AACC

Better health through laboratory medicine.

PEARLS OF LABORATORY MEDICINE

INTERPRETATION OF EPIDEMIOLOGIC STUDIES

ASSOCIATION VS. CAUSATION

Julie E. Buring, ScD

CCTC Clinical Chemistry Trainee Council

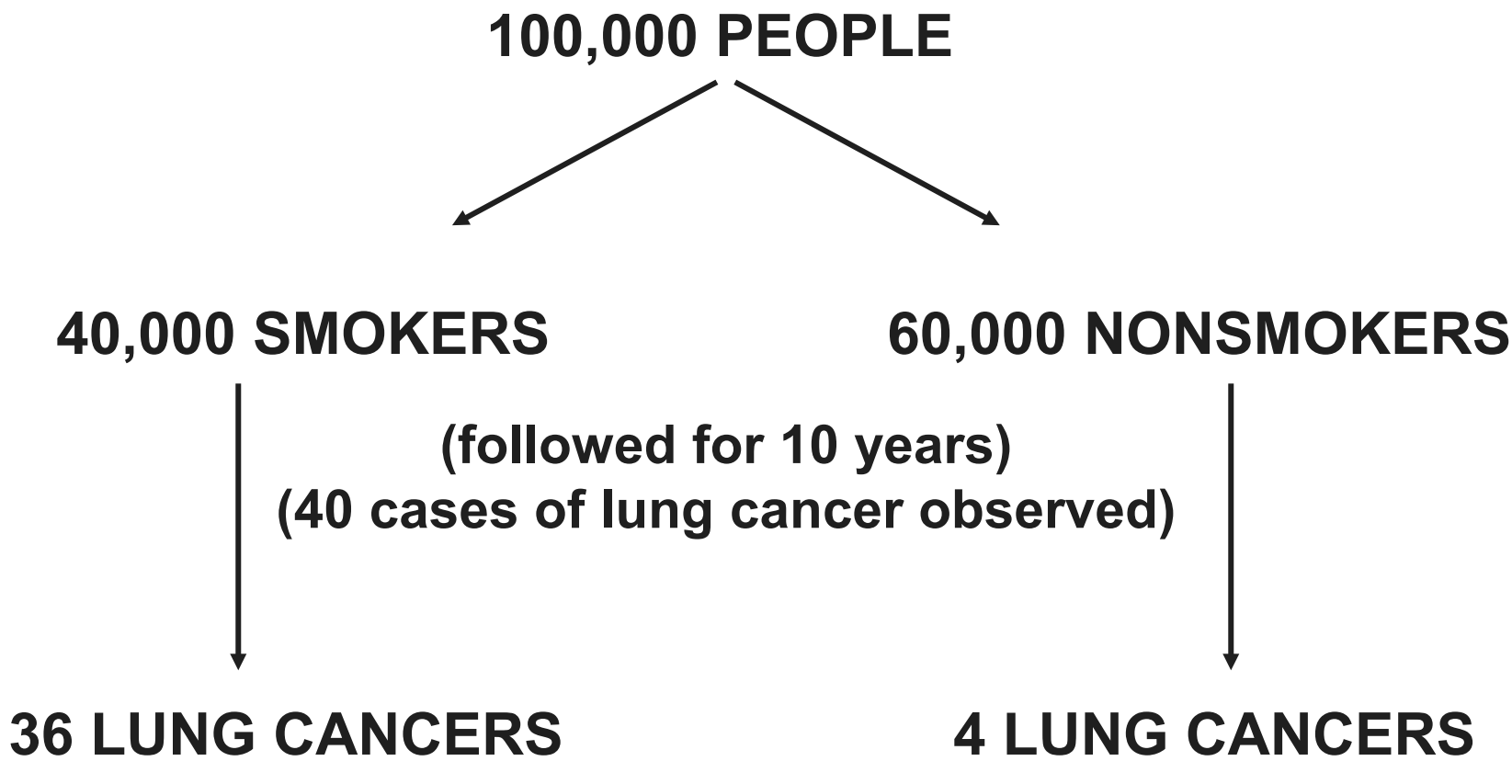
The Problem

- **What we see in epidemiologic research is a statistical association (relationship) between the disease/outcome under study and an exposure.**
- **What we are trying to do is evaluate whether that relationship is causal (i.e., that it plays an essential role in the occurrence of the disease), with the goal that an alteration in this exposure would lead to an alteration in risk of disease.**

Why is there a particular problem in assessing causality in epidemiologic research?

Latent period: Time from accumulation of sufficient exposure to manifestation of disease. Can be on the order of 15-20 years for a chronic disease.

How Do We Proceed?



CONCLUSION: There appears to be an association in these data between being a smoker and the development of lung cancer. But can we say that it is the smoking that is causing the lung cancer?

1st QUESTION: Is the observed association a valid one (i.e., a good estimate of the true association between the exposure and the disease)? What else could have accounted for the findings?

2nd QUESTION: If valid, can we judge it to be one of cause and effect?

3rd QUESTION: To whom can we generalize? To whom is the message?

1st Question – is it valid?

To determine if an association observed in a particular study is valid, need to rule out alternative explanations for the findings. We need to keep asking the question: "But what about? . . ."

Specifically, we need to consider the role of three alternative explanations:

- **Chance**
- **Bias**
- **Confounding**

Role of Chance

That the observed result may be due to chance - to random sampling variability - is always an explanation for any result.

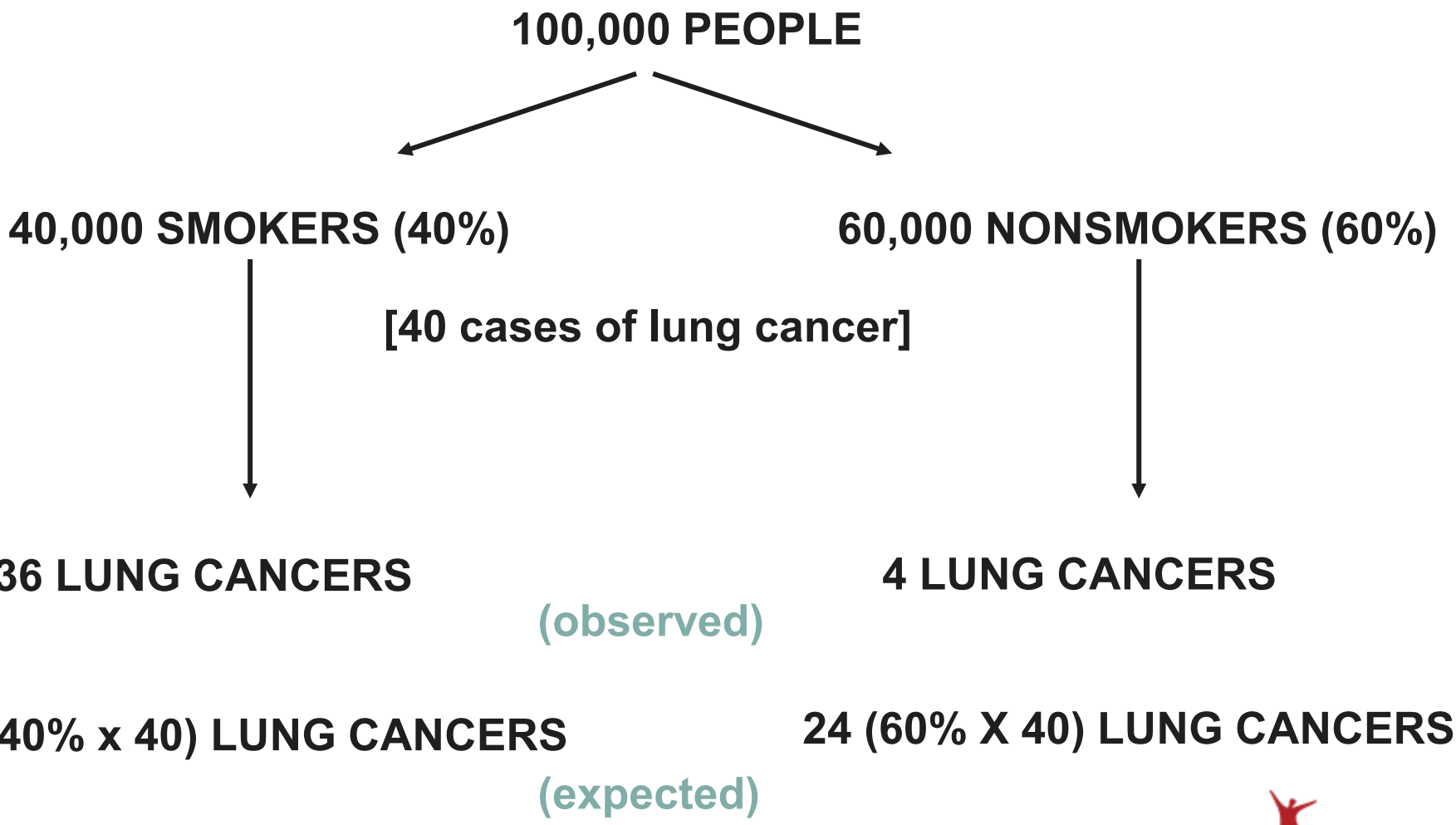
Common way to measure the effect of chance is by conducting a test of statistical significance. Learn which/how in biostatistics, but big picture approach:

Chance

- Set up a null hypothesis (H_0): nothing is going on, no difference, no association
- Test the alternative hypothesis (H_1): something is happening, there is a difference, there is an association

- Choose and conduct appropriate test of statistical significance: compare observed to expected under H_0.

Concept of Observed vs. Expected



Chance: P-value

- From test statistic, calculate the p-value: the probability that the result seen in this study or one more extreme would occur by chance alone, given H_0 is true.
- If the probability is small, reject H_0 of no association and say there is a statistically significant association between the exposure and outcome. If the probability is high, cannot reject H_0 of no association and say association not statistically significant.

Chance: P-value

- p = 0.05 (1 out of 20) is the usual (arbitrary) cut-off level for statistical significance.
- **If p <0.05 of seeing our observed values given that Ho is true, we conclude that chance is an unlikely explanation for the findings, reject H_0, and say that there is a statistically significant association between the exposure and disease.**
- **If p ≥0.05, we conclude that chance cannot be excluded as an explanation for the findings, do not reject H_0, and say there is not a statistically significant association between the exposure and disease.**

Chance: P-value

AACC Better health through laboratory medicine.

- No p-value however small excludes chance; no p-value however large mandates chance.
- The p-value is not a rule - it is a guideline to an interpretation of the likelihood that chance is an explanation for the findings.
- Report actual p-value: don't just say results are "significant" or "nonsignificant" at the 0.05 level.
- Additional information: the p-value reflects both the strength of the association and the sample size of the study (i.e., the variability). To separate out these two components, preferable to calculate the confidence interval in addition (later lecture).

Chance: P-value

- The p-value only evaluates the role of chance - it says absolutely nothing about the other alternative explanations of bias and confounding, or about causality. To draw a conclusion regarding causality based on a p-value <0.05 is totally incorrect.

- Moreover even if statistically significant, says nothing about biological importance (e.g., differences in height in women who have had, not have had children).

Nondifferential Misclassification

Misclassification is error in the ascertainment of study information.

Common in virtually all studies (e.g., self-reported weight and height, measured blood pressure, self-reported family history, diet).

If the error is nondifferential (random, or the degree of error is the same, regardless of whether the people are sick or not (i.e., same in both cases and controls) or exposed or not, it can only make the groups more similar, and will drive the estimate of association towards the null value (e.g., RR=1) by diluting the association.

Differential Misclassification - Bias

But if the degree of error is differential (different degree of error in exposed vs nonexposed groups, or diseased vs nondiseased groups), this is called BIAS.

Can affect the estimate of effect in either direction (can underestimate or overestimate depending on the direction of the error).

Bias

- Any source of systematic (differential) error in the determination of the association between the exposure and disease.
- Results in an incorrect (invalid) estimate of the measure of association.
- Can create spurious association when there really is none (bias away from the null).
- Can mask an association when there really is one (bias towards the null).
- Bias is primarily introduced by the investigator or study participants.

Bias

- Bias can arise in all study types.
- Bias occurs in the design and conduct of a study. It can be prevented or evaluated, but cannot be fixed in the analysis phase.
- The key word with respect to bias is the word "different".
- Books of names of biases. But most frequently occurs either from the way participants are brought in to the study (selection bias) or the way information is obtained once they are in the study (observation bias).

Selection Bias

- **May result when the selection of the particular individuals to be included into the study is influenced systematically (differently) by knowledge of their status regarding the other variable of interest: i.e., exposure (if a case-control study) or disease (if a cohort study).**

Selection Bias in Case-Control Study

Hospital-based case-control study of oral contraceptives and venous thromboembolism (VTE).

If women with suspected DVT are more likely to be hospitalized if they report currently taking OC's, the observed odds ratio would be biased - would be an overestimate of the true effect of OC's.

Can't be controlled in the analysis. Could do subgroup analysis of those hospitalized with severe enough DVT that they would have been hospitalized regardless of OC exposure – but different question.

Selection Bias: What are the solutions?

- Little or nothing can be done to fix this bias once it has occurred.
- You need to avoid it when you design and conduct the study, for example, by using the same criteria for selecting study groups, obtaining all relevant subject records, obtaining high participation rates, and taking into account diagnostic and referral patterns of disease.

Observation Bias

- May result when there is a different level of accuracy or completeness of information between the study groups.
- Results in participants who are systematically incorrectly classified as either exposed or unexposed or as diseased or not diseased.
- Occurs after the subjects have entered the study.
- Can affect the measure of association in either direction.
- Can introduce features into the design of the study to minimize observation bias, but cannot adjust for observation bias in the analysis of a study.

Observation Bias

- **Many types of observation bias (recall bias, interviewer bias, surveillance bias, loss to follow-up, etc).**
- **But all observation bias requires there be systematic, differential misclassification.**

Observation Bias

AACC Better health through laboratory medicine.

- **Recall bias**: Everyone forgets, but if people with disease remember or report exposures differently (more or less accurately) than those without disease, will be observation bias.
- Can result in over- or underestimate of measure of association, depending on whether they deny or exaggerate.
- **Solutions**: Use controls who are themselves sick; use standardized questionnaires that obtain complete information; use preexisting records; get information from objective records; mask subjects to study hypothesis.

Observation Bias

- **Interviewer bias: Systematic difference in soliciting, recording, interpreting information.**
- **Example of interviewers probing for "correct" answers.**
- **Solutions: mask interviewers to study hypothesis and disease or exposure status of subjects; use standardized questionnaires or standardized (preexisting) methods of outcome (or exposure) ascertainment.**

Observation Bias

- **Information Bias: Extent/quality of follow-up**
  - **Loss to follow-up: LTFU**
  - **Cohort and intervention studies**
  - **Systematic difference in following and obtaining outcome information. If LTFU different between the two groups (exposed/nonexposed) and related to the outcome under study, then observation bias.**

Loss to Follow-up

- Solution
  - Keep follow-up rate high; low rates of LTFU
  - Use standardized follow-up procedures for all subjects
  - Obtain back-up contact information at start of study
  - National Death Index for mortality

Bias

- **When interpreting study results, ask 3 questions:**

  Given conditions of the study, could bias have occurred?

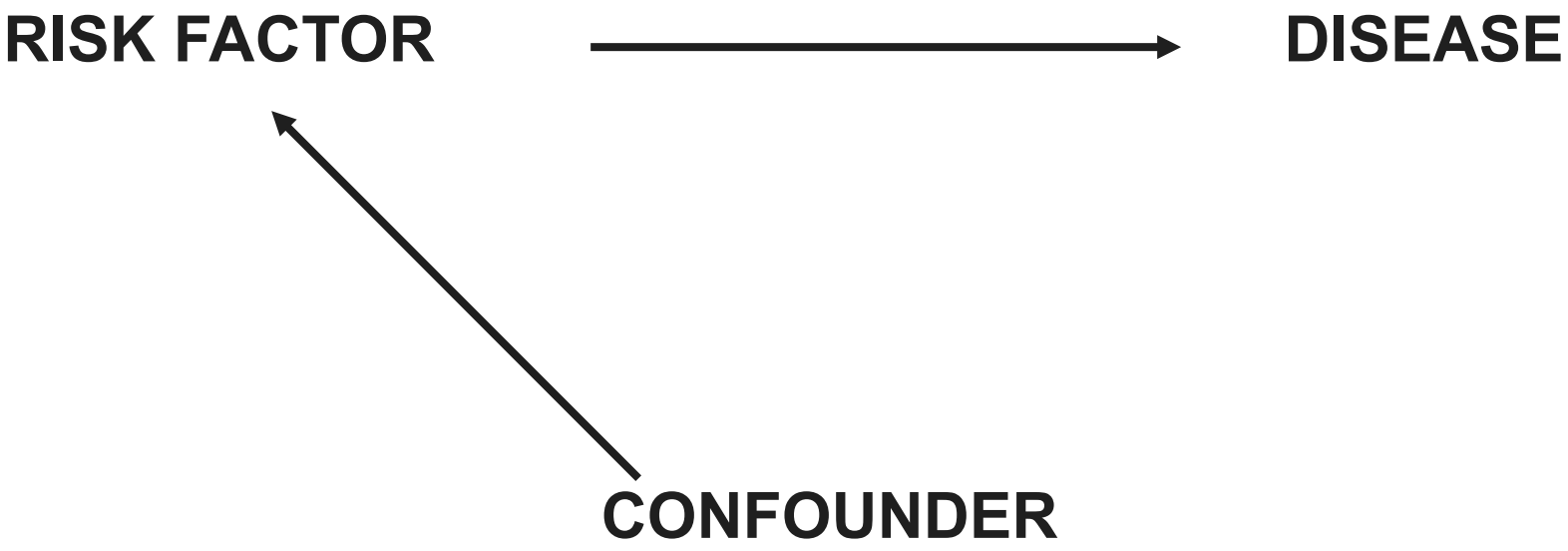
  Are consequences of the bias large enough to distort the measure of association in an meaningful way?

  Which direction is the distortion – towards the null or away from the null?

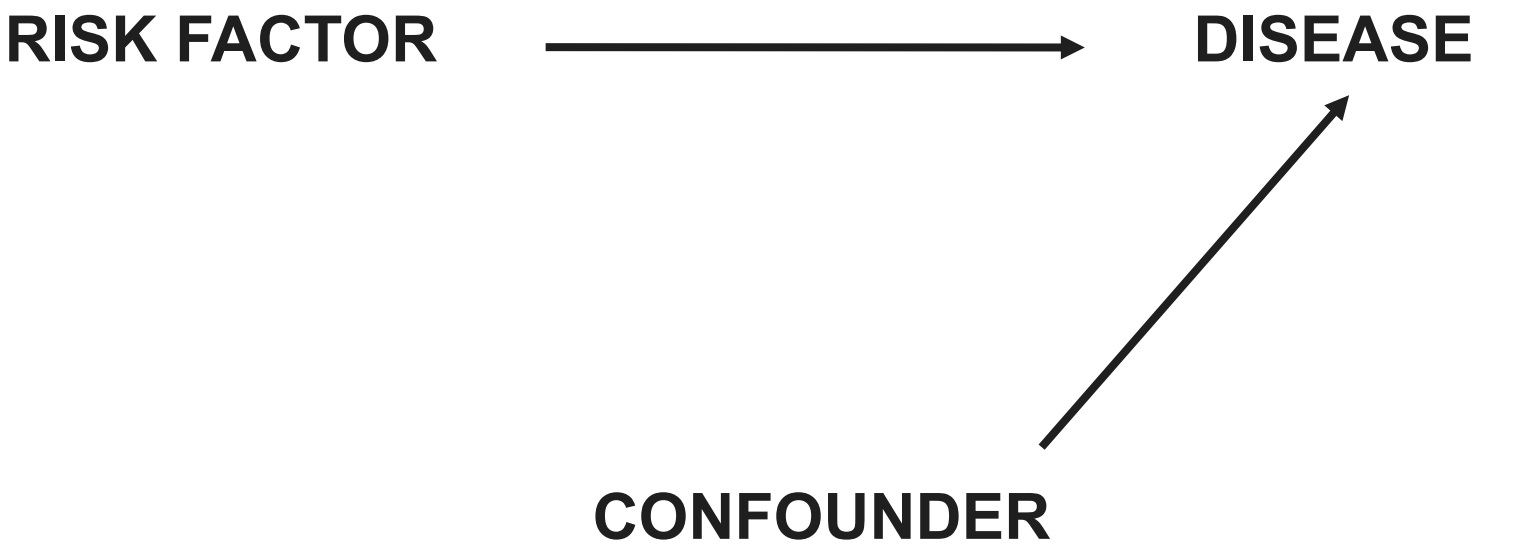
Role of Confounding

- A mixture of effects between the association under study and a third variable.
- This third factor (the confounder) must be BOTH associated with the exposure under study and, independently of the exposure, be a cause or correlate of the cause of the disease.
- The confounder may be responsible in part or totally for the association seen in the data.


EXPOSURE
DISEASE
CONFOUNDER



If potential confounder is associated with exposure but not the disease, then not an actual confounder: e.g., for smoking and lung cancer, while alcohol drinking is a potential confounder because it is associated with smoking, would not be an actual confounder because alcohol is not an independent risk factor for lung cancer.



If potential confounder is associated with disease but not the exposure, then not an actual confounder: e.g., for small to moderate alcohol drinking vs nondrinking and CHD, while stress is a potential confounder because risk factor for CHD, if stress not associated with moderate vs no alcohol drinking, not an actual confounder.

RISK FACTOR ⟶ Not CONFOUNDER ⟶ DISEASE

Factor which represents the potential mechanism of action of the risk factor. This is an intermediate marker, not a confounder. If controlled for, then would be looking at relationship of risk factor and disease over and above the effect of this mechanism: eg., obesity and stroke, hypertension would not be controlled for, unless wanted effect of obesity, over and above the effect of obesity-caused hypertension.

What Are Potential Confounders?

- We usually don't know what is associated with the exposure, nor the full mechanisms by which the exposure is postulated to affect the disease of interest.
- In that case, the practical approach is to identify all known risk factors for the disease as potential confounders, and collect information on them in the design of the study.

Confounding

- **Key is that we MUST anticipate confounding and record data on potential confounders in the design of the study.**
- **To discuss later lecture: Can control confounding in the design of a study and/or assess and adjust for confounding in the analysis (Note: this is different than for the case of a bias). But ONLY if we have information on the potential confounding variables. We cannot control in an observational study for the effects of confounders for which we have not collected information.**

2nd Question: Is the valid association one of cause and effect?

- Once the alternative explanations of chance, bias and confounding have been assessed, the investigators may conclude there is a valid, statistically significant association between the exposure and outcome.
- ONLY THEN is the issue of whether that valid association is one of cause and effect to be considered.
- Causality is an issue of judgment, which must be based on the totality of all available evidence, well beyond one study.
- Many sets of criteria for judging causality. But commonly used (in discussion sections of manuscripts or in grant applications) is a set of 4 positive criteria to support a judgment of causality, that include:

Positive Criteria for Causality

1. **Strength of the association: the stronger the association, the more likely the association is to be causal. It minimizes the chance of unsuspected confounders. A weak association can be causal - but it is harder to prove.**
2. **Totality of evidence, or consistency: if other investigators studying different populations using different methodologies show similar results, strong support for causality.**

Positive Criteria for Causality

3. **Biologic credibility: does the association "make sense"? If no biologic mechanism can be postulated, however, may merely be due to limits of current knowledge.**

4. **Dose-response: does level of risk or disease increase as dosage increases? Problems are that first, a dose-response relationship could be due to the effect of a confounder and second, a dose-response relationship may not be present if there is a threshold effect.**

3rd Question: Generalizability

- If the observed association is considered valid (internally validity), related issue is whether the findings are generalizable (external validity), i.e., to whom are they applicable.
- Technically, study results are only applicable to the population in which study done. But want to make a judgment to broaden inference.
- Validity trumps generalizability. Primary concern is validity, since you cannot generalize an invalid result. Watch that validity is not compromised in an effort to achieve generalizability
- Where are we in our knowledge? To whom is the message?: to researchers, to health care providers, to the public, to regulatory agencies?

Summary

AACC Better health through laboratory medicine.

Framework for assessing statistical association and cause-effect relationships in epidemiology

A. Is there a valid statistical association? Exclude

1. **Chance**
2. **Bias**
3. **Confounding**

B. If there is a valid statistical association, can we judge it to be one of cause and effect? Positive criteria:

1. **Strength of association**
2. **Totality of evidence**
3. **Biologic credibility**
4. **Dose-response**

C. Generalizability and public health implications. For whom and to whom is the message?

AACC Better health through laboratory medicine.

Thank you for participating in this *Clinical Chemistry* Trainee Council Webcast

Find our upcoming Webcasts and other Trainee Council information at www.traineecouncil.org

Follow us



CCTC Clinical Chemistry Trainee Council