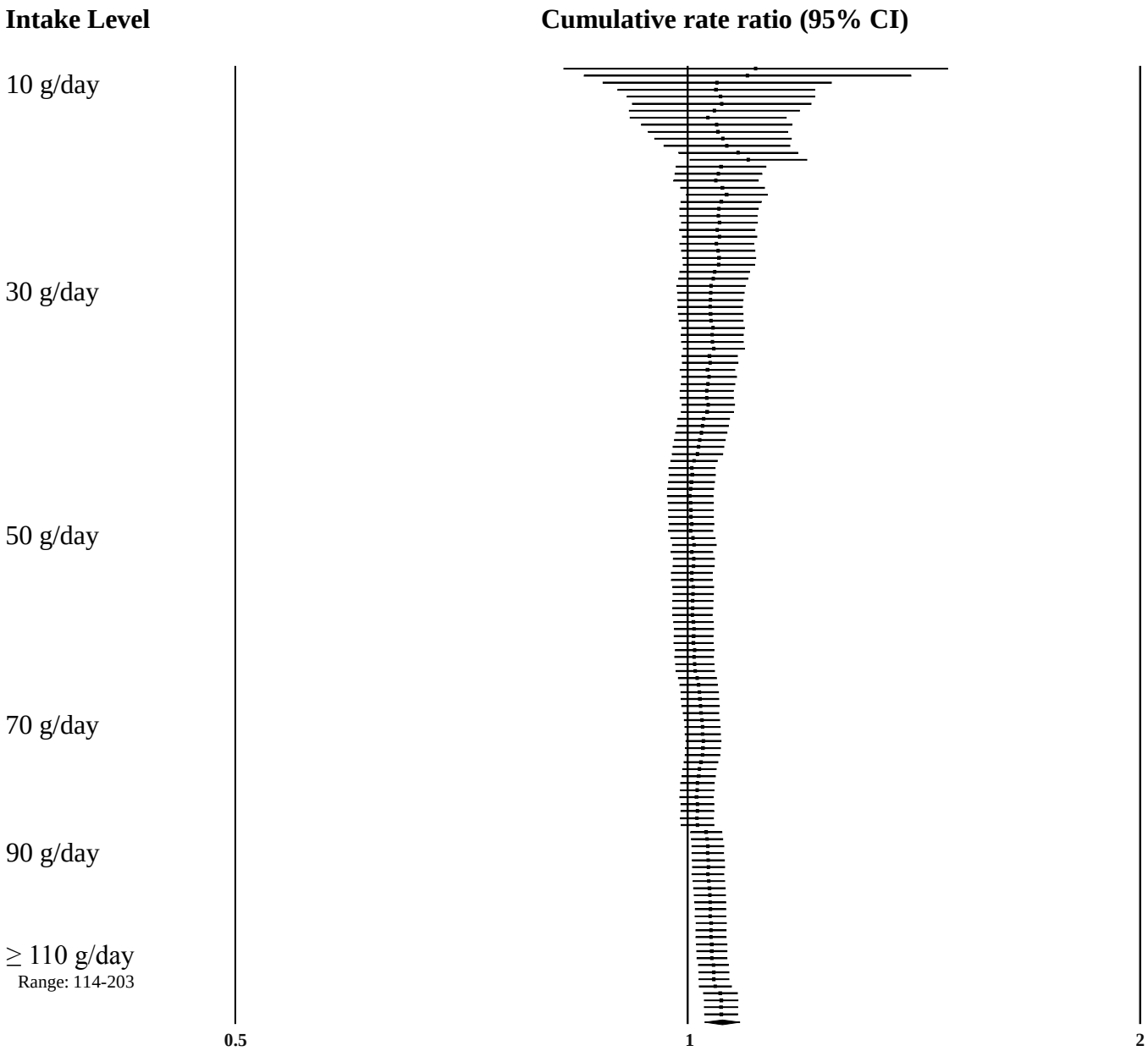

Read meat intake and risk of colorectal cancer
Cumulative meta-analysis

Issues in nutritional epidemiology

- Exposure misclassification
  - repeated measurements
  - intra-individual variation
  - use of biomarkers
  - biologically relevant temporal interval
    - early-life nutrition
- Residual confounding
  - correlations between foods and nutrients
- Level of analysis
  - nutrients, foods, patterns

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Experimental vs. observational studies
Trials of ß-carotene and lung cancer mortality

Study	*Setting, population, age*	*Follow-up*	*Dose*	*RR*	*CI*
Blot et al., 1994	Linxian, China; 29,584, 40-69	1986-91	15 mg	0.55	0.26-1.14
ATBCCPSG 1994	Finland; 29,133 m smokers, 50-69	1985-93	20 mg	**1.18**	1.03-1.36
Hennekens et al., 1994	USA; 22,071 m physicians, 40-84	1982-95	25 mg	0.93	NA
Omenn et al, 1994	USA; 18,314 smk/asbestos workers, 45-74	1985-95	30 mg	**1.28**	1.04-1.57

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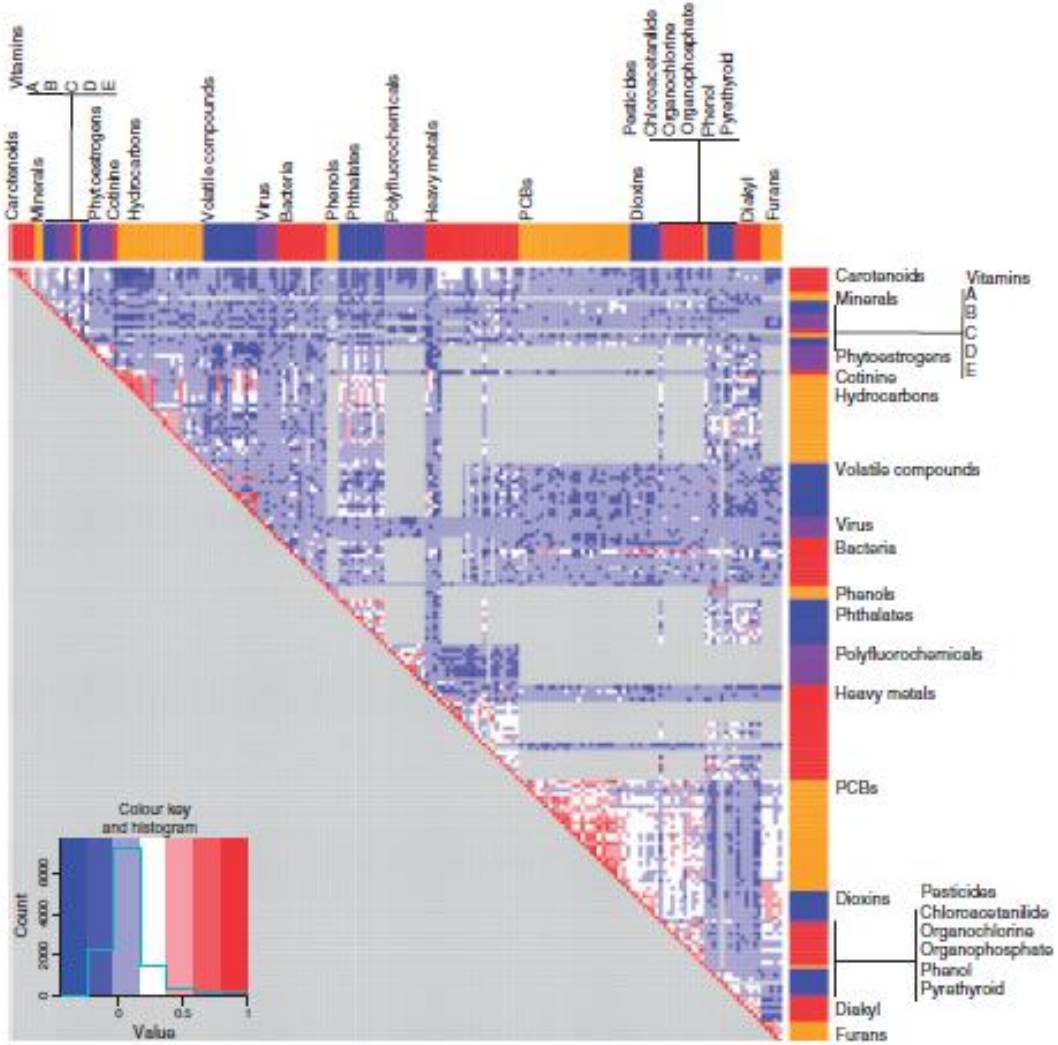
Correlation between 188 nutritional, microbial and environmental biomarkers NHANES



Patel et al., 2012

Food safety
The epidemiologic perspective

- Epidemiology cannot provide definite evidence for lack of risk
- Even if the absence of an association, positive results are generated because of chance and bias
- Role of critical reviews and meta-analyses
- Need for new guidelines

Toxicology and Epidemiology: Improving the Science with a Framework for Combining Toxicological and Epidemiological Evidence to Establish Causal Inference

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Conclusions

- Weak associations represent a major challenges to epidemiologic research
  - environmental, genetic, nutritional epidemiology
- Way forward
  - increase statistical power via large studies and consortia
  - use of valid study design
  - improvement in exposure assessment
  - integration of knowledge from biology
- Proactive role of food industry

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