The role of epidemiology in cancer hazard identification by the *IARC Monographs* programme

Mary Schubauer-Berigan, PhD, MS

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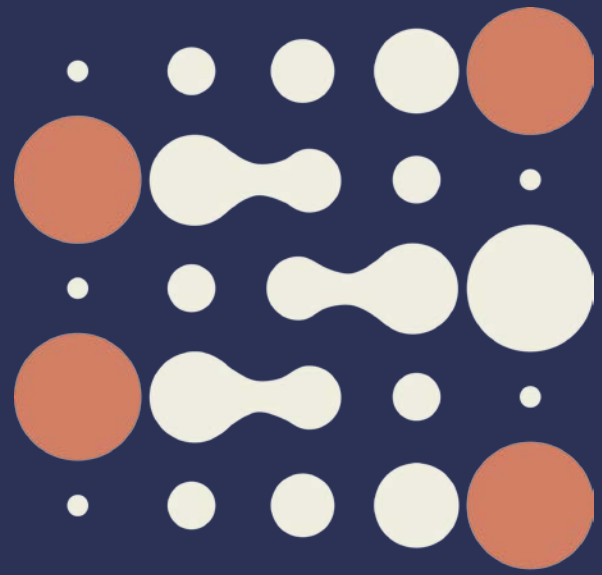
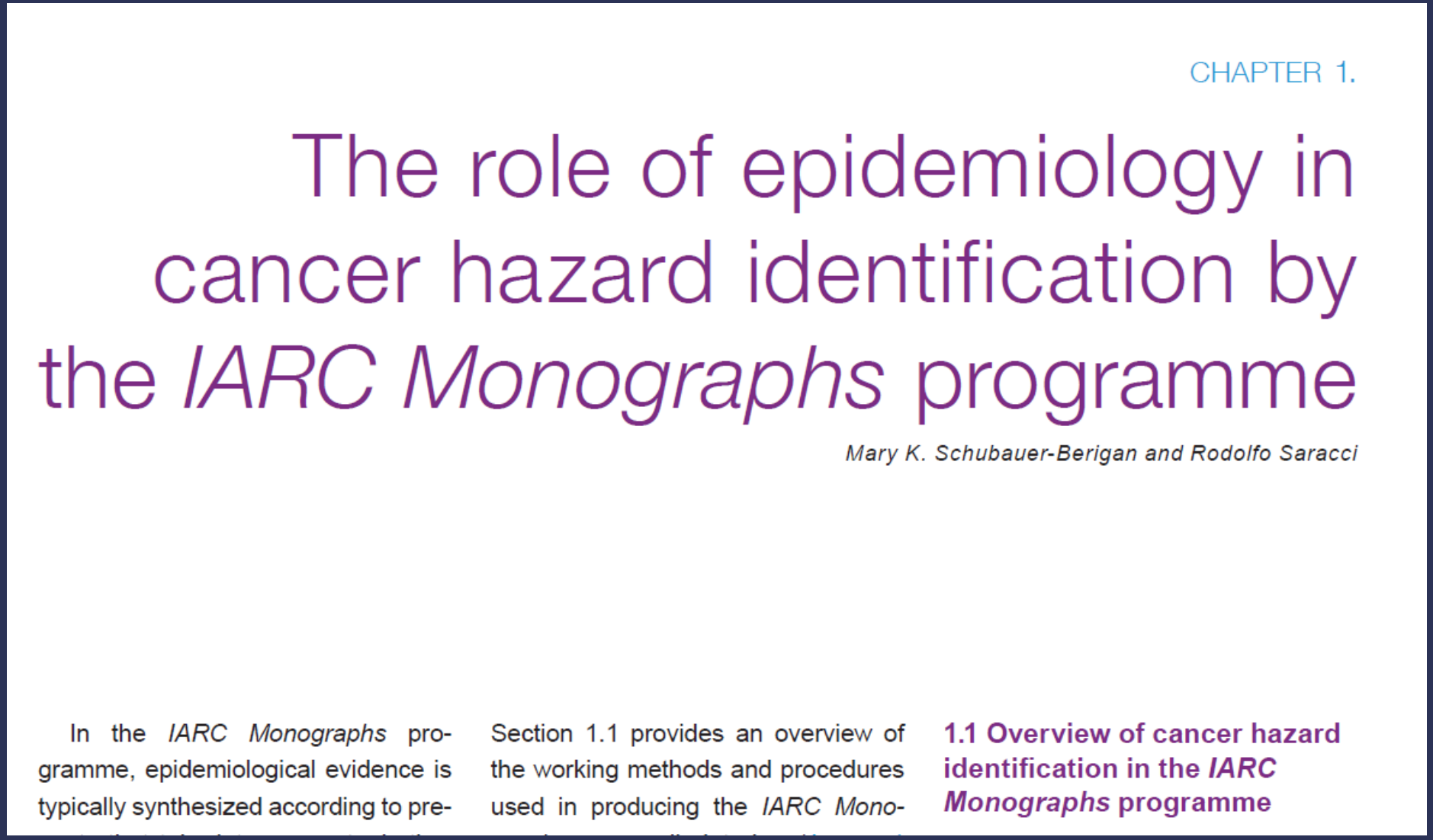
Evidence Synthesis and Classification Branch
International Agency for Research on Cancer, Lyon, France

International Agency for Research on Cancer

World Health Organization



I have no competing interests to declare



CHAPTER 1.

The role of epidemiology in cancer hazard identification by the *IARC Monographs* programme

Mary K. Schubauer-Berigan and Rodolfo Saracci

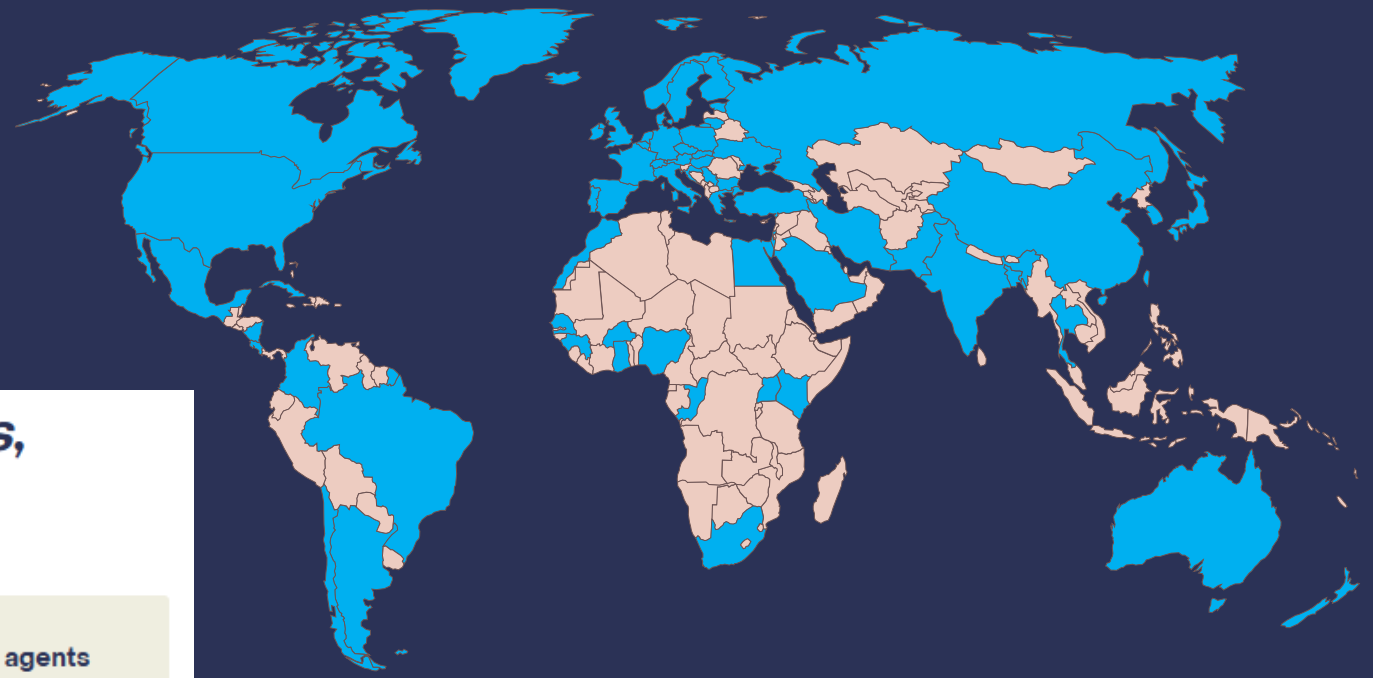
In the *IARC Monographs* programme, epidemiological evidence is typically synthesized according to pre-

Section 1.1 provides an overview of the working methods and procedures used in producing the *IARC Mono-*

1.1 Overview of cancer hazard identification in the *IARC Monographs* programme

IARC Monographs: a comprehensive global programme of cancer hazard identification

Chemicals · physical & biological agents · pharmaceuticals · metals · particles · fibres · complex mixtures · occupational circumstances



Agents Classified by the *IARC Monographs*, Volumes 1–137

Group 1	Carcinogenic to humans	132 agents
Group 2A	Probably carcinogenic to humans	96 agents
Group 2B	Possibly carcinogenic to humans	320 agents
Group 3	Not classifiable as to its carcinogenicity to humans	499 agents

Since 1971, >1400 scientists from 59 countries have participated in *Monographs* meetings

IARC Monographs on cancer hazard identification

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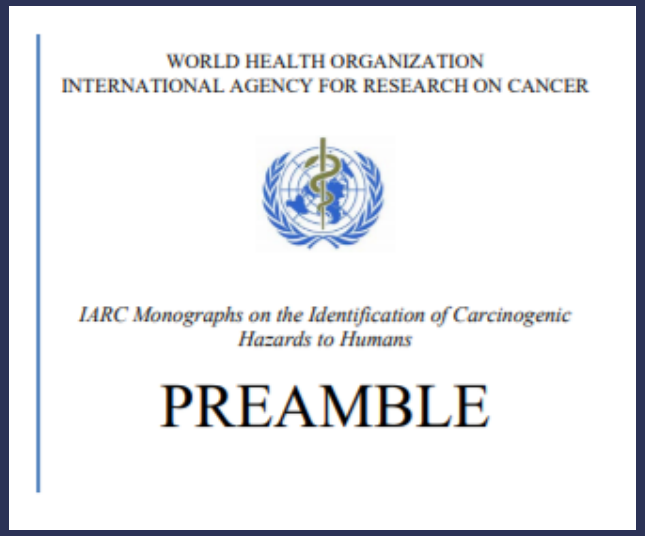


Step 1 Identify relevant information

Step 2 Screen, select & organize studies

Step 3 Evaluate study quality

Step 4 Report study characteristics

Step 5 **Synthesize evidence → overall evaluations**

Preamble to the *IARC Monographs* (amended January 2019):
https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf

Who does the *Monographs* evaluations?

Attend meetings but do not draft text or contribute to evaluations

IARC Secretariat
Scientists who coordinate all aspects of the evaluation and guide adherence to the Preamble

Working Group
Independent expert scientists without conflicts of interest
Review science and develop evaluations

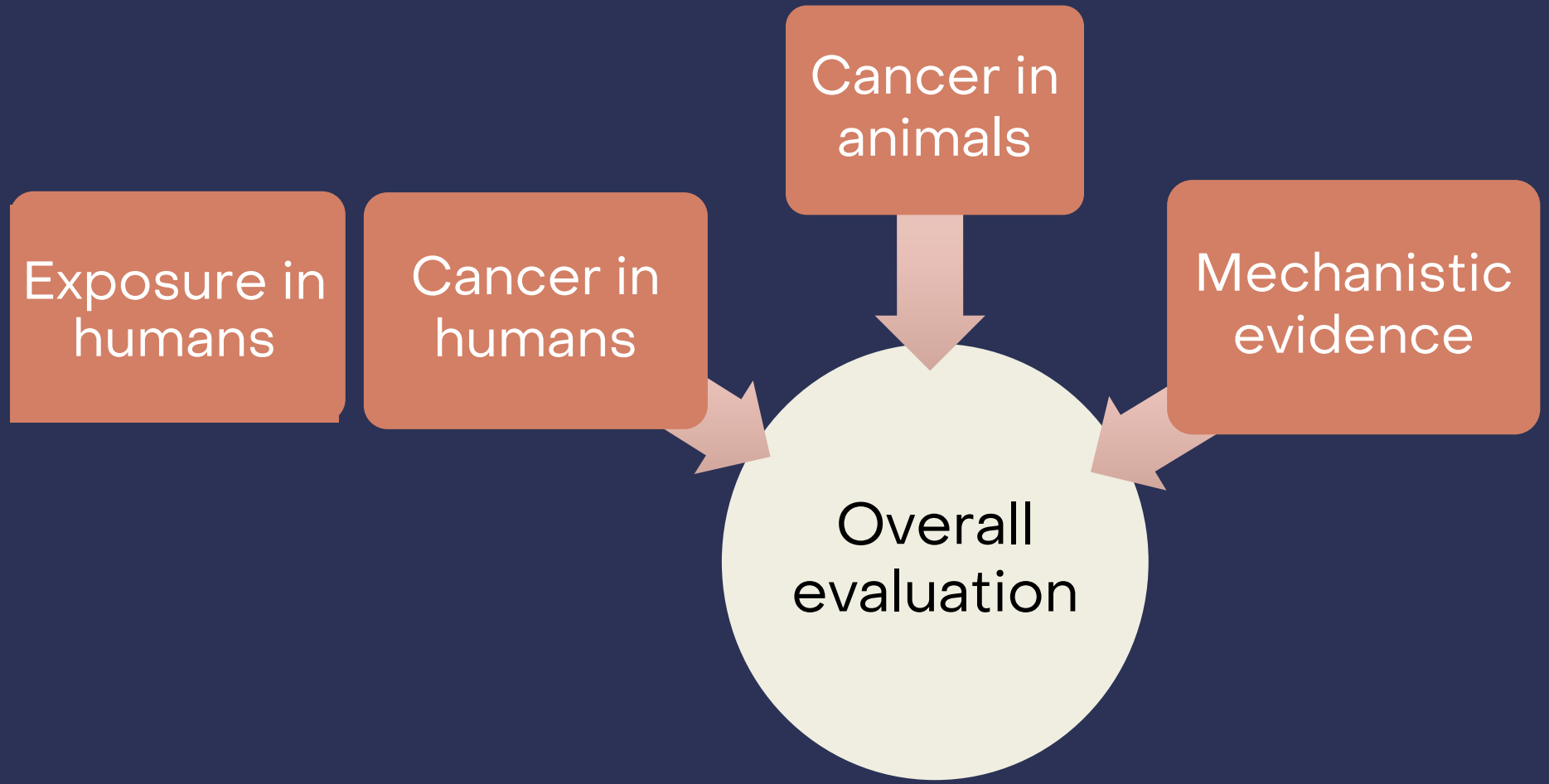
Invited Specialists
Scientists with relevant knowledge but a competing interest

Representatives of governments and health agencies

Observers
Scientists who may have a competing interest: observe but do not influence outcomes

Preamble to the IARC Monographs (amended January 2019):
https://monographs.iarc.fr/wp-content/uploads/2019/01/Preamble-2019.pdf

What evidence is considered?



Preamble to the *IARC Monographs* (amended January 2019):
https://monographs.iarc.fr/wp-content/uploads/2019/01/Preamble-2019.pdf

How is evidence evaluated?

Cancer in humans — Preamble Part B, Section 6(a)	Cancer in experimental animals	Mechanistic evidence

Sufficient	*Limited*	*Inadequate*	ESLC
• Causal relationship has been **established** • Chance, bias, confounding could be **ruled out with reasonable confidence**	• Causal interpretation is **credible** • Chance, bias, confounding **could *not* be ruled out with reasonable confidence**	• Studies permit **no conclusion** about a causal association, or • **No data** were available	• High-quality studies covering the full range of exposure are consistent in not showing a positive association at any level of exposure

Overall evidence classification

Evidence of Cancer in Humans	Evidence of Cancer in Experimental Animals	Mechanistic Evidence	Evaluation
Sufficient			Carcinogenic (Group 1)
	Sufficient	Strong (exposed humans)	
Limited	Sufficient		Probably carcinogenic (Group 2A)
Limited		Strong	
		trong (human cells or tissues)	
		rong (mechanistic class)	
Limited			Possibly carcinogenic (Group 2B)
	Sufficient		
		Strong	
	Sufficient	Strong (does not operate in humans)	Not classifiable (Group 3)
All other situations not listed above			

Sufficient for cancer in humans

Overall evidence classification

Evidence of Cancer in Humans	Evidence of Cancer in Experimental Animals	Mechanistic Evidence	Evaluation
Sufficient			Carcinogenic (Group 1)
	Sufficient	Strong (exposed humans)	
Limited	Sufficient		Probably carcinogenic (Group 2A)
Limited		Strong	
	...fficient	Strong (human cells or tissues)	
		Strong (mechanistic class)	
Limited			
	Sufficient		
		Stro	
	Sufficient	Strong (does ... in hum	
All other situations not listed above			

Limited cancer in humans + either (or both) *Sufficient* cancer in animals or *Strong* mechanistic evidence

Consideration of study quality and informativeness

Study quality

- Quality of exposure and cancer outcome assessment
- Potential selection bias
- Adequate consideration of confounding
- Quality of data collection methods
- Appropriateness of statistical analysis methods

Study informativeness

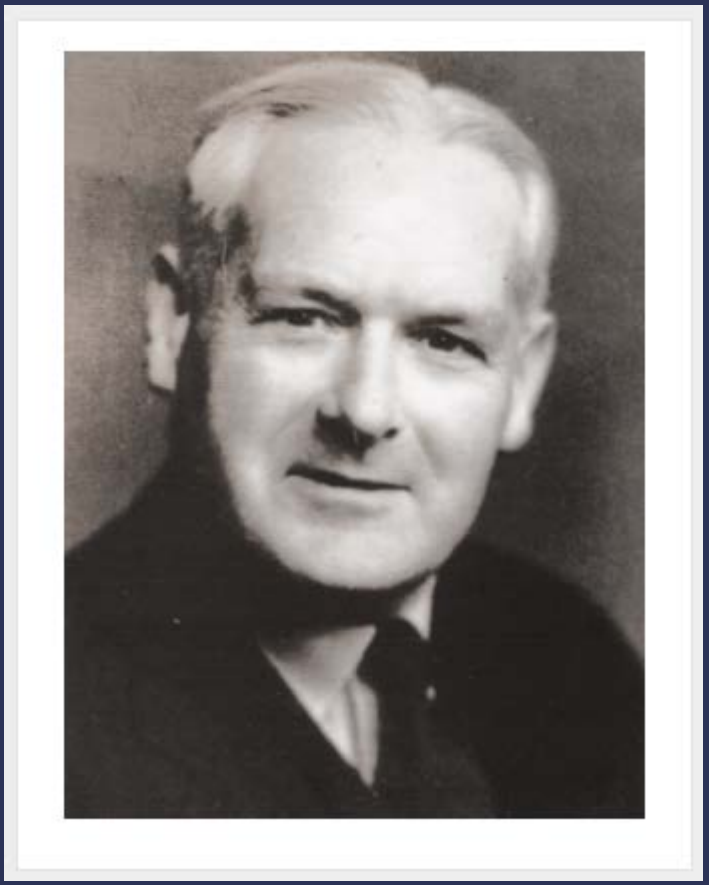
- Ability to detect presence of a true association, or absence of a null association
- Goes beyond study power, to consider, e.g.:
  - Presence of exposure contrast
  - Adequacy of latency
  - Exposure to target organ

Synthesizing body of human cancer evidence

An adaptation of Bradford Hill viewpoints

- Strength of association (but weak associations may be causal)
- Consistency of association, accounting for study quality and informativeness
- Presence of exposure-response
- Temporality of association
- Biological plausibility

Described in *Monographs* Preamble



Challenges in evidence synthesis for hazard identification

Questions posed by recent Working Groups during deliberations:

- Could selection bias caused by differential participation rates of cases and controls completely explain the OR of 2.0 in this key study of night shift work?
- Is confounding by co-exposure to arsenic likely to explain the excess lung cancer seen for antimony among smelter workers?
- Could smoking confounding completely explain the elevated risk of bladder cancer in these key studies of opium consumption?
- What is the relative importance of non-differential measurement error vs recall bias in studies of mobile phone radiation or red meat?

Challenges in evidence synthesis for hazard identification

- Consideration of the roles of confounding and bias is essential to *Monographs* evaluations

but

- Minimal guidance on methods to formally evaluate direction and magnitude of biases in context of cancer hazard identification
- Recent (problematic) focus on algorithmic scoring approaches

Examples carried through the publication

RF-EMF

Night shift work

Red meat

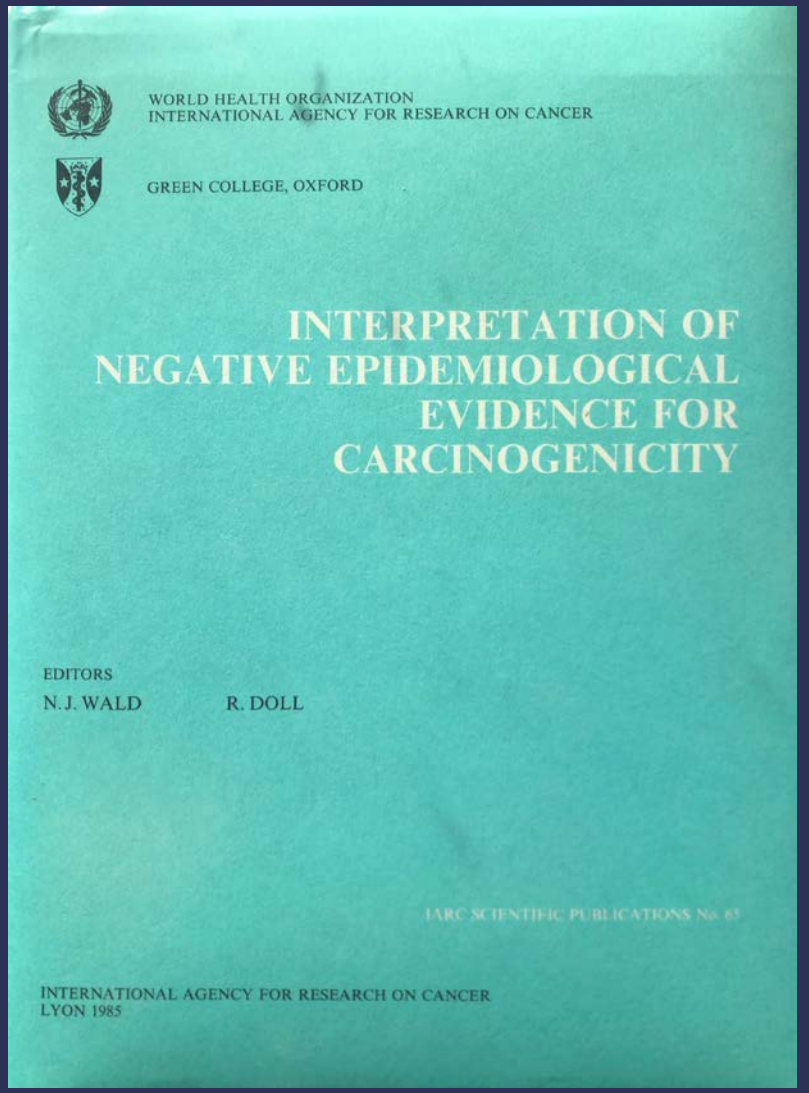
Opium consumption

Are expert judgments robust?

- *IARC Monographs* Vol. 100
  - ~100 Group 1 agents re-evaluated by different Working Groups
  - Nearly all were re-affirmed as Group 1 (one HPV type → Group 2A)
  - For many, evidence had strengthened since previous evaluation
- Broad concordance with evaluations by other hazard identification programs using different approaches

Are expert judgments robust?

- What about agents with *inadequate* evidence in humans?
  - In 1985, a workshop discussed interpretations of "negative evidence" in human studies for 10 agents with *sufficient* evidence from cancer bioassays
    - For most agents, they concluded evidence likely to remain *inadequate* or *ESLC*
    - In subsequent years, 3/10 agents had *sufficient* and 4/10 had *limited* evidence in humans
- Improvements in epidemiologic study number, quality, and informativeness were key to these changes



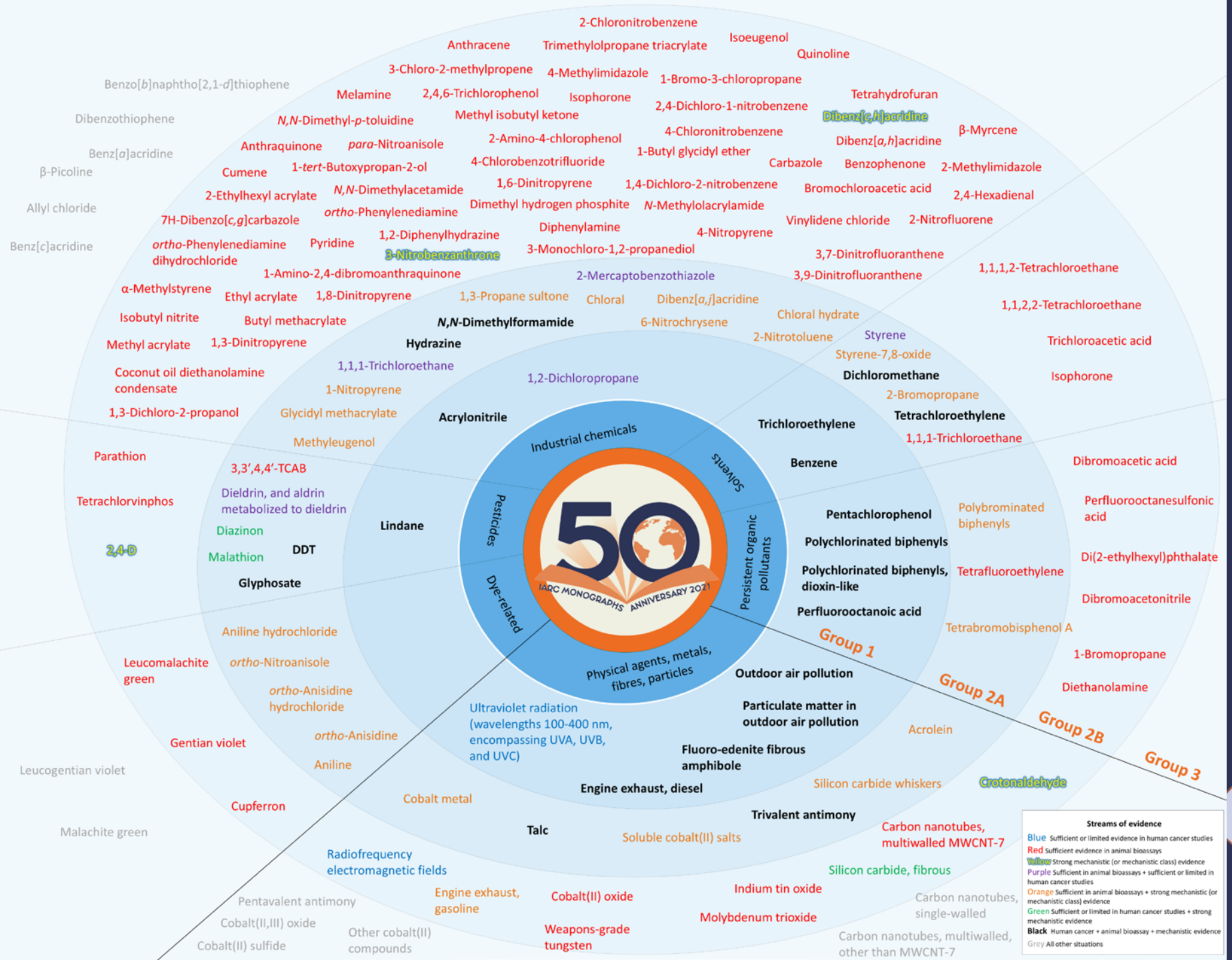


Fig. 1.5 in Bias Assessment in Case-Control and Cohort Studies for Hazard Identification. IARC Scientific Publication No. 171: Statistical Methods in Cancer Research Volume V.

Thank you for your attention!

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Sources of Bias and Causal Diagrams

Matthew Fox, Onyi Arah, Sonja Swanson, Vivian Viallon

Matthew Fox

Professor

Department of Epidemiology and Global Health

mfox@bu.edu

@ProfMattFox

Free Associations podcast https://shorturl.at/ruYbN

SERious Epi podcast https://seriousepi.blubrry.net

BOSTON UNIVERSITY

Introduction

- Understanding factors that prevent observed associations from reflecting true causal effects
- Using causal directed acyclic graphs (DAGs) to identify sources of bias
- Essential for evaluating epidemiological evidence

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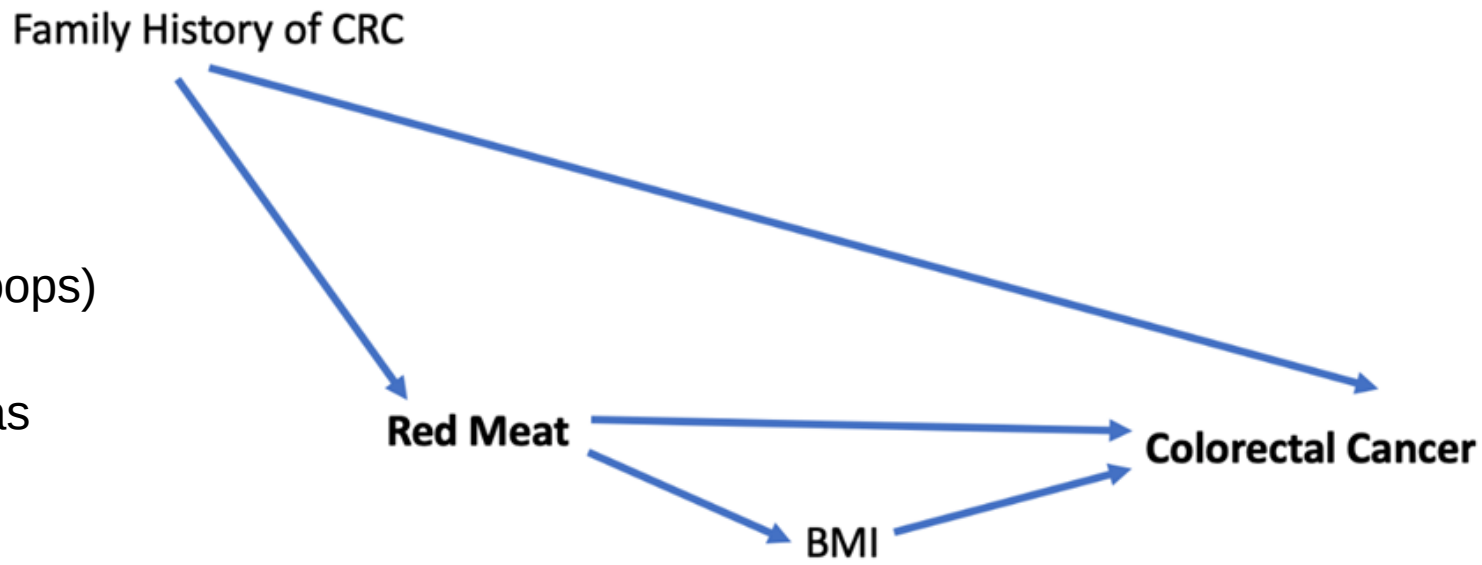
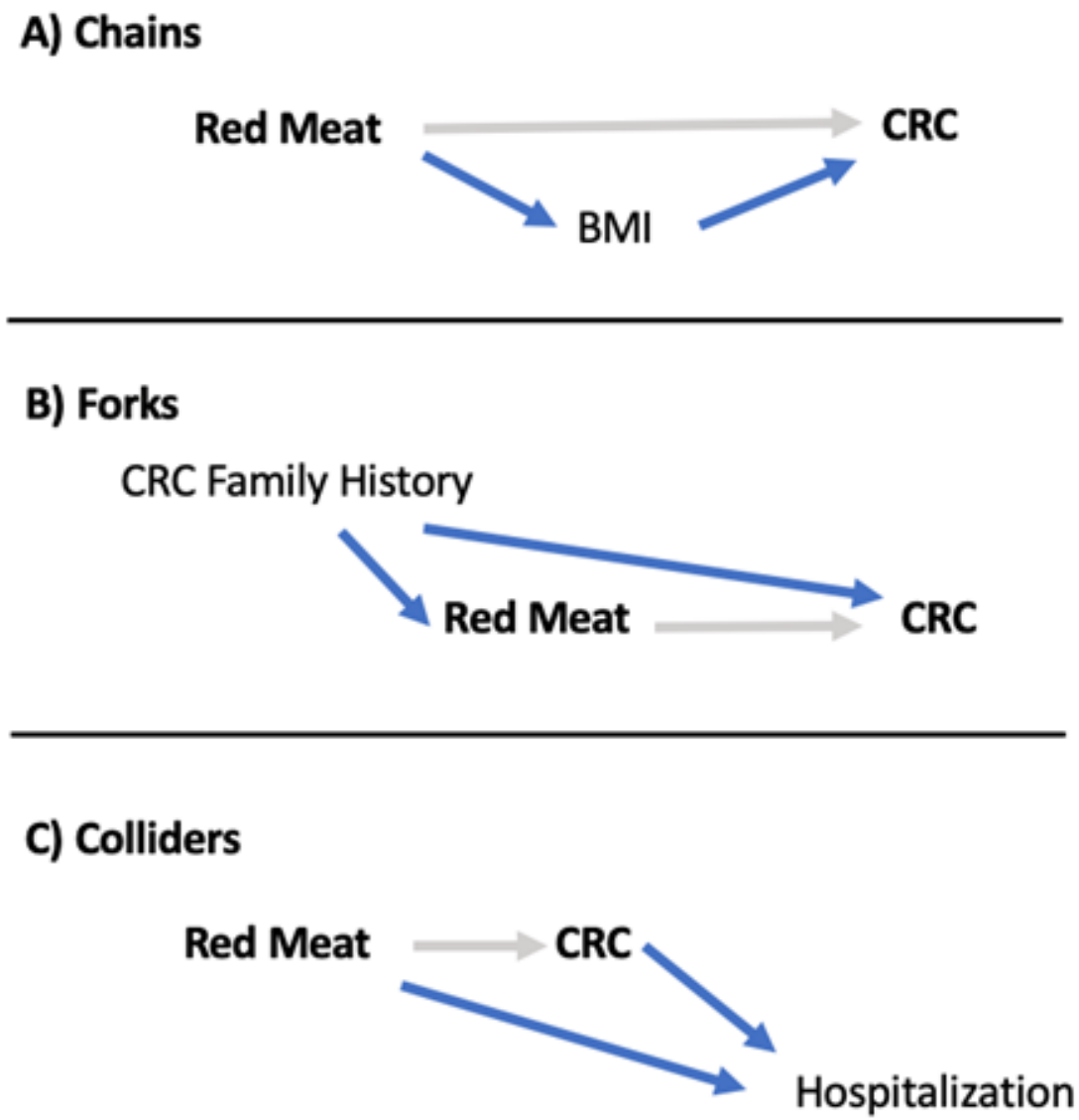
What are DAGs?

- **Graphical tools representing causal relationships between variables**
- **Components:**
  - Nodes (variables)
  - Directed edges (arrows showing causation)
  - Must be acyclic (no feedback loops)
  - Help communicate and analyze potential sources of bias
  - Make assumptions explicit and testable



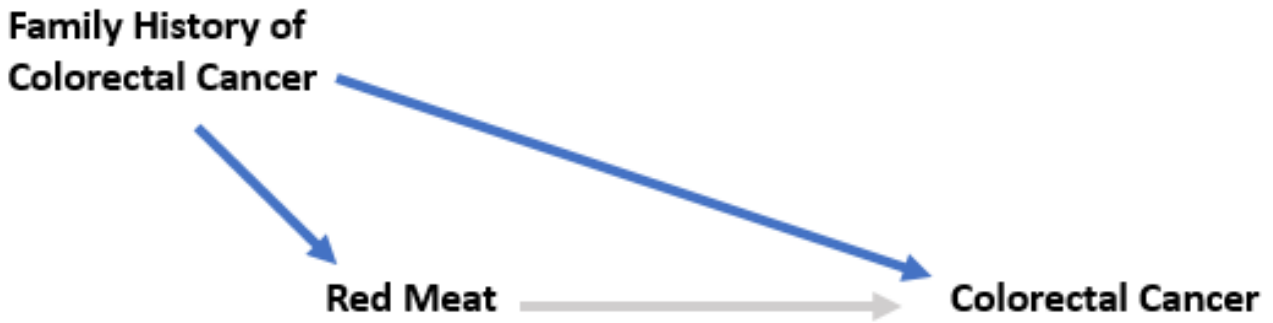
Basic Structures in DAGs

- **Chains: A → B → C**
  - Represents direct and indirect causal effects
  - Example: Red meat → BMI → Colorectal cancer
- **Forks: A ← B → C**
  - Creates confounding
  - Example: Red meat ← Family history → Colorectal cancer
- **Colliders: A → B ← C**
  - No association between A and C unless conditioned on B
  - Example: Red meat → Hospitalization ← Colorectal cancer



Confounding

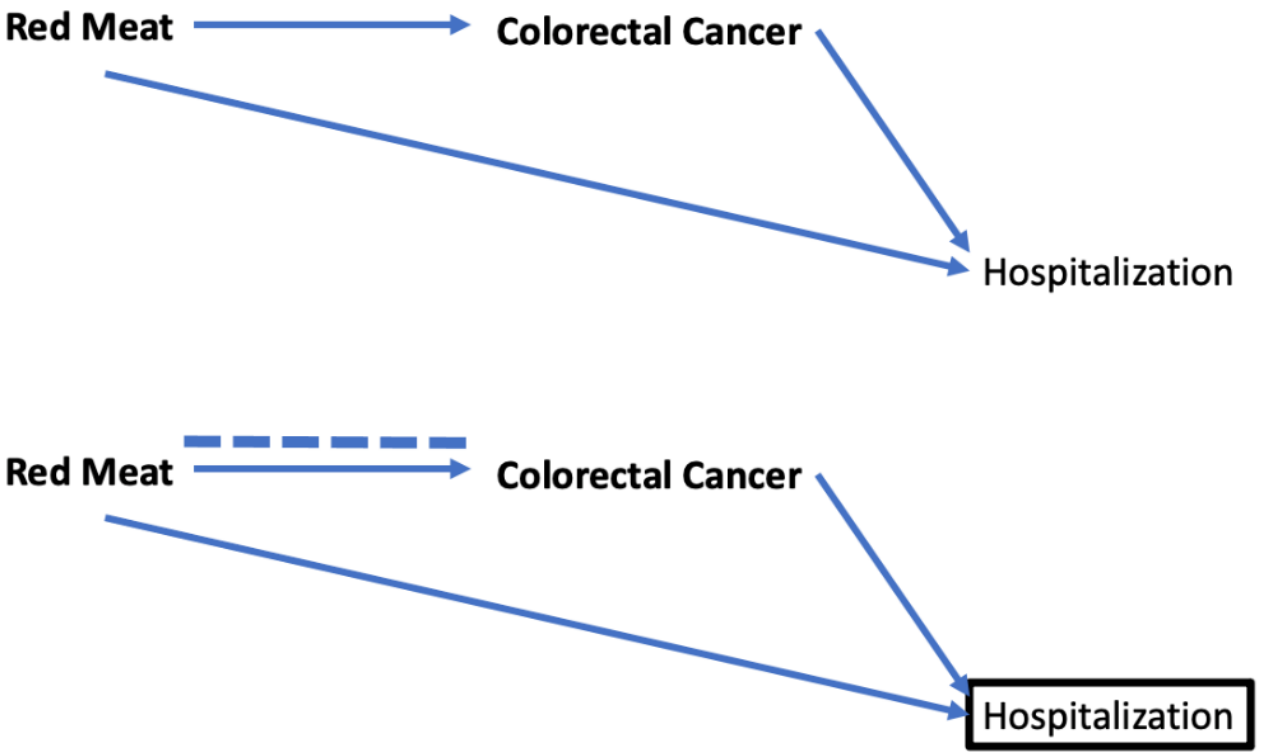
- **Occurs when exposure and outcome share common causes**
- **Represented by fork structures in DAGs**
- **Key characteristics:**
  - Creates non-causal associations
  - Can be controlled through proper adjustment
  - Must be identified to get valid causal estimates



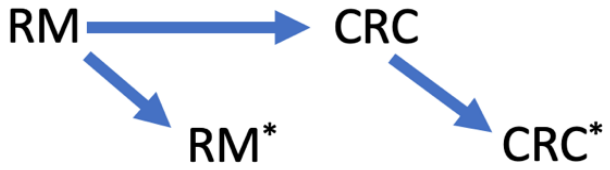
- **Example: Family history affecting both red meat consumption and colorectal cancer risk**

Selection Bias

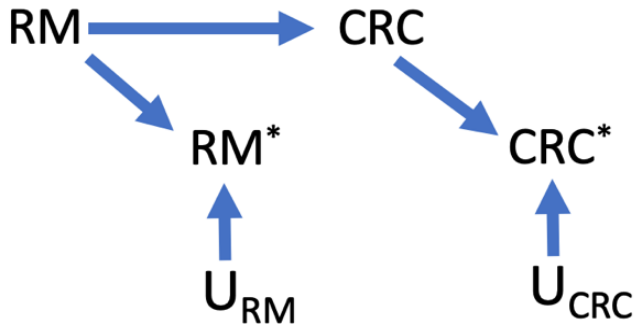
- **Occurs when selection into study related exposure and outcome**
- **Can happen through:**
  - Study recruitment
  - Loss to follow-up
  - Missing data
  - Analytic choices
- **Often represented as conditioning on colliders**
- **Can create artificial associations**



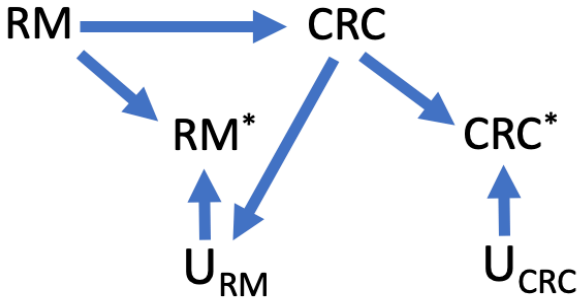
Information Bias



- **Types of measurement error:**
  - Non-differential: Error independent of other variables
  - Differential: Error depends on other variables
  - Independent: Errors uncorrelated between variables
  - Dependent: Errors correlated between variables



- **Impact:**
  - Can bias results toward or away from null
  - Direction and magnitude vary by type



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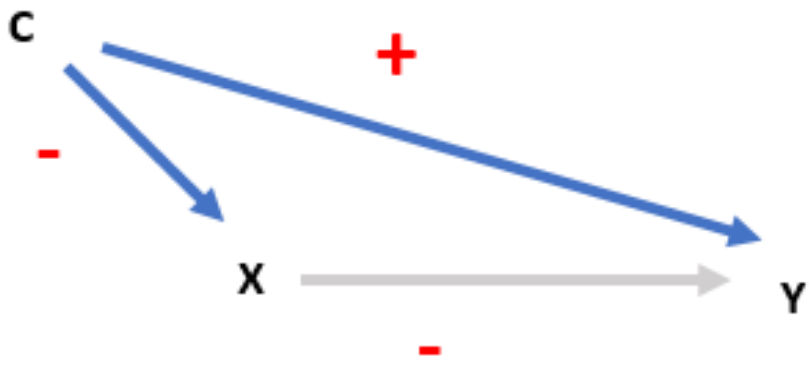
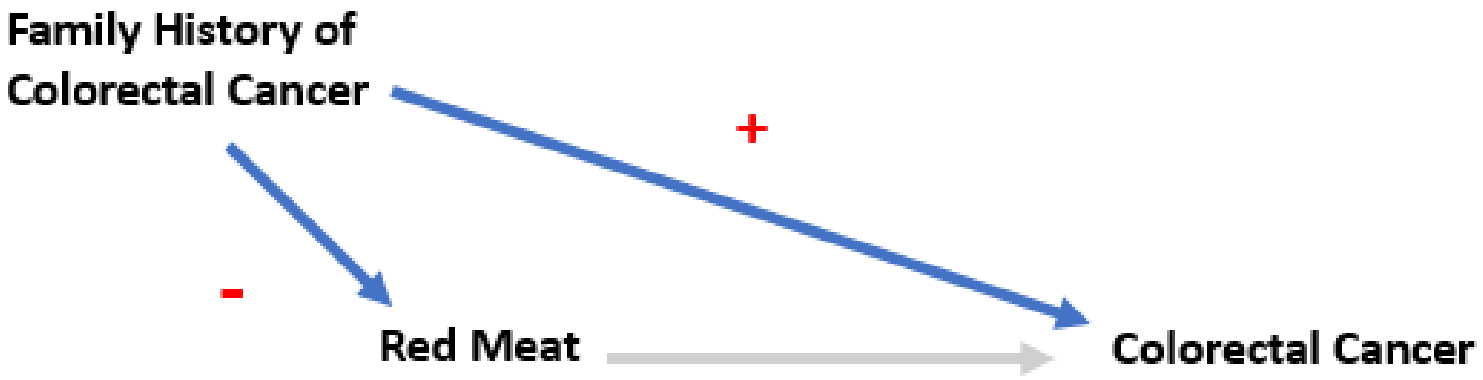
Using DAGs to Identify Bias

- **Steps:**
  - List all relevant variables
  - Draw arrows representing causal relationships
  - Identify backdoor paths
  - Determine necessary adjustment sets
  - Assess potential for selection/information bias
- **Tools:**
  - DAGitty (online tool)
  - Causal Fusion platform

Signed DAGs

- **Add +/- signs to arrows to indicate direction of effects**
- **Help determine likely direction of bias**
- **Useful for:**
  - Assessing whether confounding could explain observed associations
  - Understanding impact of unmeasured confounders
  - Limited to monotonic effects



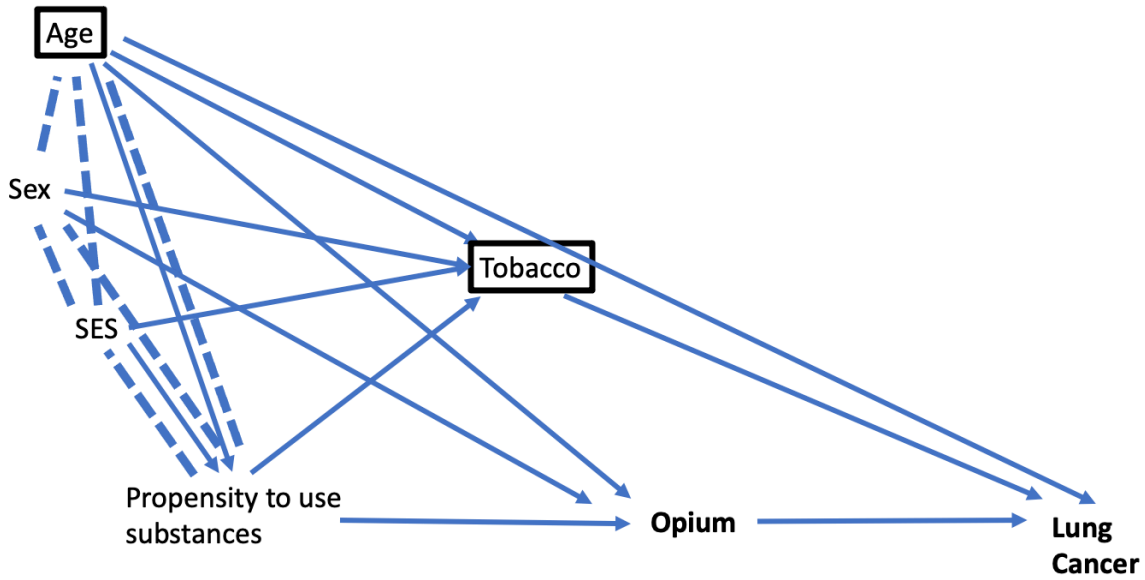


Multiple Sources of Bias

- **Biases can interact:**
  - Additive effects
  - Canceling effects
  - Multiplicative effects
- **DAGs help identify but not quantify combined impact**
- **May need multiple DAGs to represent different assumptions**
- **Important to consider study-specific contexts**

Key Takeaways

- **DAGs make causal assumptions explicit**
  - Help identify necessary adjustments
  - Reveal potential sources of bias
  - Guide study design and analysis
  - Support evidence synthesis
- **Limitations:**
  - Cannot show magnitude of bias
  - May oversimplify complex relationships
  - Require subject matter expertise



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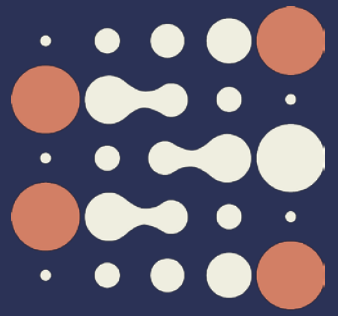


Confounding: a routine concern in the interpretation of epidemiological studies

David B. Richardson

University of California, Irvine

CHAPTER 3.

Confounding: a routine concern in the interpretation of epidemiological studies

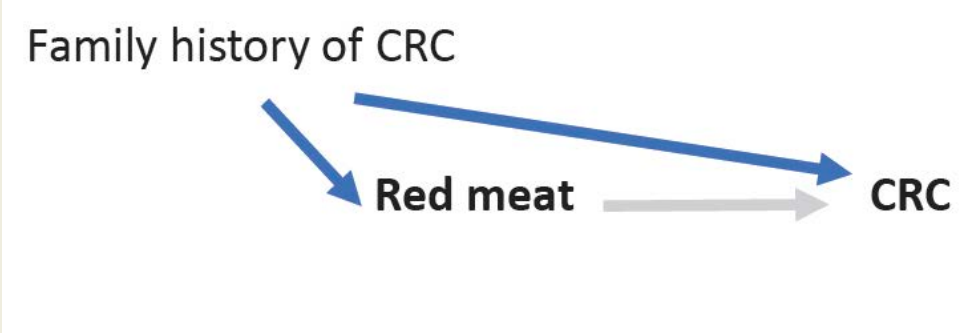
David B. Richardson, Sadie Costello, Jay S. Kaufman, Kaitlin Kelly-Reif, Sarah Lewis, Kyle Steenland, and Eric J. Tchetgen Tchetgen

3.1 Introduction

As noted in the Preface, confounding arises when the exposure and the outcome of interest share a common cause. Informally, confounding may be described as a condition in which the association of exposure with the outcome is, in part, due to differences in outcome risk between the exposed and the unexposed that are not due to exposure effects on the outcome. A confounder is then defined as a variable that is responsible for confounding; typically, such a variable is a cause of the outcome that is associated with exposure but not affected by exposure. More precise definitions can be provided within formal causal models, such as potential-outcome and graphical models (Greenland et al., 1999a; Hernán and Robins, 2023; see also Chapter 2); these models will not be discussed here, but the reader is warned that there can be various definitions of confounding and confounders in these more formal discussions.

At an *IARC Monographs* meeting, the epidemiological studies under review are typically observational, meaning that the investigators did not have control over the exposure of interest (or any other variables) and, importantly for this chapter, did not randomly assign study participants to exposure. In observational studies, it is seldom reasonable to assume that pre-exposure factors that affect the outcome are equally distributed across subgroups defined by exposure; rather, exposure is often influenced by other factors, some of which may be risk factors for the cancer outcome of interest. Consequently, confounding is a common concern for Working Group members. Thus, one of the primary questions posed to reviewers in an *IARC Monographs* Working Group is "Can we reasonably rule out confounding as an explanation for an observed exposure–cancer association?"

A standard approach to the problem of confounding is to measure the important factors (e.g. pre-exposure factors that are predictive of the outcome in a cohort study) that may differ between exposure groups and to match on them in the study design (to the extent possible) or adjust for them in the analysis. If all the important confounders were accurately measured, an investigator might be able to obtain a valid estimate of the causal effect of the exposure on the outcome. However, the choice of which variables to control for (a judgement informed by causal, in



Can we reasonably rule out confounding as an explanation for an observed exposure–cancer association?

Uncontrolled confounding

Discussion of limitations

Established causes of outcomes

Confounder-Exposure association

Covariate measurement and control

Controlled confounding

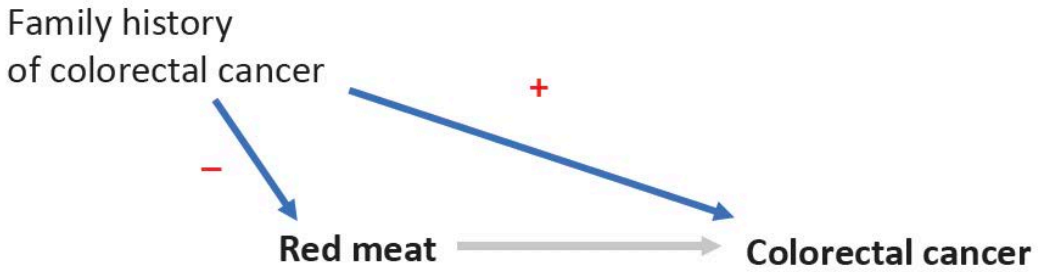
Study design

Study setting and restrictions

Covariate adjustment

Tools and Examples

DAGs and signed DAGs



Sign of arrow 1 from family history of colorectal cancer to red meat consumption ($C \rightarrow X$)	Sign of arrow 2 from family history of colorectal cancer to colorectal cancer ($C \rightarrow Y$)	Likely direction of confounding
+ (*C* increases risk of *X*)	+ (*C* increases risk of *Y*)	+ (positive[a])
− (*C* decreases risk of *X*)	− (*C* decreases risk of *Y*)	+ (positive[a])
+ (*C* increases risk of *X*)	− (*C* decreases risk of *Y*)	− (negative[b])
− (*C* decreases risk of *X*)	+ (*C* increases risk of *Y*)	− (negative[b])

C, uncontrolled confounder (family history of colorectal cancer); *X*, exposure (red meat consumption); *Y*, outcome (colorectal cancer).
[a] Positive uncontrolled confounding: not adjusting for *C* induces a positive association between *X* and *Y*, even when *X* does not affect *Y*.
[b] Negative uncontrolled confounding: not adjusting for *C* induces a negative association between *X* and *Y*, even when *X* does not affect *Y*.

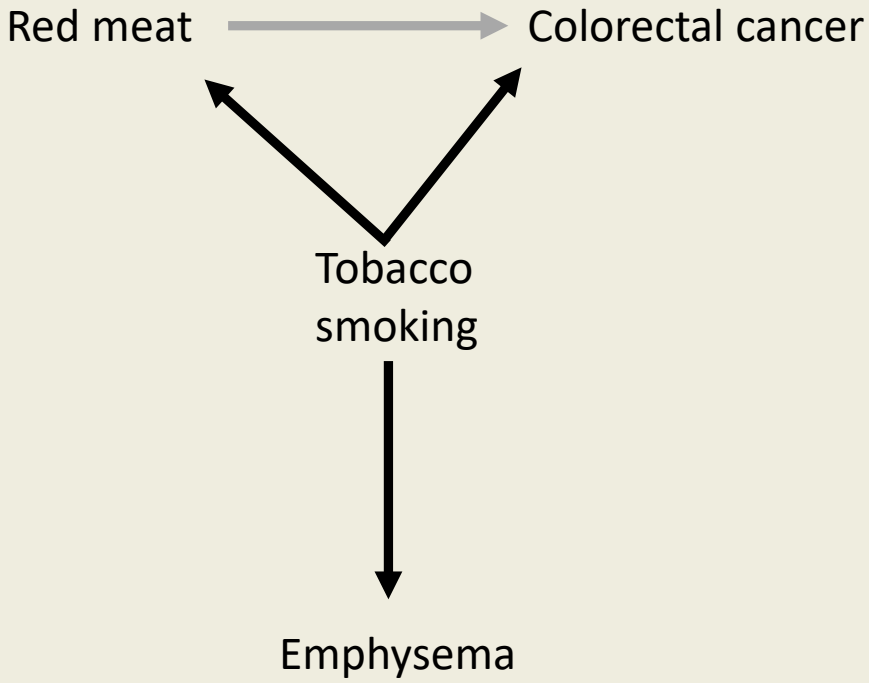
Example: Red meat consumption and CRC

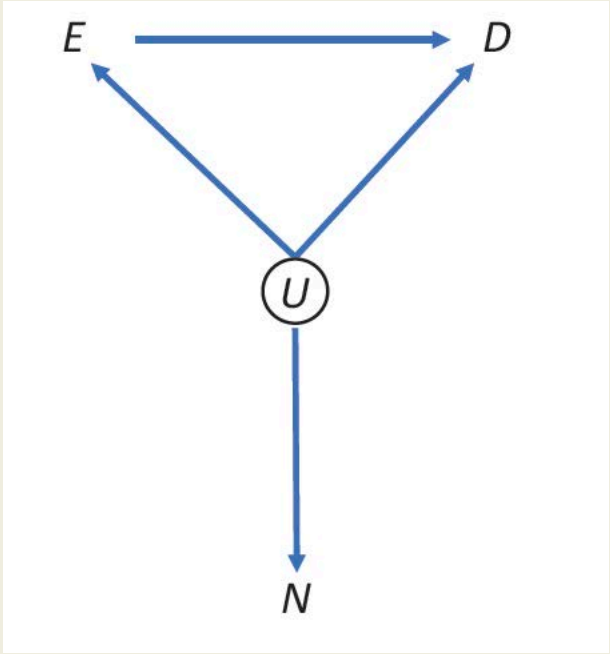
In a study in which family history of CRC was not adjusted for, a positive association was observed between red meat consumption and CRC (RR=1.36).

Based on the signed DAG, if family history of CRC had been adjusted for the estimate of effect would be expected to be even larger than what was observed.

Tools and Examples

Negative controls and proxies



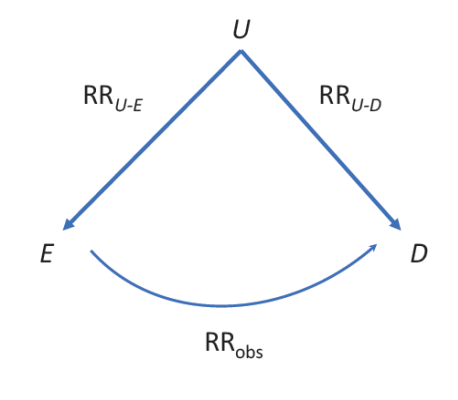


Example: In an investigation of the effect of red meat consumption on CRC, where tobacco smoking is not measured but is a potential confounder, an investigator might posit emphysema as a negative control outcome.
If that assumption was correct, the absence of association between red meat consumption and emphysema would be evidence that tobacco is not a confounder of the red meat consumption–CRC association.

Tools and Examples

Quantitative bias analyses

$RR_{U\text{-}D} \geq RR_{obs}$ and $RR_{U\text{-}E} \geq RR_{obs}$



$$\text{E-value} = RR_{obs} + \text{Sqrt}(RR_{obs}[RR_{obs} - 1])$$

Example: A positive association was observed between red meat consumption and CRC (RR=1.36); however, family history of CRC was not adjusted for.
An E-value=2.06 means that for the association (RR=1.36) to be entirely due to confounding by family history of cancer $RR_{U\text{-}D}$ and $RR_{U\text{-}E}$ must equal or exceed 2.06.

A more flexible range of scenarios can be easily explored with worksheets.

Suppose prior literature suggests RR(Fam Hx-CRC)=1.85, and p(Fam Hx|RM-)=0.05. For the association (RR=1.36) to be entirely due to confounding by family history of cancer, p(Fam Hx|RM+) > 0.5.

Enter bias parameters in blue cells to the right and the crude data in the blue cells below. Cells in green give the results after adjusting for the uncontrolled confounder.

Variable Names		Bias Parameters	
Outcome	CRC	p(Fam Hx+|RM+)	0.50
Exposure	RM	p(Fam Hx+|RM-)	0.05
Confounder	Fam Hx	RR(Fam Hx-CRC)	1.85
Error Check:	No errors found		

Data (Enter Crude RM-CRC Data in Blue Cells)

	Total		Fam Hx +		Fam Hx -	
	RM +	RM -	RM +	RM -	RM +	RM -
CRC +	498 a	366 b	323.3 A_1	32.5 B_1	174.7 A_0	333.5 B_0
CRC -	30218 c	30350 d	15034.7 C_1	1503.3 D_1	15183.3 C_0	28846.7 D_0
Total	30716 m	30716 n	15358.0 M_1	1535.8 N_1	15358.0 M_0	29180.2 N_0

Crude and Uncontrolled Confounder Specific Measures of RM-CRC Relationship

Crude	Measure (95% CI)	Fam Hx +		Fam Hx -	
RR (RM-CRC)	1.36 (1.19 - 1.56)	RR (RM-CRC)	1.00	RR (RM-CRC)	1.00

Conclusions

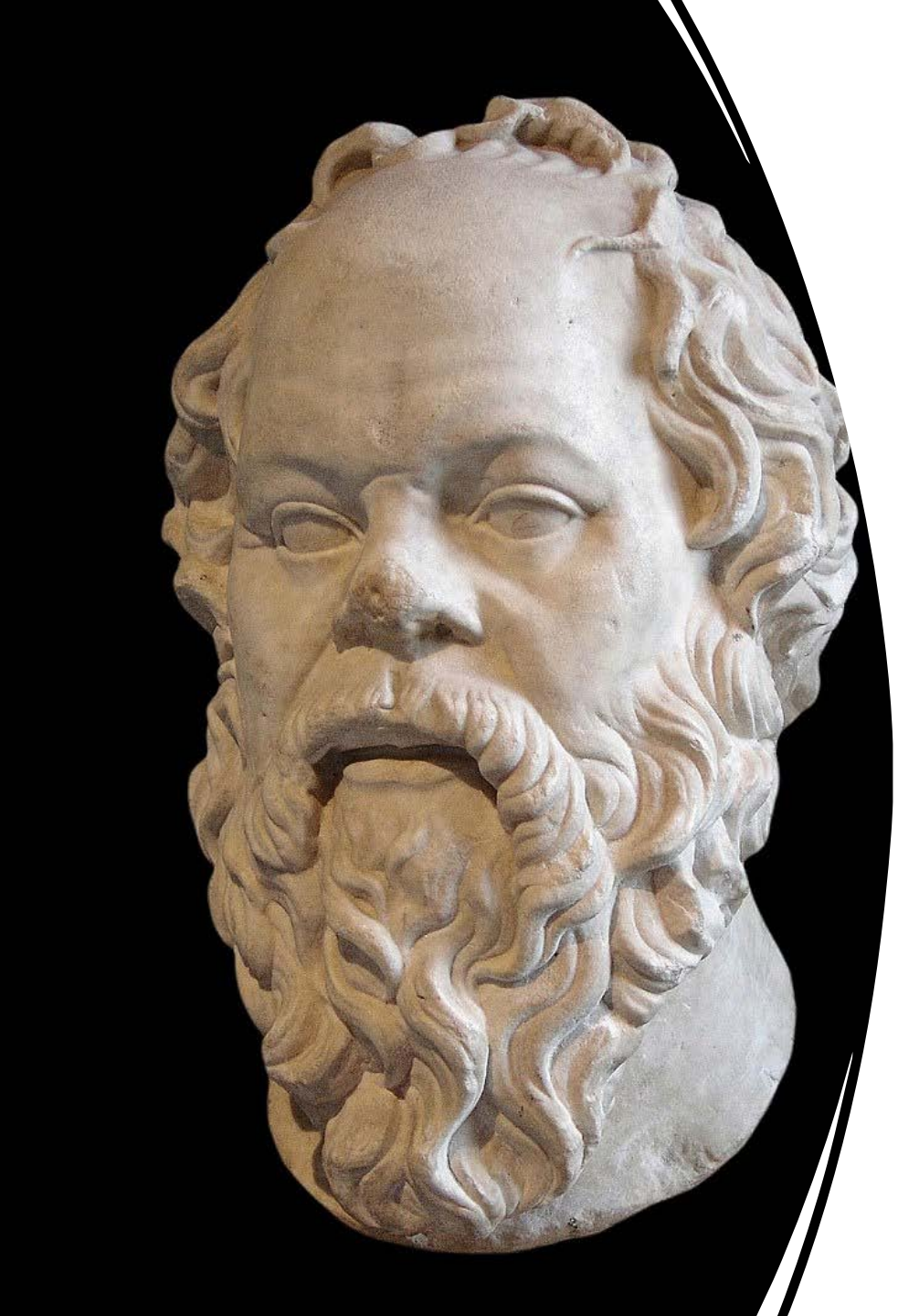
Consider design, restriction, and adjustments

Identify likely important unmeasured confounders

Leverage background information on causal structures to assess direction and magnitude of residual confounding

Information bias: misclassification and mismeasurement of exposure and disease

- *Leslie Stayner, Neil Pearce, Ellen Aagaard Nøhr, Laura Beane Freeman, Veronika Deffner, Pietro Ferrari, Laurence S. Freedman, Manolis Kogevinas, Hans Kromhout, Sarah Lewis, Richard MacLehose, Marie-Elise Parent, Lorenzo Richiardi, Pamela Shaw, and Roland Wedekind*



“The Only Thing I Know For Sure Is That I Know Nothing At All, For Sure” - Socrates

Non-Differential Error in Exposure

- It is often assumed that if the errors are non-differential with respect to the disease, then the bias is towards the null.
- This may be true **on average** but not always
- The direction of the bias is determined by the type of exposure metric (i.e. continuous or categorical), and error model

Non-differential errors and categorical exposures

- Non-differential errors in exposure in analyses using binary exposure measures (i.e., yes/no) are on average biased towards the null
- Non-differential errors in exposure in analyses using several categories of exposure may result in overestimation of risk in the intermediate categories, and underestimation of risk in the highest category

The direction of bias for analyses using continuous exposure depends on the error model

- Classical Model: $X^* = X + U$
  - Where X^* is the measured value, X is the true value and U is the random error which is on average 0 and independent of the true value X
- Linear Model: $X^* = a_o + a_X X + U$
  - Where a_o and $+ a_X$ are the intercept and slope, and U is not on average 0 (i.e., biased)
- Berkson Model: $X^* = X + U$
  - Where U is independent of the measured value and on average 0

Non-differential errors and continuous exposure

- Classical errors are expected to cause underestimation of the dose-response relationship
- Berksonian errors are not generally expected to bias the dose-response relationship but do increase the variance
- Note - any study may obtain a result that is biased bias away from the null due to random variability.

Quantifying Bias Due to Misclassification Errors

Bias analyses for binary exposures can be performed if one knows or guesses the sensitivity and specificity of the measures, which can be used to predict what data would be observed if the data were correctly classified.

Table 4.1. Relation between correctly classified (uppercase) and observed (lowercase) data in a case–control study with misclassification of exposure

	Correctly classified		Total	Observed data	
	Exposed	Unexposed		Exposed	Unexposed
Case participants	A	B	N_1	$a = se_1A + (1 - sp_1)B$	$b = (1 - se_1)A + sp_1B$
Control participants	C	D	N_0	$c = se_0C + (1 - sp_0)D$	$d = (1 - se_0)C + sp_0D$

se_0, sensitivity for control participants; se_1, sensitivity for case participants; sp_0, specificity for control participants; sp_1, specificity for case participants.

Non-Differential Errors: Simple bias analysis for study by Fritschi et al 2013 of breast cancer and "graveyard" shiftwork assuming Se=0.90 and Sp=0.80 for both cases and controls

Data (Enter Graveyard Shift-breast Cancer Data in Blue Cells)

Observed Data

	Shiftwork		No Shiftwork		Total
breast Cancer +	288	a	914	b	1202
breast Cancer -	381	c	1404	d	1785
Total	669	m	2318	n	

Observed	Measure (95% CI)
RR (Graveyard Shift-brea	1.09 (0.99 - 1.21)
OR (Graveyard Shift-brea	1.16 (0.98 - 1.38)

Bias Adjusted Data

Adjusted Data

	Shiftwork		No Shiftwork		Total
breast Cancer +	239.7	A	962.3	B	1202
breast Cancer -	289.3	C	1495.7	D	1785
Total	529.0	M	2458.0	N	

Adjusted	Measure
RR (Graveyard Shift-brea	1.16
OR (Graveyard Shift-brea	1.29 (0.96 - 1.73)

Fox MP, MacLehose R, Lash TL. Applying Quantitative Bias Analysis to Epidemiologic Data. Springer. 2021.

Tools for Assessing Differential Misclassification of Exposure

- Negative controls – Examine association of exposure with another outcome that is known to not be associated with the exposure
- Positive controls – Examine other outcomes that are known to be associated with the exposure
- Evaluation of exposure from other sources – Are they strongly correlated
- Comparison with external data
- Stratify by index versus proxy interviews
- Triangulation using comparisons across studies.

Differential Errors: Simple bias analysis for study by Mohebbi et al 2021 of head and neck cancer and "graveyard" shiftwork assuming Se=0.79 among cases and 0.68 among controls, Sp=0.83 among cases and 0.93 among controls

Data (Enter Opium-HN Cancer Data in Blue Cells)

Observed Data

	Opium		No		Total
HN Cancer +	295	a	368	b	663
HN Cancer -	401	c	2664	d	3065
Total	696	m	3032	n	

Observed	Measure (95% CI)	CI)
RR (Opium-HN Cancer)	3.49 (3.07 - 3.97)	7)
OR (Opium-HN Cancer)	5.33 (4.42 - 6.41)	1)

Bias Adjusted Data

Adjusted Data

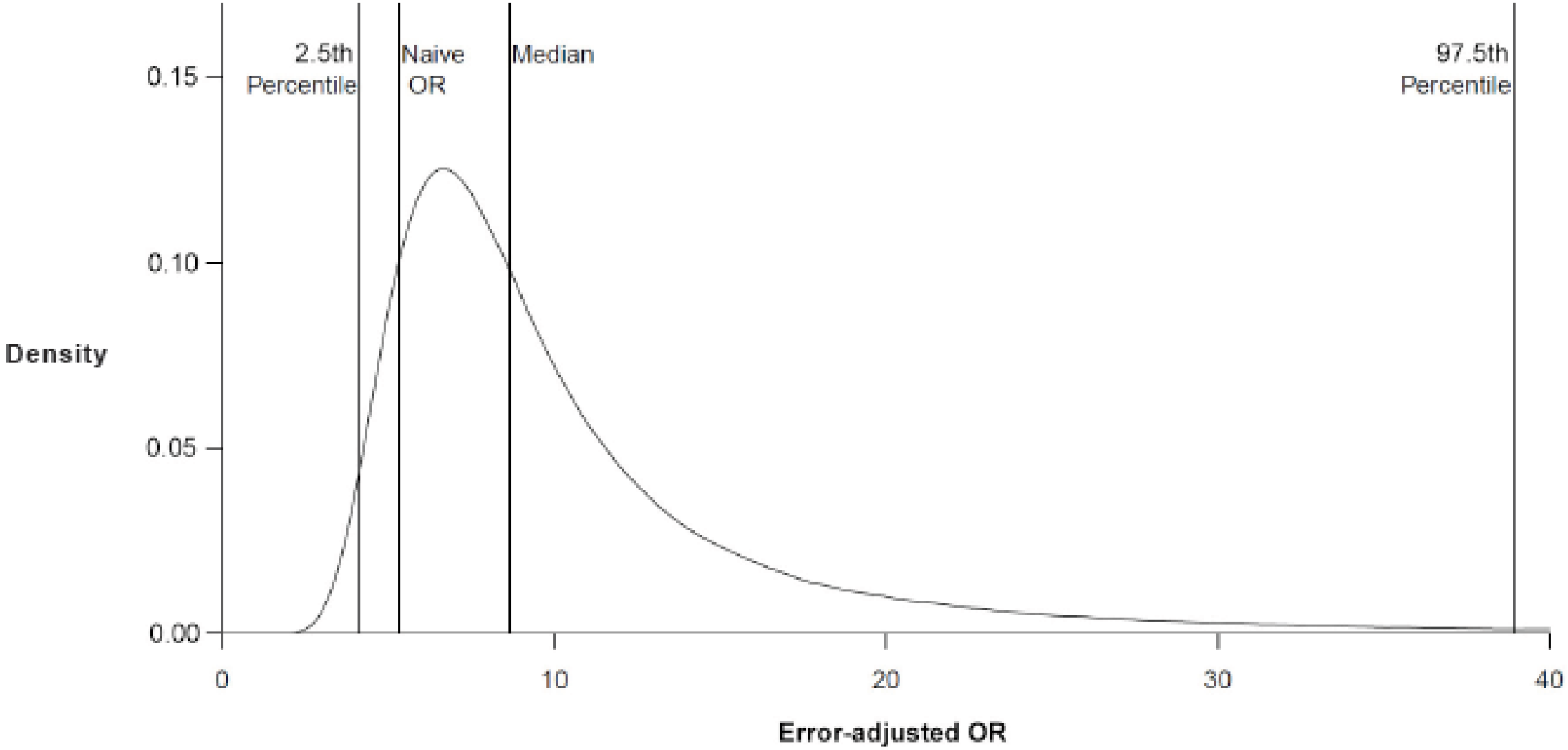
	Opium		No		Total
HN Cancer +	294.0	A	369.0	B	663
HN Cancer -	305.7	C	2759.3	D	3065
Total	599.7	M	3128.3	N	

Adjusted	Measure
RR (Opium-HN Cancer)	4.16
OR (Opium-HN Cancer)	7.19 (5.17 - 10)

Simple methods for bias assessment of bias may be extended to

- Multi-dimensional analyses
- Multiple categories analysis
- Probabilistic analysis – includes uncertainty related to Se and Sp measure

Distribution of error adjusted ORs resulting from probabilistic bias analyses of data from Mohebbi et al. 2021 on misclassified opium use and head and neck cancer.



Several other advanced methods are reviewed which with exception of Bayesian require access to individual data or validation data

- Regression calibration
- Simulation extrapolation (SIMEX)
- Bayesian methods
- Multiple imputation

Misclassification of Disease

- Generally, less common source of information bias than exposure misclassification
- Errors that are non-differential with respect to exposure will on average result in bias towards the null in most cases
- Methods described for adjusting for exposure misclassification may also be applied to bias analyses for disease outcomes

To err is human, to
correct one’s errors is divine

Extra Slides

Common Sources of Mismeasurement and Misclassification Errors

- Questionnaire Data – inaccurate recall, next of kin
- Interviewer and Recall Bias
- Use of a Job Exposure Matrix – not all workers in a group have the same exposure
- Lack or Inadequate Historical Data - Cancer studies need data from 10 or more years earlier.
- Categorization of continuous exposure
- Instrumentation Error

Differential Errors in Exposure

- Differential errors may bias the study in either direction
- Differential errors may occur in case-control studies that rely on interviews.
  - If interviewers know the study subject's disease status (i.e. interviewer bias)
  - If cases are more or less likely than controls to recall past exposures (i.e., recall bias)
  - If next of kin are interviewed if a case died or was ill
- Differential errors in exposure may also occur in cohort studies.

Referral Centre for Epidemiology and Oncological Prevention
in Piedmont

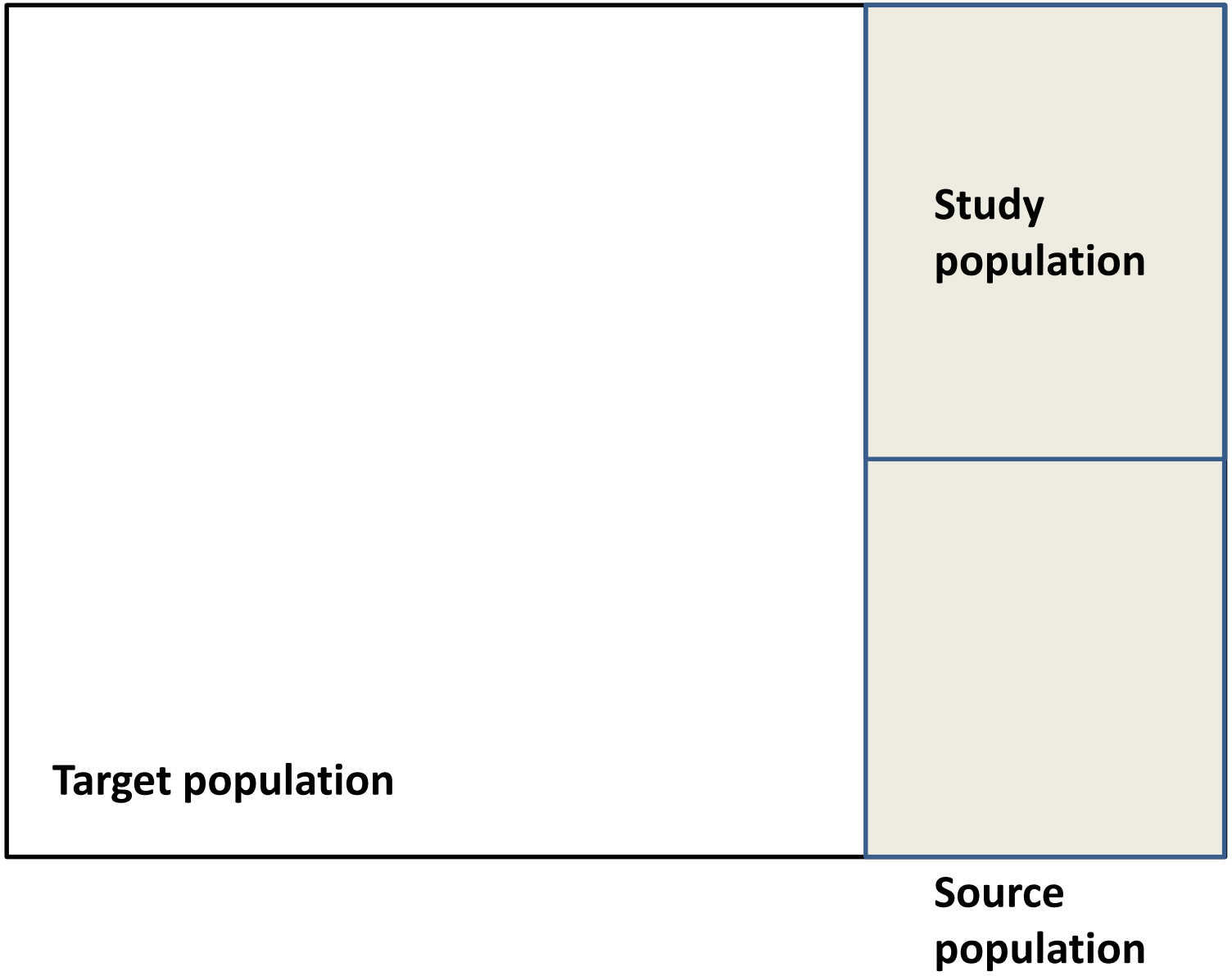
University of Turin

Chapter 5: selection bias

Neil Pearce, Laura Beane Freeman, Manolis Kogevinas, Richard MacLehose, Ellen Aagaard Nøhr, Marie-Elise Parent, Lorenzo Richiardi

Lorenzo Richiardi

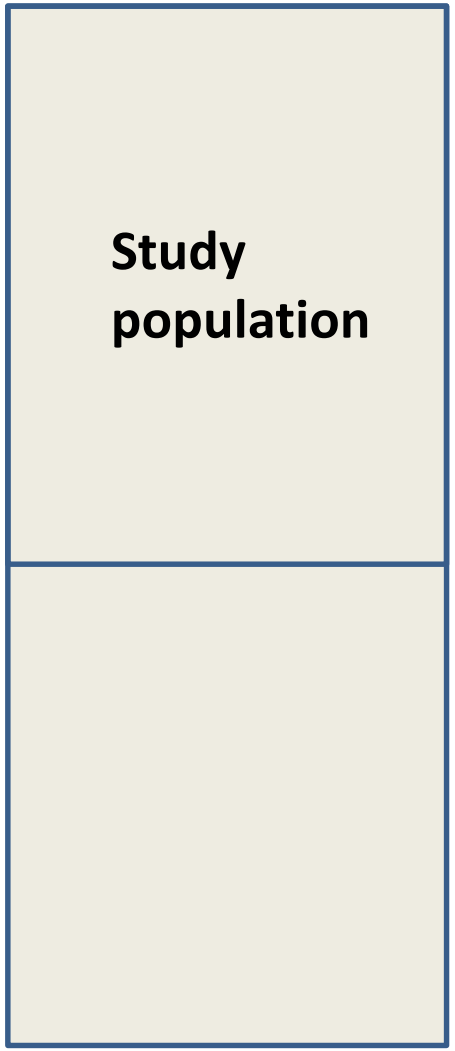
Populations



Populations

"In most studies, the concept of the target population is left undefined"

Target population



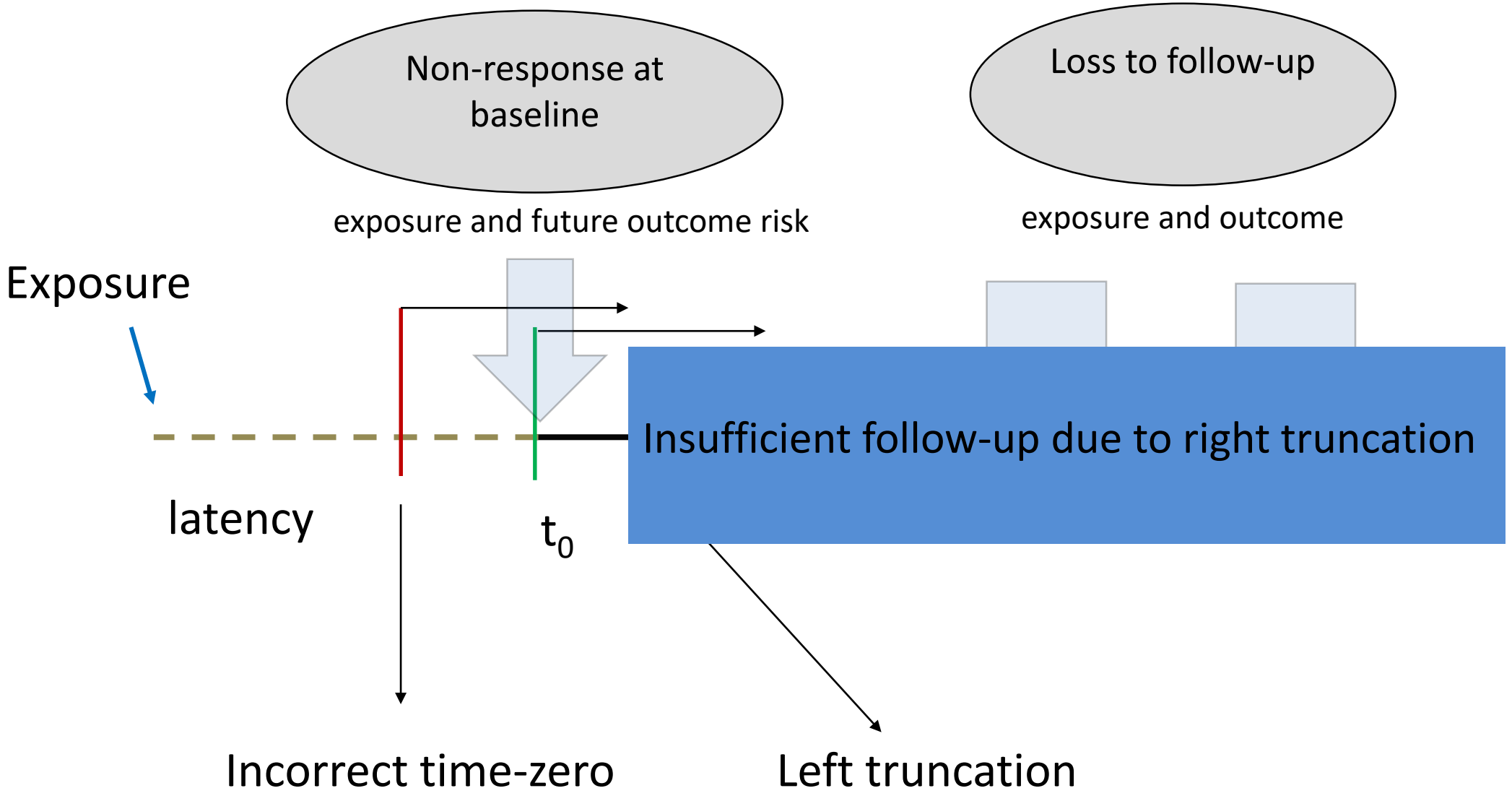
Definition of selection bias

- **Target population ⇔ Source population**
  - (lack of) generalizability/transportability
- **Source population ⇔ Study population**
  - Selection bias:

    "the estimate in the study population is different from that in the source population (and it is non causal), because of selective recruitment or loss to follow-up"

Within the context of IARC Monographs, it is of concern if an exposure has a non-null causal effect in a defined source population, or even in a specific study population → transportability is less relevant; selection on effect modifiers is less relevant

Identifying selection bias in cohort studies



Identifying selection bias in case-control studies

Same as cohort studies

All of biases seen for cohort studies can occur in a corresponding case–control study based on the same source population followed up over the same period

Selection of cases

- Source of case ascertainment
- Type of diagnosis confirmation
- Exclusion of case participants based on previous history of cancer
- Disease detection issues
- Inclusion of prevalent cases

Selection of controls

Selection of population controls
Selection of hospital controls
Berkson bias

Participation of cases and controls

There is a potential for selection bias when both the disease and the exposure status affect participation in the study

Assessing selection bias

Selection does not always imply selection bias

Selection bias is often the most mathematically simple bias for which estimates of effect can be bias-adjusted

However the information needed for such bias adjustment is rarely available or reported in published papers

Most published studies provide little or no discussion of the potential for selection bias

Assessing selection bias: some tools (1)

1. Using substantive knowledge (e.g. DAGs) for considering whether selection bias is possible and evaluating any strategies that the authors may have adopted to minimize, control for, or assess it

2. Negative control exposure / outcome approach: assessment of the association with another exposure /outcome that is believed to not be associated with the outcome / exposure of interest but is subject to a similar selection bias

3. Re-analysis of published data: e.g. dose-response analysis in the exposed

4. Comparisons with external data: e.g. comparison with prevalence exposure data in the source population

Assessing selection bias: some tools (2)

5. Use of several control groups , if they are expected to produce selection bias in opposite directions

6. Comparison through studies: for example, studies with population controls vs. those with hospital controls

Example 5.27 (based on Shakeri et al, 2012)
Two case-control studies of opium use and oesophageal cancer conducted in the same region of the Islamic Republic of Iran by the same group with a similar design except for the use of hospital-based vs. population-based controls
The prevalence of opium use was 0.16 in a cohort enrolled in the same geographical areas, 0.17 in the population-based controls and 0.23 in the hospital-based controls

Selection bias adjustment in a case-control study

Table 5.1. True and observed cell counts in a case–control study with selection bias[a]

	True cell counts		Observed cell counts	
	Exposed	Unexposed	Exposed	Unexposed
Case participants	A	B	$a = A \times s_{11}$	$b = B \times s_{10}$
Control participants	C	D	$c = C \times s_{01}$	$d = D \times s_{00}$

[a] Uppercase letters, unobserved true cell counts; lowercase letters, observed cell counts; s_{ce}, selection probability by case status (c = 0, 1) and exposure (e = 0, 1).

$$OR_{adj} = \frac{\frac{a}{s_{11}} * \frac{d}{s_{00}}}{\frac{b}{s_{10}} * \frac{c}{s_{01}}}$$

- add uncertainty calculated from the biased OR
- conduct multidimensional bias analysis changing the bias parameters
- conduct probabilistic bias analysis by sampling from parameter distributions

Centro di Riferimento per l'Epidemiologia e la Prevenzione Oncologica in Piemonte

Università di Torino

Chapter 5: selection bias

Neil Pearce, Laura Beane Freeman, Manolis Kogevinas, Richard MacLehose, Ellen Aagaard Nøhr, Marie-Elise Parent, Lorenzo Richiardi

ICR The Institute of Cancer Research

Chapter 6: Incorporating bias assessments into evidence synthesis

Amy Berrington de Gonzalez, DPhil
Professor of Clinical Cancer Epidemiology

January 2025

CHAPTER 6.

Incorporating bias assessments into evidence synthesis

Amy Berrington de González, Nathan DeBono, Alexander P. Keil, Deborah A. Lawlor, Ruth M. Lunn, and David A. Savitz

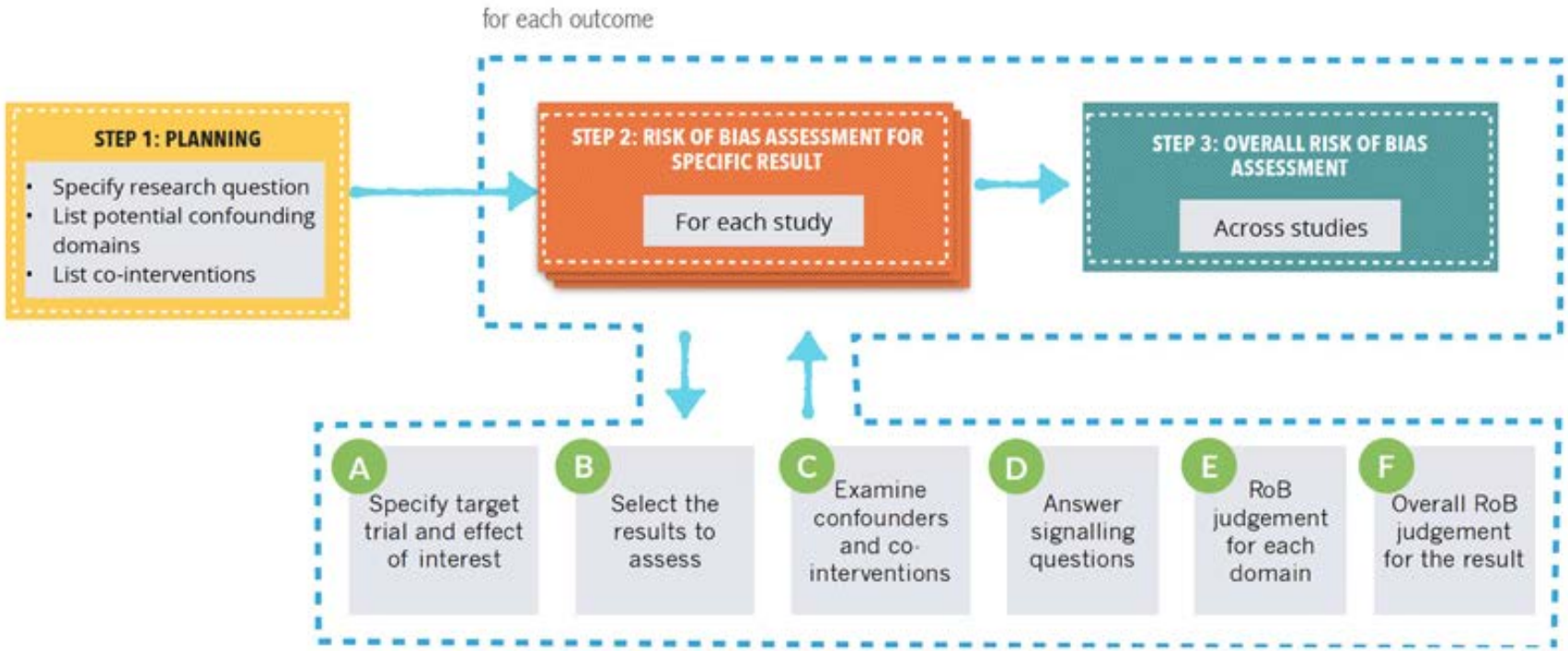
Frameworks: Risk of Bias Algorithms

Strengths

- Clear sets of rules and procedures
- Replicable
- (Should be) Objective

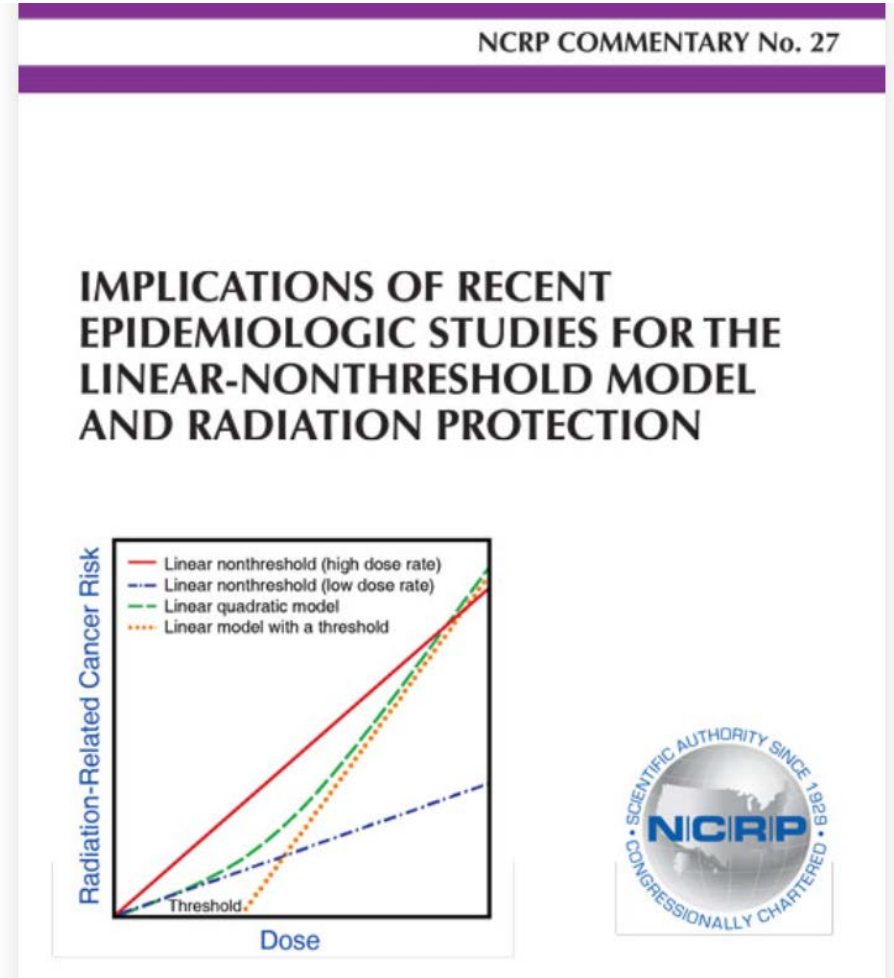
Weaknesses

- Direction & magnitude of bias not considered
- Excludes (many) informative studies
- Subject-matter expertise not prioritised



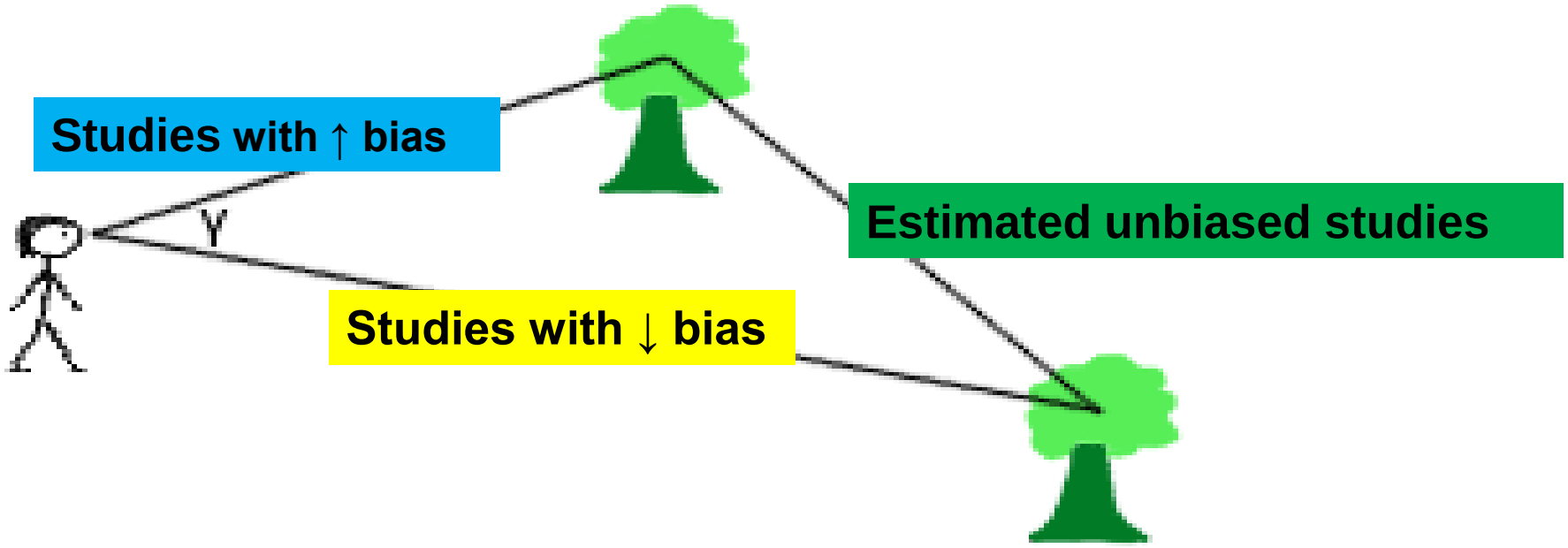
Algorithm Example: Low-dose Radiation Studies

- 11 of 29 studies rated as high-quality
- Remainder considered “uninformative”
- Quality scores based on factors like “dose error”
- No assessment of direction or magnitude of bias

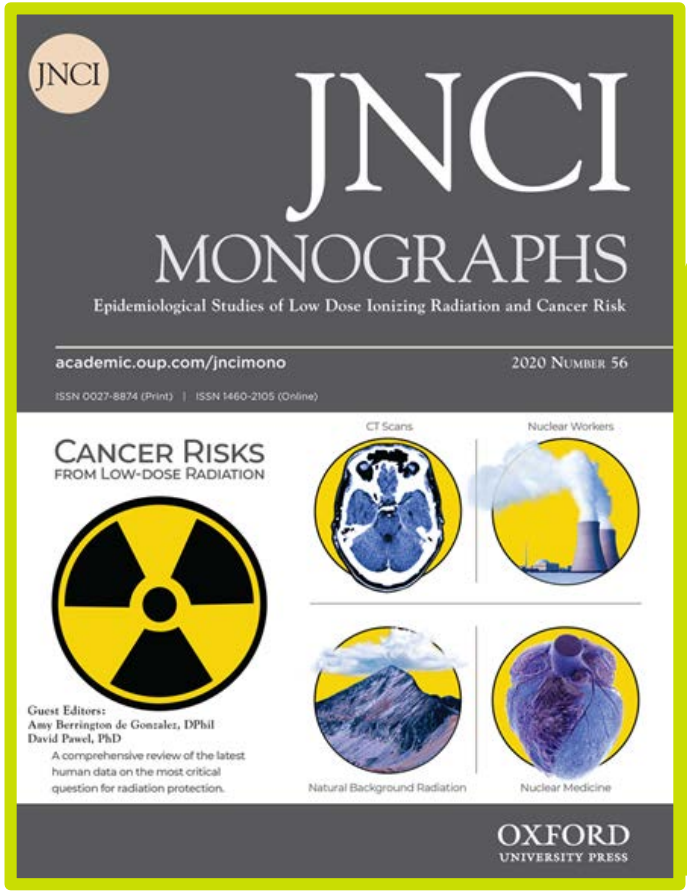


Frameworks: Triangulation

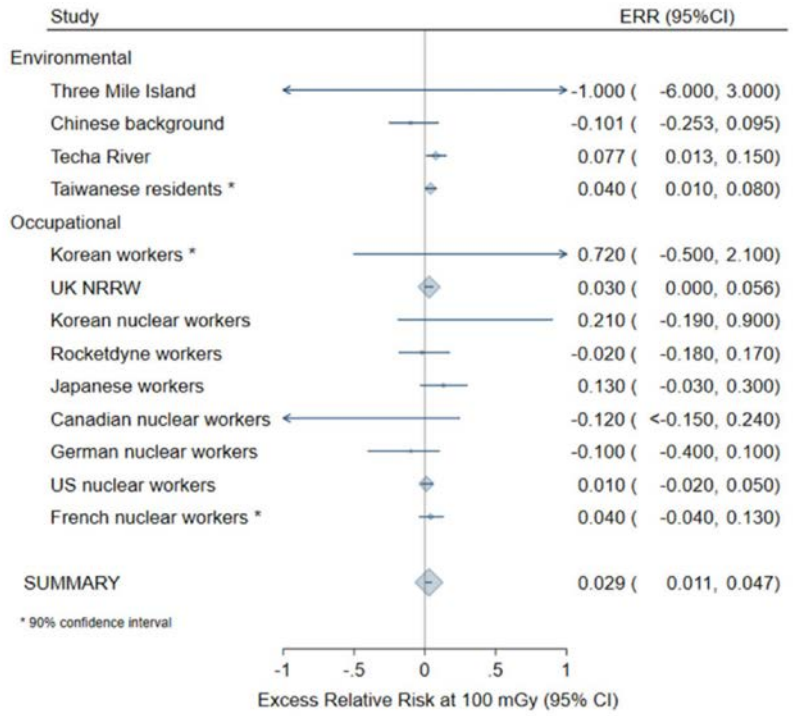
Strengths	Weaknesses
• Retains all informative studies • Emphasizes corroboration (Hill viewpoint) • Emphasizes exploration of heterogeneity • Evaluation of direction & magnitude of bias	• Not specific • Lacks standardisation • Potentially subjective • Not many examples yet

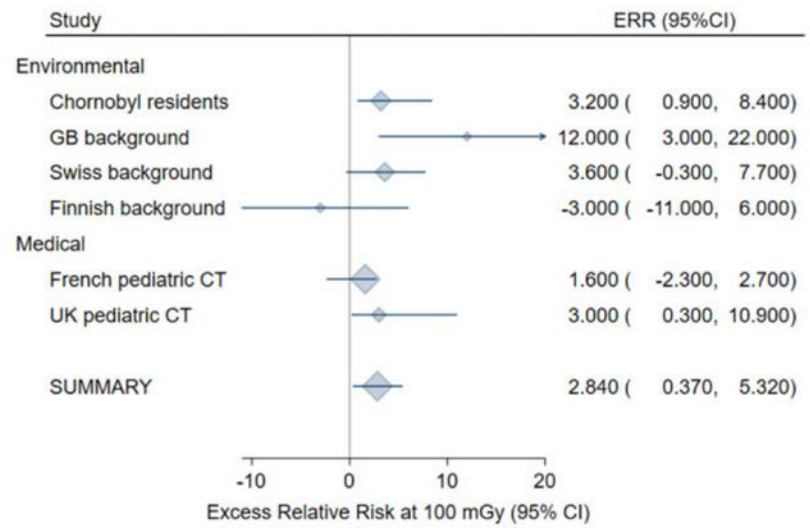


Triangulation Example: Low-dose Radiation Studies



- 26 eligible studies
- Only 4 positive studies with potential positive bias
- Meta-analysis with & with-out these studies
- Contrast results across different exposure settings





Bias Review Process: Recommended Framework

. 6.1. Steps in the bias-review process.

Step 1: Define key biases for the exposure–outcome

- Define key confounders (causes of the outcome that plausibly influence exposure)
- Determine types of measurement error, including classical, Berkson, differential, non-differential
- Consider other biases, including selection bias, outcome misclassification, reverse causation, protopathic bias

Step 2: Review informative studies for each key bias

- Use methods described in Chapters 3–5, including indirect assessment approaches
- Determine direction and magnitude of bias wherever possible
- Summarize findings for each study in bias assessment summary table

Step 3: Assess influence of key biases on the study findings

- Identify subsets of studies with or without key biases
- Identify subsets of studies with biases in opposing direction
- Assess consistency of results across these subsets of studies

Step 1: Define key biases for the exposure–outcome

- Define key confounders (causes of the outcome that plausibly influence exposure)
- Determine types of measurement error, including classical, Berkson, differential, non-differential
- Consider other biases, including selection bias, outcome misclassification, reverse causation, protopathic bias

Example 6.1. Selection of key biases for night shift work

Because night shift work is a complex exposure scenario, the *IARC Monographs* Working Group stated in its assessment of the evidence in humans that "exposure assessment quality of night shift work was a key parameter for the evaluation of the studies" (IARC, 2020), and the reviewers conducted an extensive evaluation of this aspect of each study. In contrast, the Working Group noted that although differences in lifestyle factors exist between day and night shift workers, these differences are usually small; this suggests that the reviewers considered confounding to be of lesser concern. Because there were many informative case–control studies, which tended to have more detailed exposure assessment, selection bias was examined, along with recall bias. (text continues on page 162)

Step 2: Review informative studies for each key bias

- Use methods described in Chapters 3–5, including indirect assessment approaches
- Determine direction and magnitude of bias wherever possible
- Summarize findings for each study in bias assessment summary table

Table 6.1. Potential key confounders for night shift work and female breast cancer

Potential confounding factors	Causes of female breast cancer[a]	Key confounders (and expected directions)
Reproductive and family history factors	Early age at menarche, late age at first full-term pregnancy, nulliparity, menopausal status or age at menopause, no breastfeeding, family history of breast cancer	Young age at first full-term pregnancy or parity. These are protective for breast cancer and are probably negatively associated with night shift work; therefore, confounding away from the null.

Table 6.4. Bias assessment summary for studies on bladder cancer and opium consumption (ever, never used) based on major concerns, as defined and identified by Miranda Filho et al. (2023)[a]

Study (first author)	OR or RR (CI)[b]	Design	Confounding	Reverse causation	Selection bias	Information bias	Protopathic bias
Sheikh	2.86 (1.47–5.56)	co					
Aliasgari	2.60 (0.80–8.47)	c–c(h)			←	↔	
Aliramaji	4.10 (1.59–10.55)	c–c(h)			←	↔	
Sadeghi	2.70 (0.18–40.81)	c–c(h)			←	↔	
Nourbakhsh	3.87 (1.98–7.57)	c–c			↔	↔	
Tootoonchi	2.45 (0.98–6.14)	c–c			↔	↔	
Abdolahinia	8.23 (3.82–17.71)	c–c			↔	↔	
Akbari	3.90 (1.28–11.85)	c–c					
Hadji	3.40 (2.69–4.29)	c–c					
Rashidian	4.40 (2.94–6.59)	c–c					
Ghadimi	4.96 (1.07–22.96)	c–c(h)			←	↔	
Hosseini	4.16 (2.67–6.47)	c–c(h)			←		
Ketabchi	7.99 (5.20–12.27)	c–c			↔	↔	
Lofti	3.01 (1.73–5.23)	c–c				↔	
Shakhssalim	2.57 (1.55–4.26)	c–c				↔	

c–c, case–control; c–c(h), hospital-based case–control; CI, confidence interval; co, cohort; OR, odds ratio; RR, relative risk.

[a] Arrows indicate the direction of the biases: ←, towards the null; ↔, uncertain direction. Blank indicates that the reviewers concluded that there was no substantial bias.

Step 3: Assess influence of key biases on the study findings

- Identify subsets of studies with or without key biases
- Identify subsets of studies with biases in opposing direction
- Assess consistency of results across these subsets of studies

Table 6.6. Example triangulation exercise, comparing meta-analysis results from studies of an association between red meat consumption and colorectal cancer

Strata	Source of bias*	Direction of bias	Number of studies[a]	Meta-effect estimate (95% CI)[a]	Triangulated meta-effect estimate
Cohort studies	Non-differential exposure misclassification	Downwards and towards the null	9	1.27 (1.11–1.45)	1.27–1.36
Case–control studies	Recall bias	Upwards and away from the null	14	1.36 (1.17–1.59)	

CI, confidence interval.

[a] Results from Norat et al. (2002) for the highest quantile of red meat consumption.

Multiple bias analysis

- What direction do the biases act in?
- Are they likely to act independently?
- Target-adjusted multiple bias analysis not recommended
- Bias-level sensitivity analysis – use sequential approach
- Adjust in the reverse order the biases occur
- Eg confounding-selection-measurement error
- See worked example by Alex Keil with R-code (Annex 3)

Summary: Incorporating Bias Assessment into the Evidence Synthesis

Recommendations

- Pre-specified plan for major biases
- Retain all informative studies
- Use tools (Chs 3-5) to assess direction & magnitude of bias
- Gain insights from heterogeneity

Challenges

- Multiple biases within studies
- Not guaranteed a clear answer
- Time-consuming for multiple studies

International Agency for Research on Cancer

World Health Organization

Chapter 7
Study reporting considerations to facilitate quantitative bias assessment with access to original data

Lin Fritschi, Terry Boyle, Brigid M. Lynch, Scott Weichenthal, Irina Guseva Canu

A different approach ….

- **Our target audience is researchers with access to individual data but do not have the ability to change the study design**
- **We want to provide information for those whose goal is to:**
  - Undertake **quantitative bias analysis on their study** for the discussion section of a paper
    - Avoid writing “any biases are likely to have moved the result closer to the null”
  - Or to ensure that their study can be used in **future** systematic reviews which include **quantitative bias analysis**
- **In this chapter we explain what information researchers need to obtain and report in order to reach these goals**

When might you read this chapter?

- **When you are analysing study data and you do not have the option to change the study design**
  - Using individual-level data from a large (inter)national study or a study which is not yours
    - e.g the major national cohorts or international pooled data
  - Data collection is complete
  - Data cannot be improved
    - e.g medical records

What this chapter is not

- We do not cover checklists and tools to assess risk of bias
- While some of these might be useful, they do not give a quantitative estimate of the direction or magnitude of the bias

How chapter 7 is structured ?

- 7.1 Introduction
- 7.2 Reporting considerations to aid graphical approaches to identify biases *(refers to Chapter 2)*
- 7.3 Confounding *(refers to Chapter 3)*
- 7.4 Information bias due to exposure and outcome misclassification *(refers to Chapter 4)*
- 7.5 Selection bias *(refers to Chapter 5)*
- 7.6 Conclusions

7.2 Reporting considerations to aid graphical approaches to identify biases

- Focuses on 8 reporting principles when constructing and presenting DAGs to facilitate bias assessment
- These principles can be applied at the study analysis stage to explicitly describe assumptions
- Also can be applied in evaluating potential sources of bias that were not addressed in the initial analysis
- Hypothetical scenarios of reporting with 2 examples

Fig. 7.1. Directed acyclic graph for red meat consumption and cancer. BMI, body mass index.

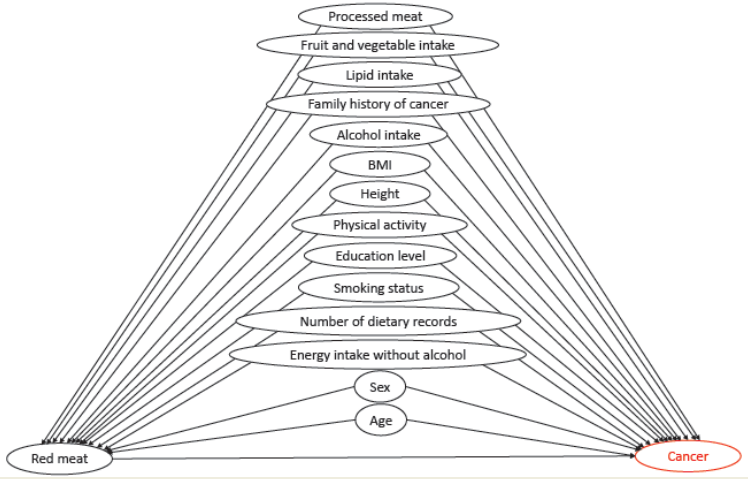
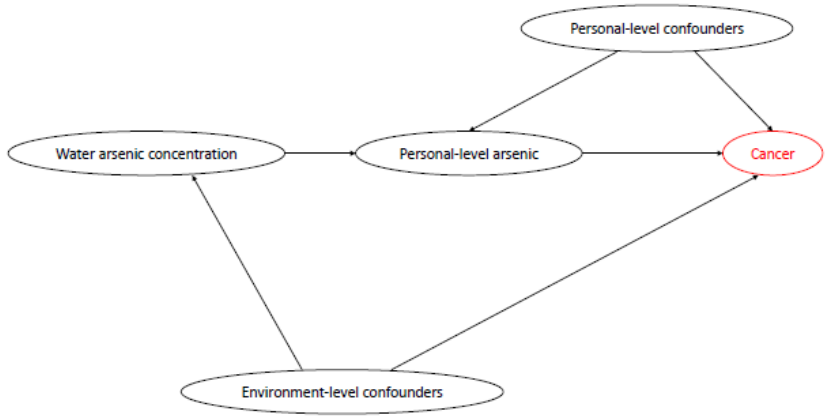


Fig. 7.2. Distinguishing between personal-level confounders and more-proxy-level confounders (here, water arsenic concentration).



Each of the sections 7.3-7.5 cover

- What the issue is and where in the volume you can find more information on methods to address this issue
- A brief description of each method in relation to the focus of this chapter
- Examples of how to do the method, and any relevant statistical packages
- A table listing the data which should be reported to facilitate use of the methods

Table 7.3. Reporting considerations for measurement error and exposure and outcome misclassification

Type of bias to be assessed	Reporting considerations	More details
Measurement error in binary exposures	Sensitivity and specificity of measures used to classify participants as exposed, along with relevant references	Section 4.2.1(b)
Measurement error in continuous exposures	Validity of exposure measurement, along with relevant references	Section 4.2.1(a)

Another example

Table 7.4. Essential information that should be reported to inform assessment of selection bias

Origin of selection bias	What should be reported	More details
Differential baseline participation	Definitions and distributions of participants and non-participants among case and control groups Prevalence of exposure and disease for non-participants Probability of selection among each subgroup	Section 5.2.1
Loss to follow-up	Rates of loss to follow-up in key subgroups of interest by baseline exposure status	Section 5.2.2

Conclusions

- We hope that this chapter will
  - assist researchers in **undertaking quantitative bias assessments** in their own studies
  - use existing large cohort studies to **apply newer conceptual and statistical methods** to address causal questions
  - **include quantitative bias assessment** as an integral component of **every epidemiological study**
  - facilitate stronger systematic reviews and hazard identifications by **ensuring that every study published contains the information required for a quantitative bias analysis**

Thank you

Terry Boyle, Lin Fritschi, Irina Guseva Canu, Brigid M. Lynch, Scott Weichenthal