Determining work-related causation of disease in individual patients

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- I have no conflict of interest in presenting this material.

Educational Objectives

At the conclusion of this session, you will be better able to:

1. Explain several decision-making concepts of work-related causation of disease in individual patients
2. Understand some common types of causal and non-causal associations and multiple causation scenarios
3. Apply this understanding to judging work-related causation in individual patients

Determining causation of illness in individual patients is important in medicine

- ICU patient noted to have acute kidney injury while being treated for a life threatening multi-drug-resistant infection with a potentially nephrotoxic antibiotic
  - The patient has had recent imaging with a potentially nephrotoxic contrast agent
  - Second line antibiotic is known to be much less effective.
- Continue or change the antibiotic?
- Forced to determine the cause of the kidney injury: antibiotic, contrast medium, both, something else?
- **Forced decision making under uncertainty**, requiring determination of causation in individual patients

Why is determining WR causation of disease in individual patients important?

- Prevention
  - Continue working safely, Evidence-based Safe Return To Work
  - ID the causal exposure(s) to protect co-workers at risk
  - Primary prevention of Work-Related Disease WRD is by far the best approach but often fails
- Compensation for WRD losses when prevention fails
  - Necessary for fairness of wage replacement in Workers' Compensation systems
- Improve overall health of patient
  - ID and elimination of exposure is a key part of treatment of some diseases eg, WRA, CTS, latex allergy
  - Preserve access to medical care for WRDs denied by Med Insurance
  - Prevent delays in correct medical diagnosis and treatment

What does “Work-Related” mean?

OSHA Standard 1904.5

“You must consider an injury or illness to be work-related if an event or exposure in the work environment either caused or contributed to the resulting condition or significantly aggravated a pre-existing injury or illness.”

- Caused
- Contributed to
- Aggravated

https://www.osha.gov/laws-regs/regulations/standardnumber/1904/1904.5

What is a Cause?

- **Necessary Cause** is a condition under which, if absent, the disease cannot occur
- **Sufficient Cause** is a condition under which, if present, the outcome will inevitably occur
- These are **Deterministic** definitions of cause, not probabilistic (stochastic)

What is a Cause? Necessary and Sufficient Causes

- Both concepts can be useful in understanding mechanisms of multiple contributing causes
- Neither concept works well as a standalone definition for causation analyses of single causes
  - Many counterexamples for which they do not align with evidence

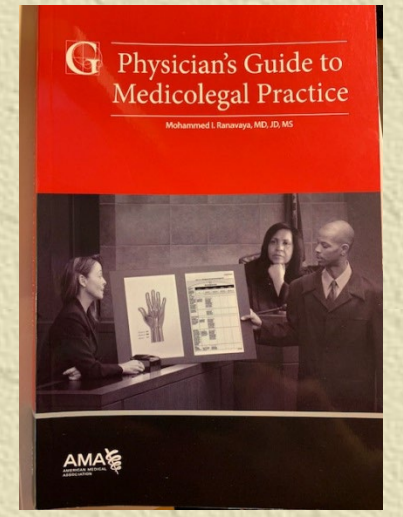
Examples of known causes of specific diseases that are neither Necessary nor Sufficient

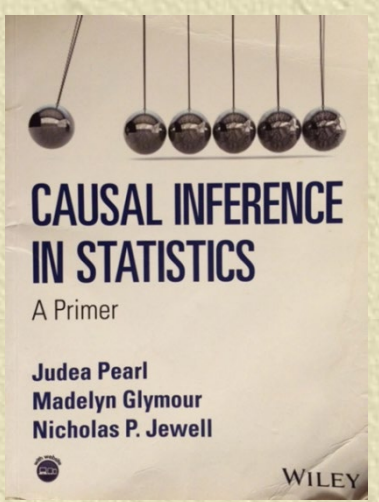
- Asbestos exposure can cause Mesothelioma
  - In absence of asbestos exposure, mesothelioma can still occur
  - Among all individuals with asbestos exposure, mesothelioma does not inevitably occur
- Hepatitis B carrier state can cause Hepatocellular Carcinoma
  - In absence of HBV carrier state, HCC can still occur
  - Many Hepatitis B carriers do not get hepatocellular carcinoma
- Smoking can cause Lung Cancer
  - 10-15% of people with lung cancer never smoked
  - 80-90% of smokers do not get lung cancer

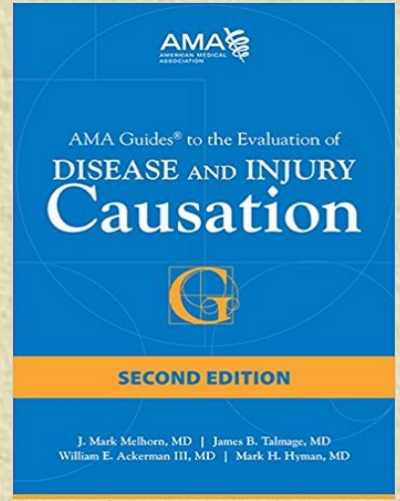
Necessary and Sufficient Causes

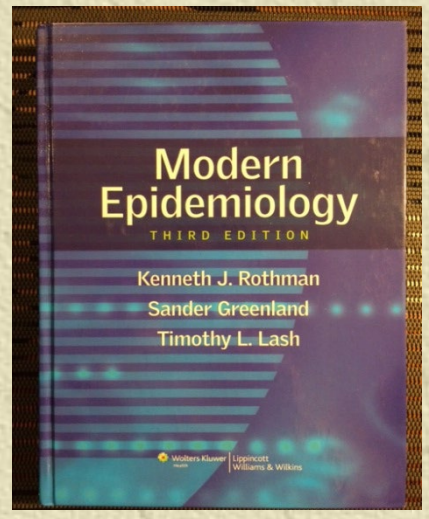
- Diseases defined by the causal factor are forced to be Necessary Causes
  - Measles virus is a necessary cause of measles
  - Mycobacterium tuberculosis is a necessary cause of TB
  - Inhalation of respirable silica dust is a necessary cause of silicosis
  - Lead exposure is a necessary cause of lead poisoning
- These definitional Necessary Causes are useful in diagnosis but less so or not at all in causation analyses

Definitions of cause









Definitions of cause (Ranavaya p. 81)

“Causation refers to an association in which one condition precedes an outcome and must be present for the outcome to occur.”

- The second part is simply the definition of a Necessary Cause, which is not met by any of the 3 examples, asbestos/meso, HBV/HCC, smoking/LC
- Not reliable for occupational medicine decision making, absence of the condition does not rule out causation

Definitions of cause (Pearl, p. 5)

"A variable X is a cause of a variable Y if Y in any way relies on X for its value."

- Useful in artificial intelligence, tested thoroughly in computer simulations
- Applicable to individuals and groups
- Quite abstract, cannot distinguish weak from strong causes
- Not very practical for medical decision making

Definitions of cause (AMA Guide, p. 10)

"Rothman defined a cause as 'an event, condition, or characteristic that plays an essential role in producing an occurrence of the disease.' **There is causation, in other words, only when one factor necessarily alters the probability of a second."**

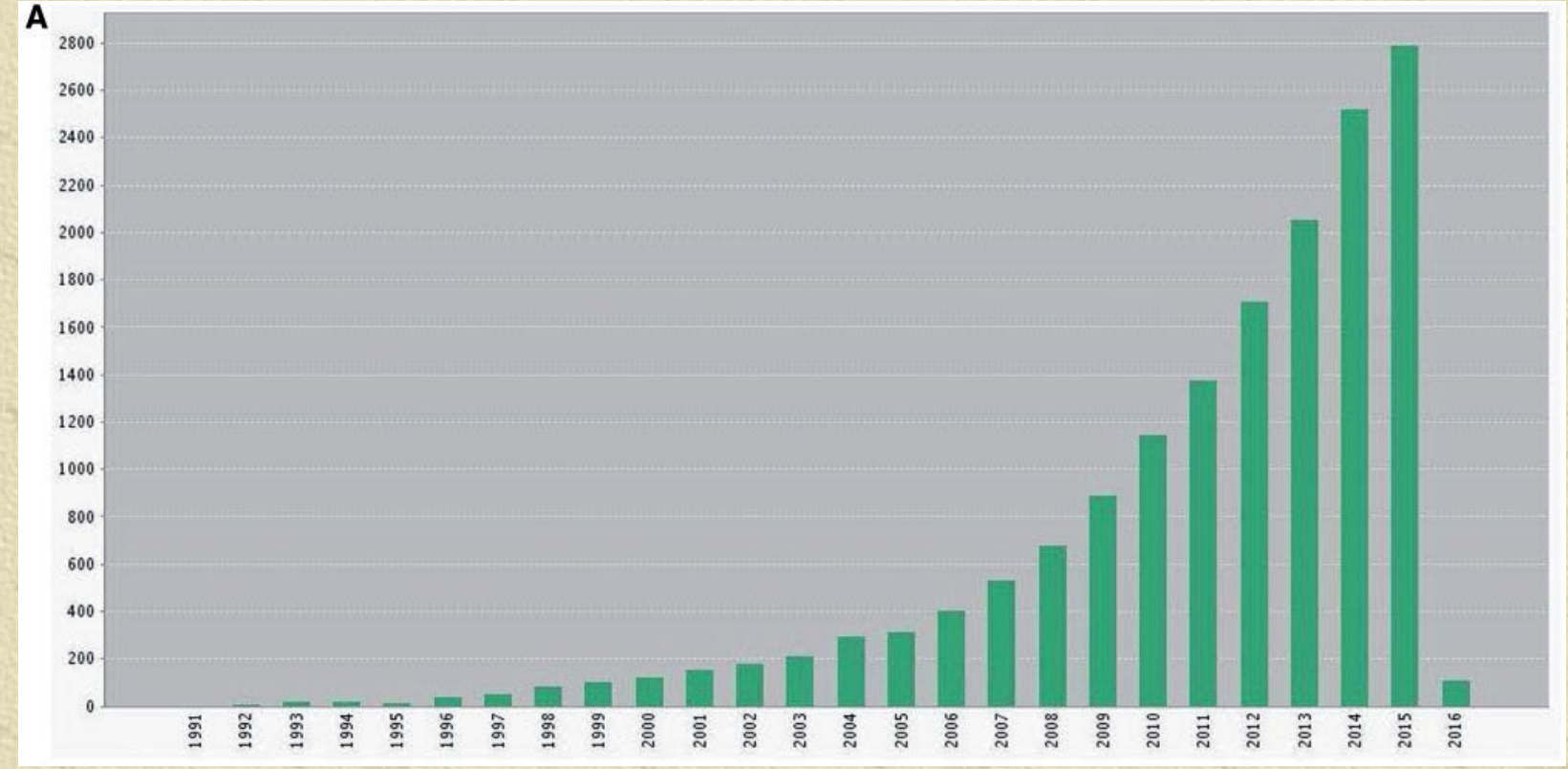
- Based on Rothman's first edition (1986) definition
- Applicable to population studies but not individuals
  - It appears that smoking could be called a cause of lung cancer even in a smoker who has not developed lung cancer
- Not very practical for occupational medicine decision making

Definitions of cause (Rothman, 2008)

"…an event, condition or characteristic that preceded the disease onset and that, had the event, condition or characteristic been different in a specified way, the disease either would not have occurred or would have occurred at a later time."

- Applicable to the cause of a specific disease occurrence in a single individual and in populations
- Explicitly considers time of occurrence
- Mathematically more precise and more useful for medical decision making than the other definitions
- More recent advanced epidemiology texts avoid defining cause

Number of published articles on causal inference in epidemiology, 1990-2015 (Source: Krieger & Davey Smith, 2016)



Population and Individual level determination of causation of Work-Related Diseases

- Population level (general or type causation):

  Can the work exposure cause the disease in a group?

- Individual level (specific or token causation):

  Did the exposure cause the disease **in this patient**?

Some examples of diseases that can be caused by WR exposures in HCWs

- Infections
  - Viral respiratory including SARS1, SARS2 (Covid-19), Influenza, varicella, rubeola
  - Bloodborne eg HBV, HCV, HIV
  - Bacterial including MTB, MRSA, C. dificile
  - Rare infections including herpetic whitlow, Ebola, emerging IDs
- Carpal Tunnel Syndrome, Tendinopathies, other WMSDs
- Asthma
- COPD
- Hypersensitivity Pneumonitis, Pulmonary fibrosis
- Allergic and irritant dermatoses
- Asbestosis, silicosis, other pneumoconioses
- Cancers (Breast, Lung, Mesothelioma, possibly leukemia and others)
- Hypertension
- Mercury toxicity (well prevented)

Occupational Medicine Causation Evaluation

- 6 step process to determine work-related causation of illness in individual patient
- NIOSH (1979) / ACOEM (2018)
    1. Evidence of disease
    2. Epidemiology
    3. Evidence of individual exposure
    4. Other relevant factors
    5. Validity of testimony
    6. Conclusion based on steps 1-5

Accuracy of determination of WR causation is important

- Diagnostic accuracy is fundamental to high quality medical and surgical practice
- Diagnostic errors are most common, costly and dangerous category of medical mistakes
- In OM we have an additional diagnostic dimension: determination of WR causation
- Errors in determining WR causation can harm patients, families, employers and other parties

Accuracy of determination of WR causation

"Truth" ⇨ / Determination ⇩	WR Causation	Not WR Causation
WR by Clinical Eval	TP	FP
Not WR by Clinical Eval	FN	TN

Harm from FP determination of WR causation in a patient

- Elimination of job exposures that are in fact not related to the patient's illness will not improve the illness
- Absences, change or loss of job or profession, demotion, lost productivity harm worker, family, employer
- Workers' Comp approval of necessary testing and treatment often delayed
- Third party medical insurance carriers often deny claims for which WC has been filed
- Delay or loss of access to medical care for that condition
- Delay or failure to make the correct medical diagnosis can delay proper medical treatment of the correct illness

Harm from FN determination of WR causation in a patient

- Non-financial and financial costs
- Delay or complete failure to identify and correctly treat the WR disease or injury
- Disease worsening with continued causal exposure
- Can jeopardize safe return to work after med leave
- Frequent or long absences from work due to incompletely treated disease of unclear etiology
- Job loss and periods of unemployment, generally accompanied by consequent psychosocial effects

Harm from FN determination of WR causation in a patient

- Lack of WC benefits can cause severe financial problems
  - Poverty
  - Family relationship difficulties
  - Loss of home
- Cost shifting of costs from WC / employer to
  - Worker/patient and family
  - Private med insurance carrier, Medicaid, Medicare
  - Unemployment and disability insurance
  - Loss of incentive to abate the hazards can lead to higher risk of WR injuries and illnesses for others

Improving accuracy of determination of WR causation

- Probabilities of FP and FN determinations may be unnecessarily high and can often be reduced
- Problem areas include
  - Incomplete clinical and exposure evaluations
  - Multiple contributing causes
  - Misinterpretation of available research results
  - Multidisciplinary expertise needed including IH, toxicology, epidemiology, ergonomics, clinical OM
- Could reduce probabilities of both FN and FP simultaneously by addressing these better

WR causation scenarios common in individual Occ Med patients

- Single event “obvious” cause with no other plausible competing or contributing causes
- WR cause being evaluated plus one plausible contributing or competing cause
- WR cause being evaluated plus one plausible competing (not contributing) cause
- Repeated WR exposure episodes associated in time with repeated illness episodes (rechallenge)

Single event “obvious” cause, no other plausible competing or contributing causes

- Box falls on warehouse worker, she falls on outstretched arm and fractures clavicle
- New onset asthma same day as high level exposure to strong respiratory irritant (RADS)
- Mesothelioma in sheet metal worker 40 years after job with 10 years asbestos exposure
- Acute hepatitis C infection in HCW 3 months after needlestick, unknown source pt HCV

WR exposure plus one plausible contributing or competing cause

- Lung cancer in smoking asbestos worker
- COPD in cadmium fume exposed worker who smokes cigarettes
- CTS in diabetic worker who does forceful repetitive grasping motions on assembly line
- HTN in chronically lead exposed bridge repainting worker with FH of HTN

WR exposure plus one plausible competing (not contributing) cause

- Recurrent abdominal pain caused either by gastritis or by lead poisoning, not both
- New back pain caused either by workplace injury or motor vehicle crash injury

Repeated WR exposure episodes associated in time with repeated illness episodes

- New onset asthma in auto body shop worker with asthma attacks on most days or nights after using spray paint containing hexamethylene diisocyanate (HDI) but rarely has asthma symptoms on days off (nonrandom re-challenges)
- Progressive sensorineural hearing loss in musician who plays frequently in local clubs, with tinnitus and worse hearing loss the night and next day after most gigs, resolves with time, recurs with re-exposure
- Choose a parameter to follow through repeated exposures

Different approaches needed for different occupational diseases

- Immediate cause/effect: may be “obvious” but clinical judgment is still often needed
  - Slip & fall
  - Instantaneous lifting injury that happened at work
- Short latency with WR reversible symptom pattern and physiology. Can sometimes do de-challenge/re-challenge. Also may require clinical judgment if high quality diagnostic testing is not available or achievable.
  - WRA: Hx and Serial Peak Flow over several weeks at and away from work
  - Acute Hypersensitivity Pneumonitis / EAA Serial CXRs
  - Mechanical LBP
- Toxicologic syndrome with validated biomarkers. Also requires clinical judgment, epidemiology
  - Pb, Hg
  - A few acute solvent-related CNS illnesses..

Different approaches needed for different occupational diseases

- Specific recognizable patterns on imaging, combined with history, clinical judgment, and sometimes histologic confirmation
  - Asbestosis
  - Silicosis
  - Diacetyl-induced obliterative bronchiolitis
  - Chronic HP / EAA
- Immunologic, also requires clinical judgment
  - EAA (HP) with positive IgG precipitins
  - Sensitizer Induced Occupational Asthma with positive ICT or WCT or Skin Prick Test
  - Allergic contact dermatitis with pos patch test

Different approaches needed for different occupational diseases

- Tendinitides and back pain with ergonomic/biomechanical exposure, also require clinical judgment, epidemiologic knowledge
  - Lateral epicondylitis
  - Trigger finger
  - Chronic rotator cuff injuries
  - Low back pain
- Multicausal chronic disease requiring epidemiologic, exposure assessment, clinical judgment
  - Occupational cancers (IARC/NTP)
  - Occ COPD/Vapors Gases Dusts Fumes
  - Occ CTS
  - WRA in unemployed workers

Different approaches needed for different occupational disease

- Presumption of causation legislatively mandated for specific diagnoses among members of groups with similar exposures based on epidemiologic, exposure, other criteria
  - Firefighters
  - WTC responders
  - Nuclear weapons production workers

Two phases of Causation Analysis

- Provisional (Initial) on first visit
  - Used to initiate treatment, decide on filing Workers' Comp
  - Based on incomplete but immediately available information
- Definitive (Confirmatory) after gathering all available information
  - Utilizes all information gathered eg, individual exposures, medical work-up, review of epi literature
- Concept of Probability of Causation in deciding if WR Causation is more likely than not

Recent recommendations to place less emphasis on p-values and statistical significance

"Control of Confounding and Reporting of Results in Causal Inference Studies: Guidance for Authors from (48) Editors of Respiratory, Sleep and Critical Care Journals". Lederer, et al. Annals ATS 2019: Quote from Table 1

Key Principle #2: Interpretation of results should not rely on the magnitude of P values

- P values should rarely be presented in isolation
- Present effect estimates and measures of variability with or without P values
- Variability around effect estimates should inform conclusions
- A conclusion of "no association" should require exclusion of meaningful effect sizes
- Avoid the word "significant" in favor of more specific language.

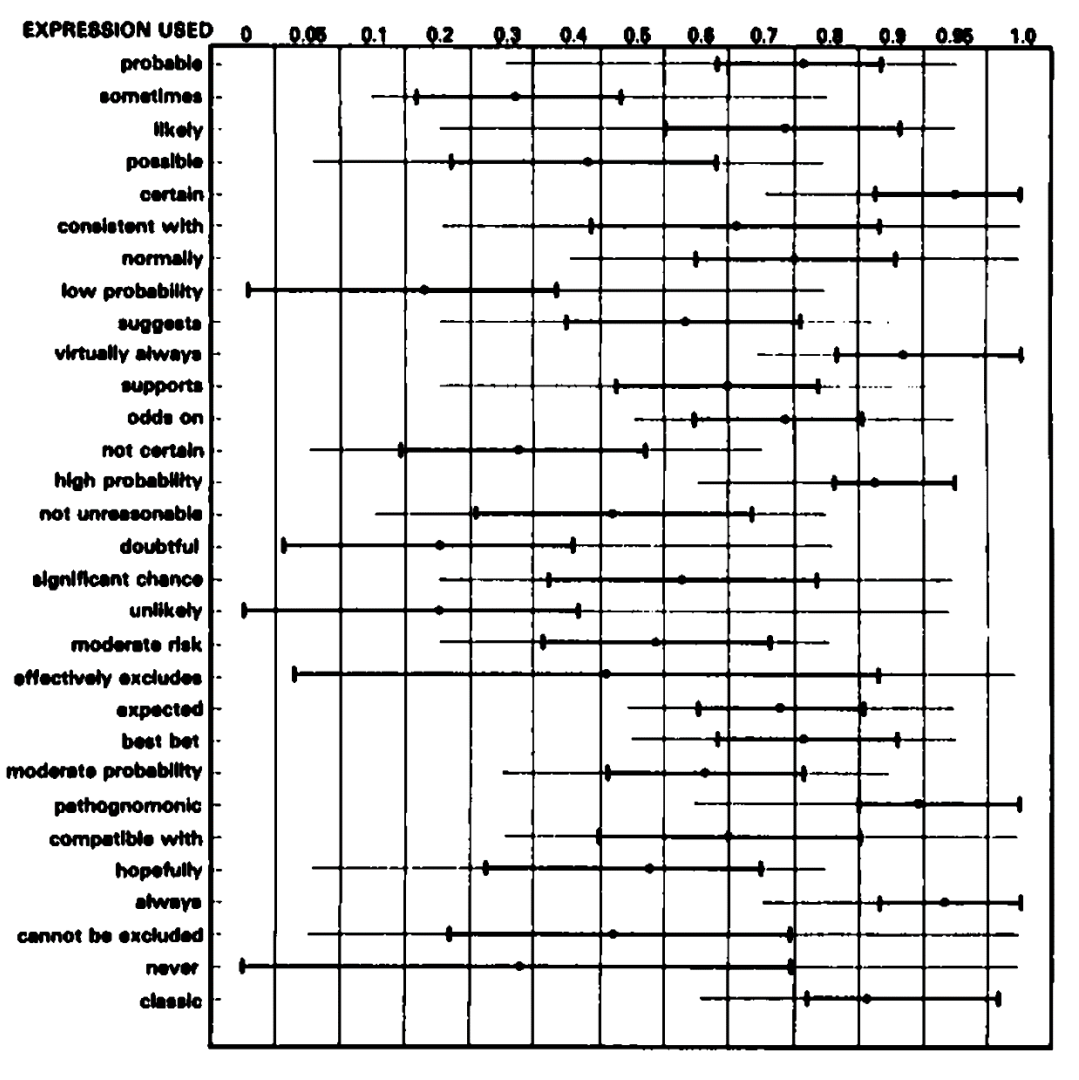
Approach suggested by Kathryn Mueller MD, ACOEM talk 9/13/20

Bottom line:

- “Without the work-related exposure or accident, is it medically probable that the patient would have the current diagnosis and require treatment?”
- “No” = Work-related
- “Yes” = Not WR
- But what does “medically probable” mean?

Expressions of Probability: Words & Numbers (Bryant, NEJM, 1980)

- Survey of 16 physicians to give probability estimates for each of 30 terms commonly used in medicine
- They concluded that physicians should use numerical probabilities in communication
- Convention in occ med is that
  - Probable is > 50%
  - Possible is < 50%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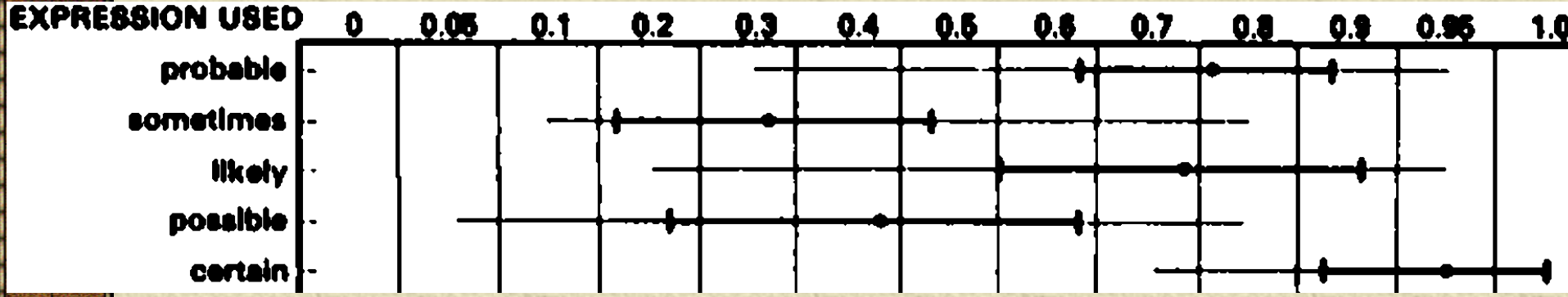
Top 5



MD assigned Probability from 0.0 to 1.0: Mean, +/-1 SD, Range

Probable: Mean 76%, +-1 SD from 64% to 88%, Range 30% - 95%

Possible: Mean 44%, +-1 SD from 23% to 64%, Range 5% - 80%

Source: Bryant G NEJM;302(7):1980 Expressions of Probability: Words & Numbers

More likely than not Criterion

Relative probability of causation by work-related vs non-work-related causes

Bradford Hill's fundamental question,

"Is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?"

Bradford-Hill, 1965, p. 299

“More Likely Than Not” Criterion and Probability of Causation

- Probability of Causation (PC) can be defined as the probability that occupation causally contributed to development of the patient’s disease (following derivations by Greenland & Robins, Jurimetrics, 2000).
- “More likely than not” implies that PC>50%.
- AMA Guides recommend using Relative Risk (RR) to estimate the incidence Rate Fraction (RF), then using RF as an estimate of PC. (p. 117)
- **RF = (RR-1)/RR**
- This formula implies algebraically that when RR>2 then RF>50% (WR) and when RR<2 then RF<50% (not WR)

“More Likely Than Not” Criterion and Probability of Causation

- Greenland and Robins have shown that, under most real life conditions, RF is a lower limit of PC, not equal to PC
- So RR>2 implies PC >50%, but RR<2 DOES NOT imply that PC<50%, unless strong assumptions are true
- If the causal effect includes acceleration of the disease development, even if RR is much less than 2, PC can be greater than 50%, even up to 100%. (Cox, 1984; Robins, 1989; Greenland, 2000)
- In addition, all calculations of PC assume a biologic model and different biological models can give very different PCs with the same epidemiologic data

Assumptions needed for PC to equal RF

- Summarized in Fed Judicial Ctr / National Research Council Reference Manual on Scientific Evidence 3rd Ed 2011.

1. Risk measure is judged to be causal, **statistically unbiased and there is no confounding** (General Causation is accepted).
2. Patient in question is similar to study subjects, with regard to all measured and unmeasured risk factors for the disease.
3. **Exposure does not accelerate development of disease** that would have occurred later in patient's lifetime if unexposed.
4. Agent operates Independent Of Baseline risk of disease (IOB), ie, **adds the same absolute risk** to each subject's risk regardless of baseline (unexposed) risk that varies with other risk factors.
5. Agent of interest does not cause any fatal diseases other than the disease of interest.
6. Exposure is never preventive in any individual.

“More Likely Than Not” Criterion and Probability of Causation

- Neither assumption of no acceleration nor that of Independence of Baseline Risk and exposure effect can be tested epidemiologically.
- Both these assumptions are unlikely to be true, and both require support from biological models or mechanistic information

NIOSH Probability of Causation Calculator for Nuclear Weapons Production Workers

- Calculates “PC” of various cancers for workers exposed to ionizing radiation
- All workers wore personal radiation dosimeters every work day
- Uses RF = (RR-1)/RR calculated from cumulative ionizing radiation dose
- Acknowledged the downward bias in PC as estimated by RF
- NCRP committee recommended to change terminology “Probability of Causation” to “Assigned Share” to avoid implying erroneously that RF = PC

NIOSH Probability of Causation Calculator for Nuclear Weapons Production

- Instead, for “more likely than not” decisions, replaced RF>50% with 99% Bayesian Credible Interval upper bound of RF for claimant > 50%
- This countervailing upward bias in RF is hoped to consistently be greater than the downward bias and favor the claimant
- So PC is not reliably calculable even based on individually measured radiation dosimeter cumulative dose and large epi studies
- Dosimetry data is a best case exposure measurement, real world exposure estimates for other exposures are much less accurate
- Numerical estimation of PC or even RF for individuals with qualitative or very crude quantitative exposure estimates is not hopeful.

“Updated Hill’s Criteria” for evaluating epi evidence of causal association

a. Temporality
b. Strength of association
c. Dose–response
d. Consistency
e. Coherence
f. Specificity
g. Plausibility
h. Reversibility
i. Prevention/Elimination
j. Experiment
k. Predictive Performance

Sir Austin Bradford Hill warned against developing "Causal Criteria"

From Bradford Hill, 1965, p. 299,

"Here then are nine different viewpoints from all of which we should study association before we cry causation. What I do not believe - and this has been suggested - is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect."

Pearl (2009): Need for expert judgment in causal inference

"Behind every causal claim there must lie some causal assumption that is not discernable from the joint distribution and, hence, not testable in observational studies. Such assumptions are usually provided by humans, resting on expert *judgment*."

Pearl, Causality p. 40, 2009

Directed Acyclic Graphs (DAGs)

- Recently developed tool to help make explicit the underlying assumptions in epidemiologic design of causal association studies
  - Choice of variables for statistical control (or not)
  - Interpretation of epi studies and causal inference

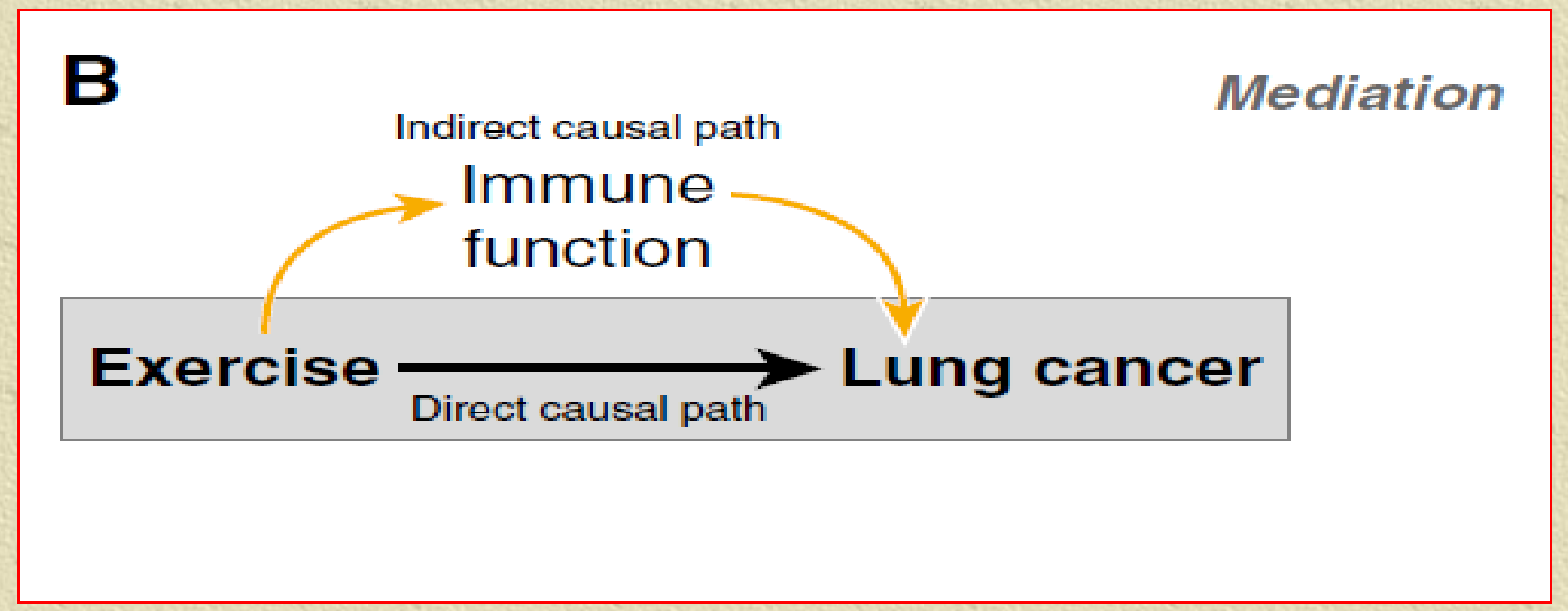
Causal Associations: Direct, Reverse, Mediation

E ⇨ D Direct causation of disease D by single exposure E
Example: smoking causing lung cancer

D ⇨ E Reverse causation of E by disease D
Example: COPD causing person to quit smoking

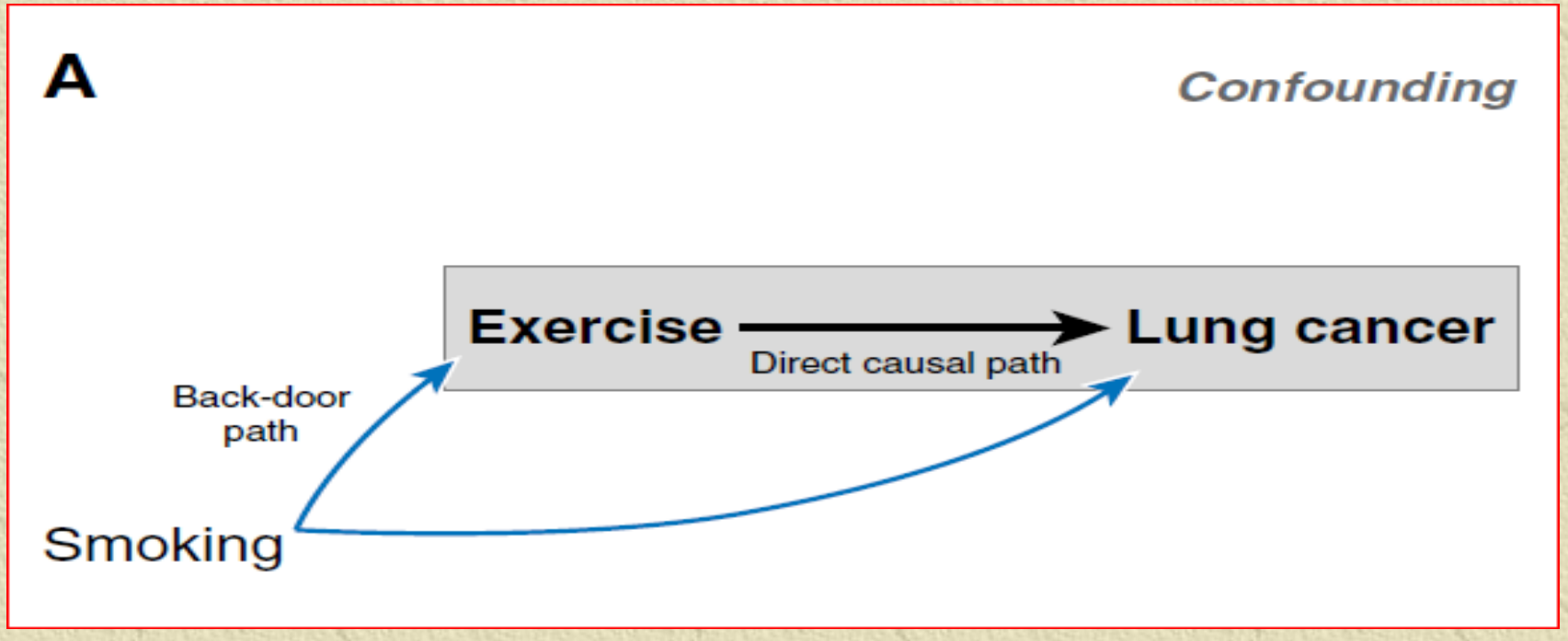
E ⇨ M ⇨ D Causal effect of E on D mediated by M

Mediation: indirect causal path or Intermediate variable on causal path



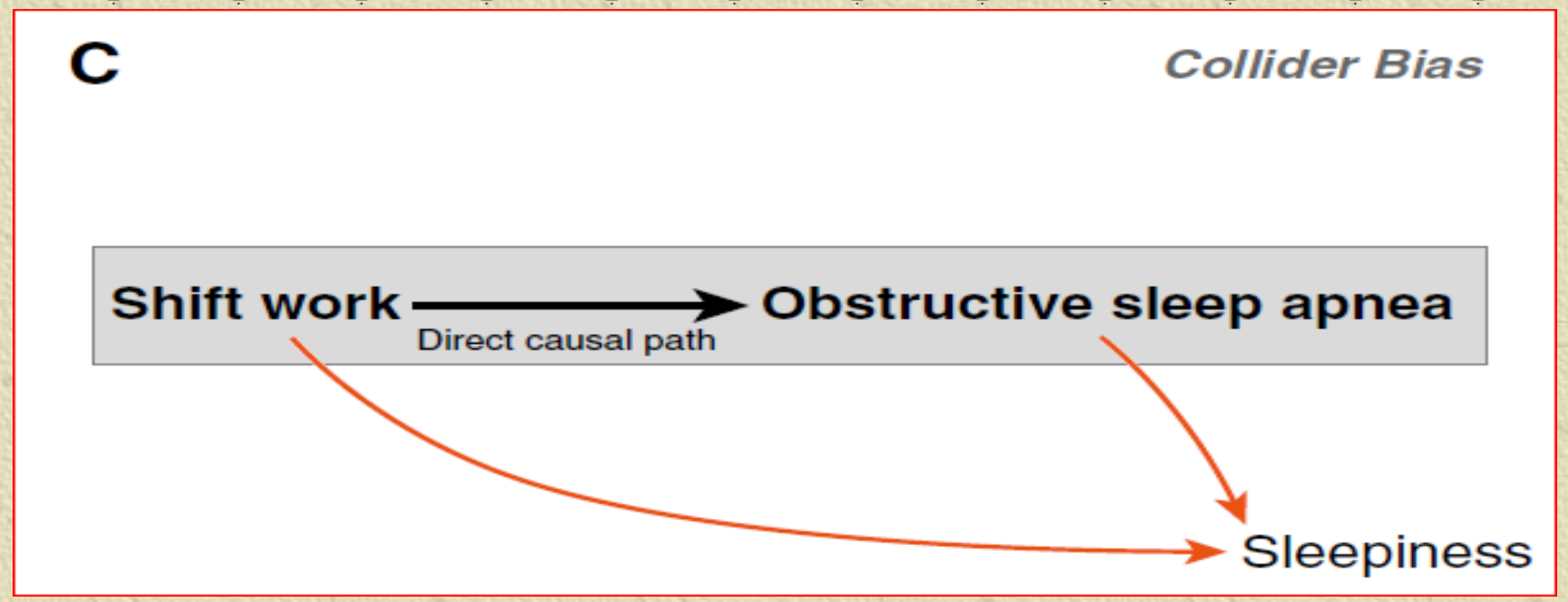
Source: Lederer et al, 2019

Non-causal associations: Confounding (backdoor path) Common cause of E and D



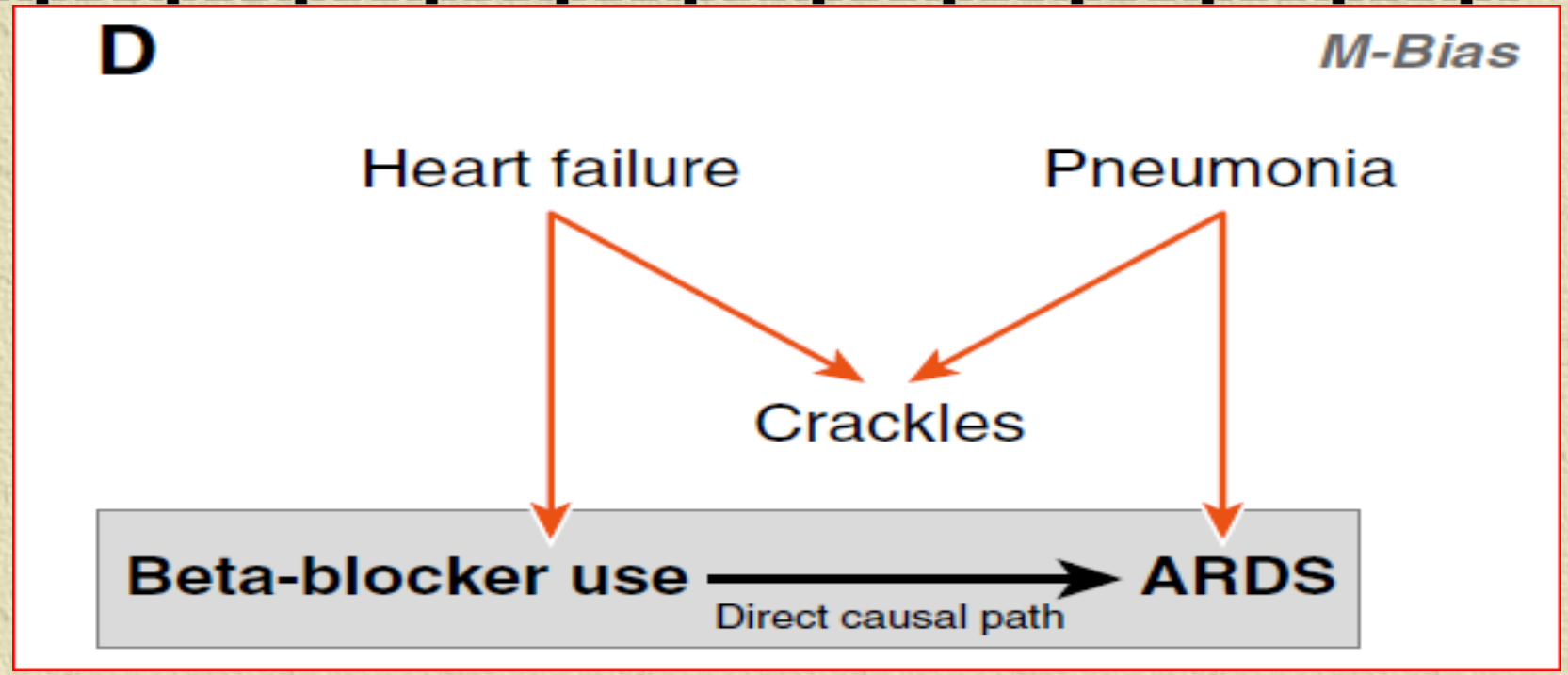
Source: Lederer et al, 2019

Non-causal association: Collider is Common Effect of E and D



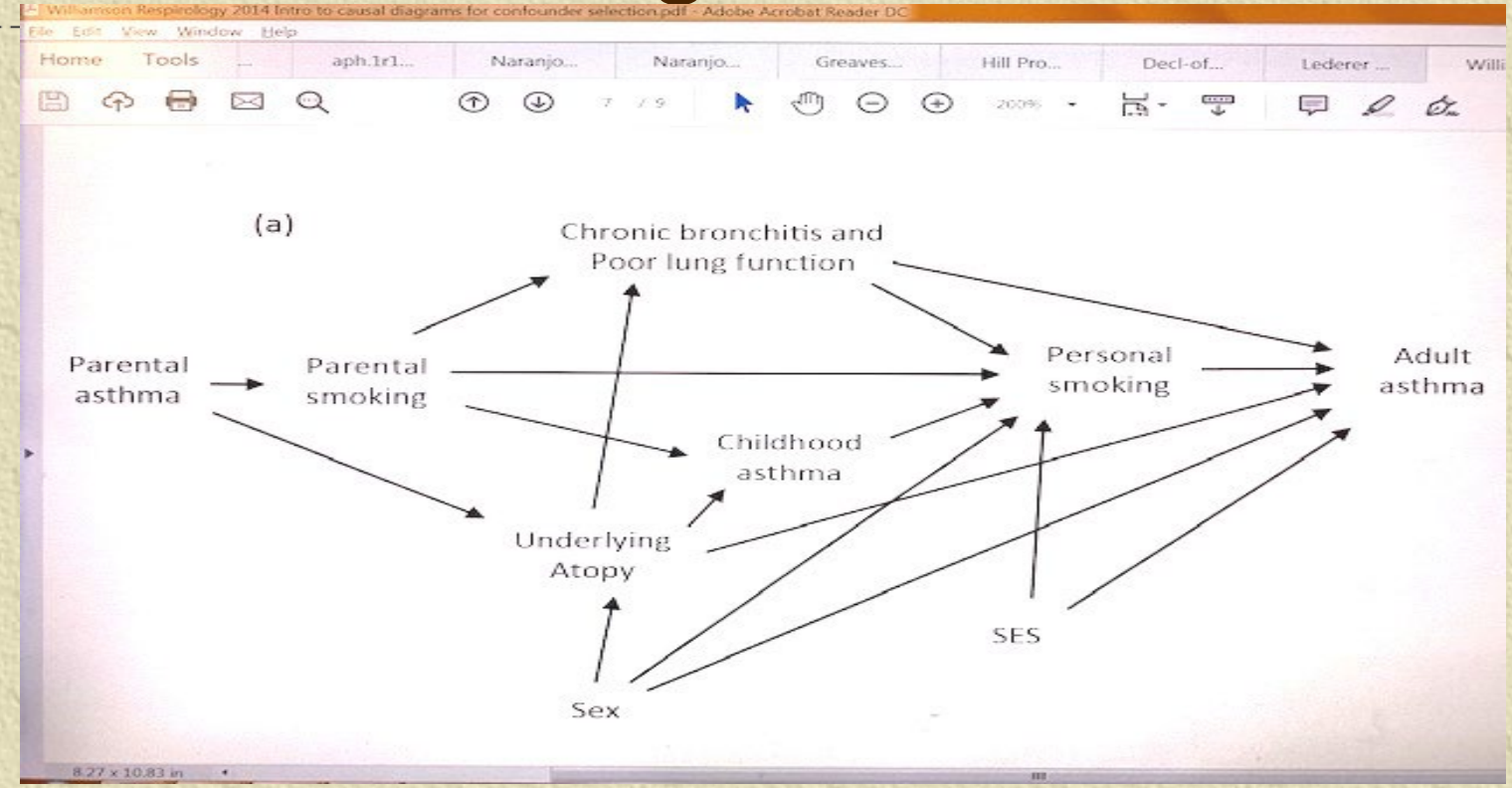
Useful to help understand selection bias as well

M-Bias



Source: Lederer et al, 2019

Illustrative DAG for study of whether Personal Smoking causes Adult Asthma



- Source: Williamson EJ et al. Respirology (2014) 19, 303-11.

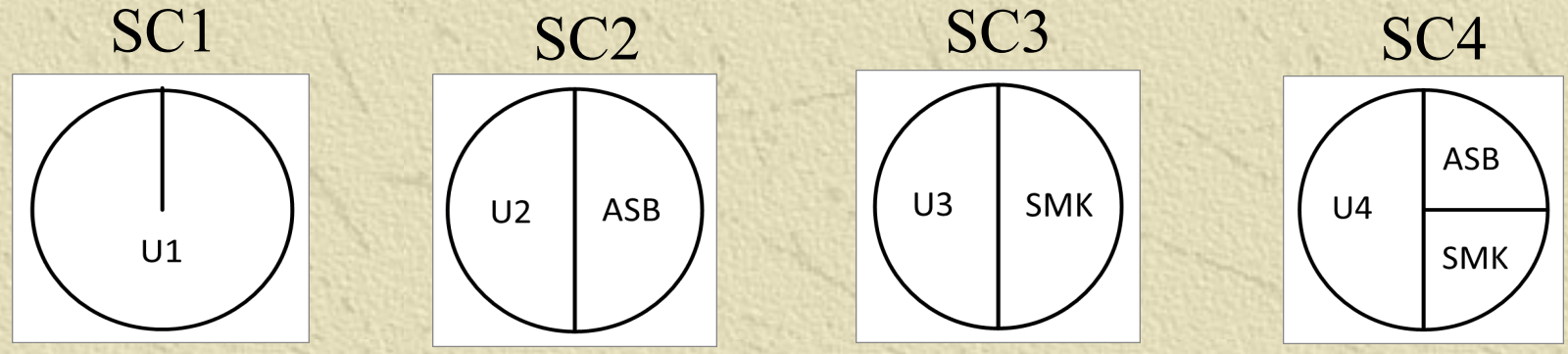
Multiple causes

- Multiple causal factors can contribute to causing one case of disease
- Multiple mutually exclusive causal factors can compete in causing a case of disease
- We are beginning to understand how to think about multiple causes

Did asbestos cause Lung CA in a smoking asbestos worker?

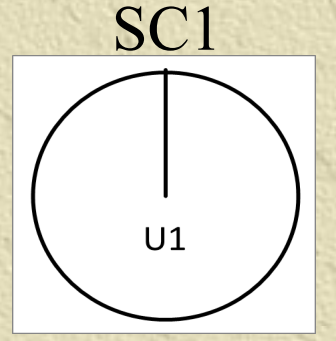
- 76 year old man, Mr. A.S., current 40 PY smoker with metastatic lung cancer
- 13 year history of asbestos insulation work, ending 1973
- This case illustrates multiple potential causes and multiple possible causal mechanisms

Rothman (1976) "Pie Model" of Sufficient Component Causes



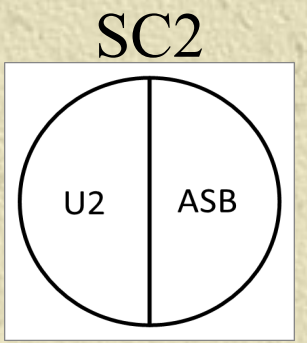
- In the simplest possible model, 4 ways Mr. A.S. could get LC
  - Each SC is a set of Component Causes that, if and when it is completed, would be sufficient to cause LC in Mr. A.S.
  - Any one of these Sufficient Causes could occur in Mr. A.S.
  - Each Sufficient Cause includes all the Component Causes necessary to complete that particular SC mechanism

Rothman (1976) "Pie Model" of Sufficient Component Causes



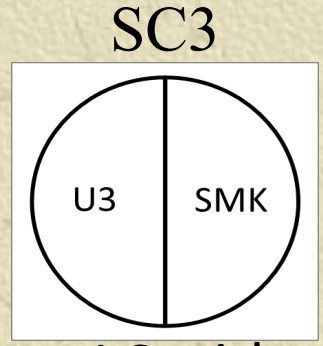
- U1 = Unmeasured set of genetic, epigenetic and environmental Component Causes sufficient to cause LC in Mr. A.S.
- LC can occur in nonsmokers with no asbestos exposure by genetic and environmental mechanisms we can call SC1

Rothman (1976) “Pie Model” of Sufficient Component Causes



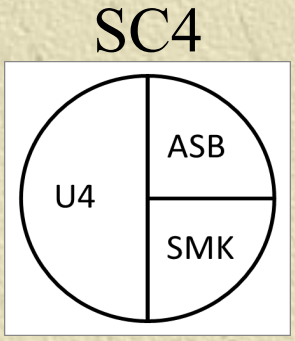
- SC2 is a different sufficient cause that requires Component Cause ASB and Component Causes U2
- U2 is different from U1, does not include ASB or SMK
- LC will not occur with ASB without U2

Rothman (1976) "Pie Model" of Sufficient Component Causes



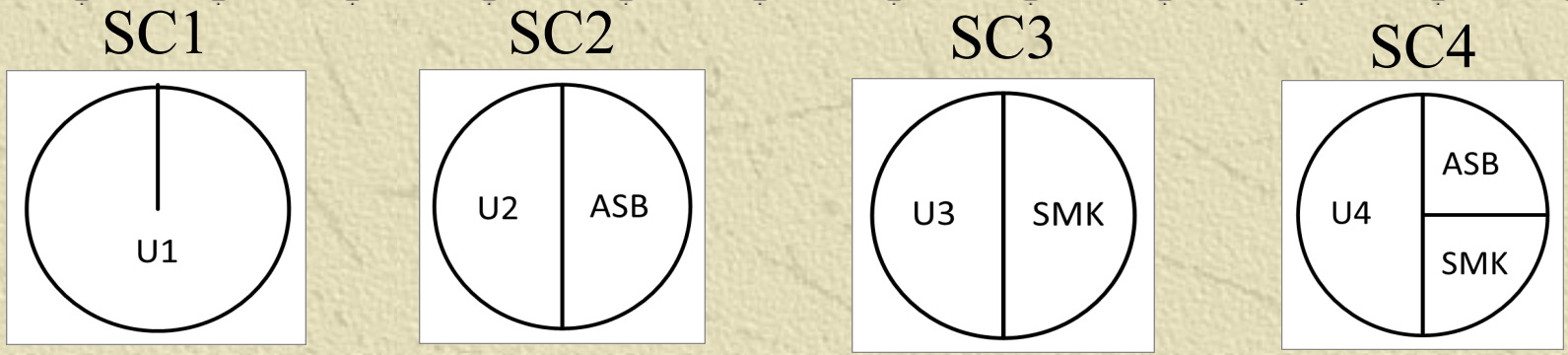
- CC Smoking is insufficient to cause LC without other U3
- U3 might include unmeasured factors such as:
  - RAS oncogene or other genetic factors
  - Downregulation of tumor suppressor microRNA let-7 that targets RAS oncogene, or other epigenetic factors
  - Adequate latency period for clinical manifestation of the LC

Rothman (1976) “Pie Model” of Sufficient Component Causes



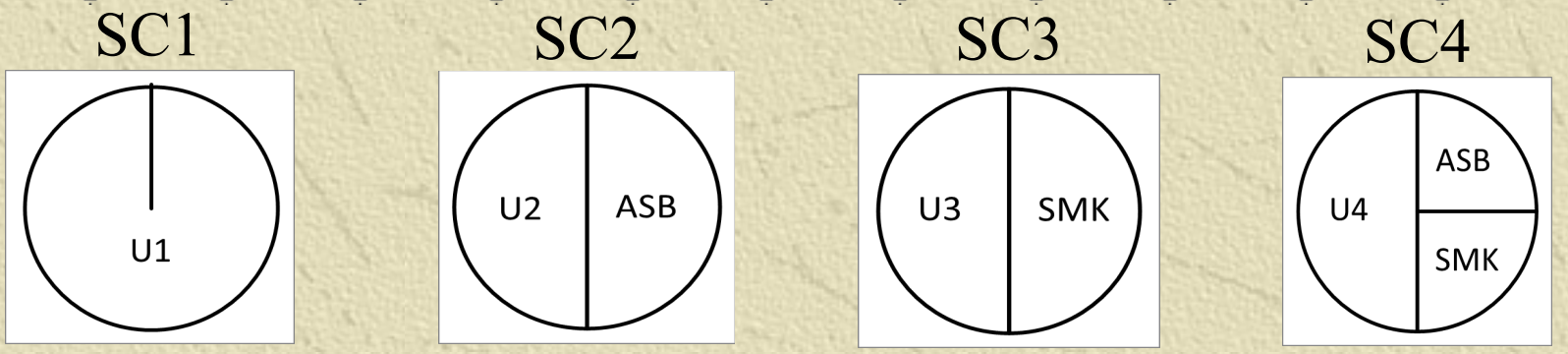
- SC4 requires both ASB and SMK as necessary Component Causes, plus unmeasured Component Causes U4
- SC4 might involve ASB damaging pulmonary macrophages, which then lose ability to eliminate carcinogens from SMK

Rothman (1976) "Pie Model" of Sufficient Component Causes



- LC could have been caused by SC4 or SC3 or SC2 or SC1
- A particular SC can be completely prevented by preventing any one or more of its Component Causes
- SC3 and SC4 would both be prevented by preventing SMK
- SC2 and SC4 would both be prevented by preventing ASB

Rothman (1976) "Pie Model" of Sufficient Component Causes



- Sufficient causes SC1, SC2, SC3 and SC4 are competing (mutually exclusive) causes, only one can happen
- Component causes U2 and ASB are **I**nsufficient, **N**ecessary components of the **U**nnecessary **S**ufficient cause SC2
- U4, ASB and SMK are INUS Component Causes of SC4

Asbestos, Smoking, and Lung Cancer, Insulators vs Blue Collar Cohort (Markowitz 2013)

Markowitz AJRCCM 2013 Asbestos Asbestosis & Lung Ca.pdf - Adobe Acrobat Reader DC

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TABLE 2. AGE-ADJUSTED LUNG CANCER MORTALITY RATE RATIOS, BY SMOKING, ASBESTOS, AND ASBESTOSIS STATUS, INSULATORS VERSUS CANCER PREVENTION STUDY II BLUE COLLAR COHORT, 1981–2008

Variable	No. of People	No. of Lung Cancer Deaths	No. of Person-Years	No. Lung Cancer Deaths/ Person-Years × 10^4	Rate Ratio	Poisson Regression: Age-Adjusted Rate Ratio	Poisson Regression: Age-adjusted Rate Ratio 95% CI
CPSE II (n = 54,243) vs all insulators (n = 2,377)							
CPS II, nonsmokers	18,843	151	377,396	4.00	1.00	1.00	Reference
Insulators, nonsmokers	468	18	8,706	20.68	5.17	5.20	3.19–8.48
CPS II, smokers	35,400	2,540	652,533	38.93	9.73	10.31	8.74–12.15
Insulators, smokers	1,909	321	29,950	107.18	26.79	28.36	23.36–34.44
CPSII (n = 54,243) vs. insulators without asbestosis (n = 918)							
CPS II, nonsmokers	18,843	151	377,396	4.00	1.00	1.00	Reference
Insulators without asbestosis, nonsmokers	253	7	5,205	13.45	3.36	3.55	1.66–7 58
CPS II smokers	35,400	2,540	652,533	38.93	9.73	10.31	8.75–12.15
Insulators without asbestosis, smokers	665	62	12,057	51.42	12.85	14.44	10.74–19.43
CPS II (n = 54,243) vs. insulators with asbestosis (n = l,459)							
CPS II, nonsmokers	18,843	151	377,396	4.00	1.00	1.00	Reference
Insulators with asbestosis, nonsmokers	215	11	3,501	31.42	7.85	7.40	4.01–13.65
CPS II, smokers	35,400	2,540	652,533	38.93	9.73	10.29	8.73–12.13
Insulators with asbestosis, smokers	1,244	259	17,893	144.75	36.18	36.79	30.08–44.99

Definition of abbreviations: CI = confidence interval; CPS II = Cancer Prevention Study II.

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Lung Cancers by ASB and SMK exposure status (Markowitz, 2013)

	NoA NoS	A NoS	NoA S	ASB SMK
N	18,843	468	35,400	1,909
LC cases	151	18	2,540	321
Person Yr	377,396	8,706	652,533	29,950
LC/10^4 PY	4	21	39	107
Excess	0	17	35	51
RR	1	5.2	9.8	27

Lung Cancers by ASB and SMK exposure status (Markowitz, 2013)

- For a group of 10,000 NoA NoS workers followed for one year, 4 LC occur
- For a group of 10,000 A NoS workers followed for one year, 21 LC occur, including 4 that would have gotten LC without ASB and 17 excess cases that got it due to ASB
- For a group of 10,000 NoA S workers followed for one year, 39 LC occur, 4 would have gotten it without SMK and 35 excess due to SMK

Lung Cancers by ASB and SMK exposure status (Markowitz, 2013)

- In a group of 10,000 ASB and SMK exposed workers followed for one year 107 cases of LC occur
  - 4 would have gotten it without ASB or SMK
  - 17 got it due to ASB only, could prevent by preventing ASB
  - 35 got it due to SMK only, could prevent by preventing SMK
  - 107-4-17-35 = 51 got it due to joint effect of ASB and SMK not including the 17 ASB alone or the 35 SMK alone or the 4 idiopathic
- 17+51=68 of the 107 LC cases could have been prevented by preventing ASB, 39 would have occurred without ASB

Inference to the Best Explanation, at both population and individual levels

- Lipton, 2004, p. 58, “The best of the available potential explanations is an actual explanation”
- “Better” explanations explain
  - more types of phenomena
  - with greater precision
  - provide more information about underlying mechanisms
  - unify apparently disparate phenomena, or
  - simplify our overall picture of the world.

  (Lipton, Encyclopedia.com, 2005)
  https://www.encyclopedia.com/humanities/encyclopedias-almanacs-transcripts-and-maps/inference-best-explanation
- When used as viewpoints rather than checklist type criteria, Hill’s viewpoints have been interpreted to be similar to IBE (Ward, 2009)

Suggestions to improve determination of WR causation in individual patients

- Strive to reduce FP and FN determinations of WR causation
- NIOSH 6 step approach is vague but a useful start
- Different approaches for different WR diseases
- Improve clinicians' understanding of modern tools to aid determinations of WR causation in individuals
- Better methods needed for exposure assessment that do not rely on employer controlling access to workplace for industrial hygienist or ergonomist (eg, job exposure matrices, validated exposure biomarkers for more toxicants)
- Recognize the need for clinical judgment in determination of WR causation
- Fund more OM research using methods that support causal inferences
- Improvement of **prevention** of WR illnesses and injuries to avoid the difficulties, costs and errors in determining WR causation in individuals

Conclusions

- Accurate determination of WR causation of disease in individual patients
  - Straightforward in some cases, labor intensive but achievable in many cases
  - Difficult or impossible in many cases
- Role for use of multidisciplinary expert panels
  - Conduct causation assessments for the most difficult individual cases
  - Development of guidelines for presumptions
- Expanded use of presumptions of exposure or causation
  - For the most clearcut and simple cases
  - To “debulk” the workload and free up resources for achievable but labor intensive cases
  - Critically important to provide access to individual causation assessments for those who don’t meet presumption criteria
- **Prevention** of WR exposures offers a way to avoid many of the difficulties, costs and errors inherent in determining WR causation in individuals